SIXTH EDITION

PHARMACOTHERAPY

PRINCIPLES AND PRACTICE

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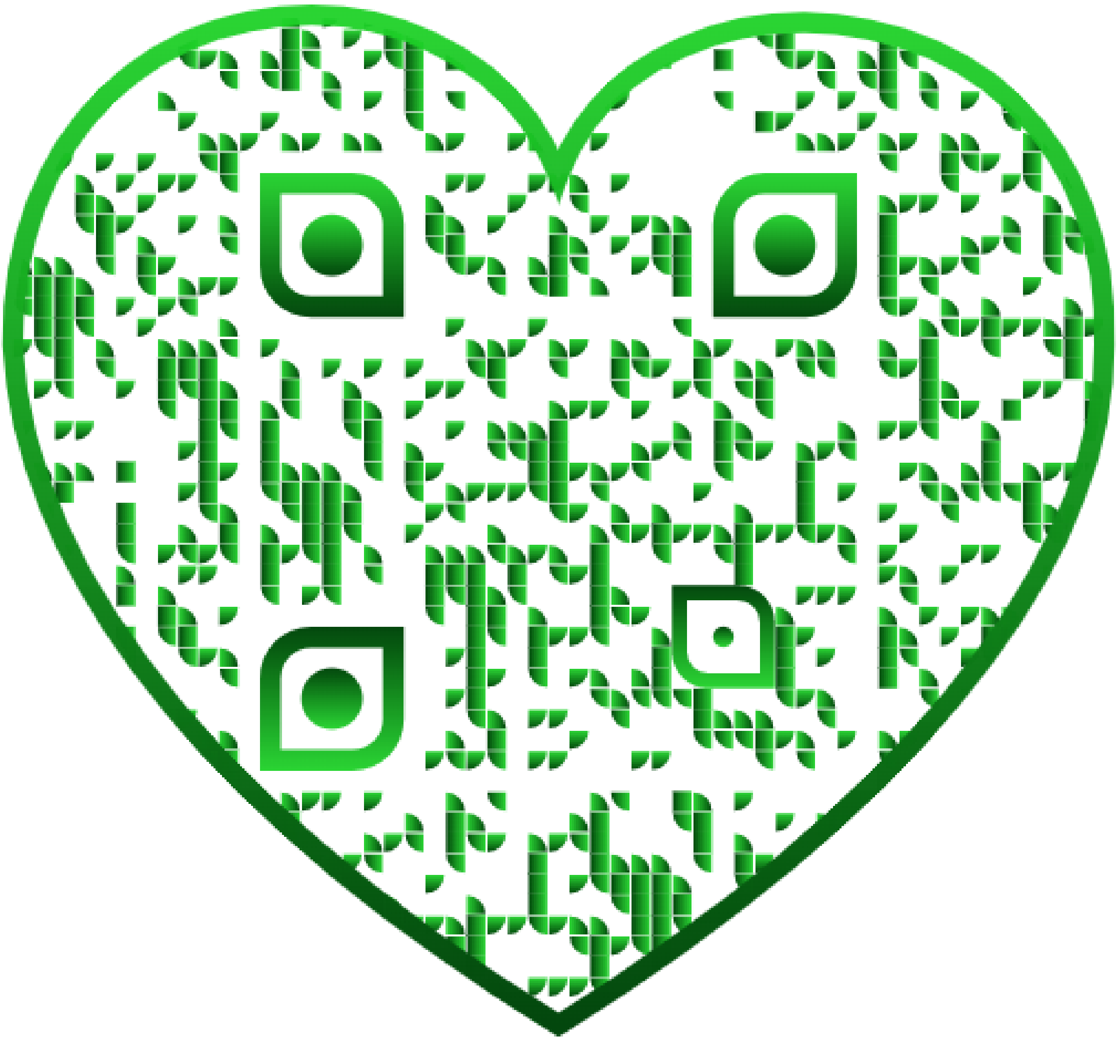

Pharmacotherapy Principles & Practice

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Pharmacotherapy Principles & Practice

SIXTH EDITION

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The editors dedicate this edition to our families for their support
and express immense gratitude to healthcare workers around the world.

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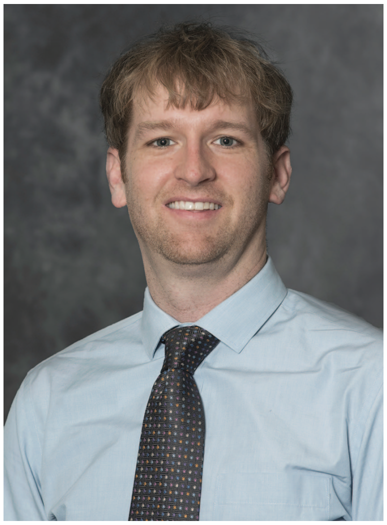

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PREFACE

Safe and effective use of pharmacotherapy is critical for preventing and treating acute and chronic medical conditions. Although biomedical research continues to lead to production of medications with great potential to improve health, medications are often overused, underused, or misused, leading to suboptimal or unsafe results. As healthcare practitioners, we are responsible for optimizing positive health outcomes and limiting adverse effects from pharmacotherapy.

Providing high quality, cost-effective pharmacotherapy requires integration of scientific knowledge and clinical practice skills combined with patient-centered care. The development of healthcare practitioners occurs through structured educational processes that include didactic and experiential learning, independent study, mentorship, interprofessional experiences, and direct involvement in patient care.

The sixth edition of *Pharmacotherapy Principles & Practice* is designed to provide student learners and healthcare practitioners with essential knowledge of the pathophysiology and pharmacotherapy of acute and chronic diseases likely to be encountered in routine practice. Chapters are written by content experts and peer reviewed by pharmacists, nurse practitioners, physician assistants, and physicians who are authorities in their professional disciplines.

Pharmacotherapy Principles & Practice, sixth edition, opens with a brief Introduction chapter followed by five chapters focused on special populations: pediatrics, geriatrics, palliative care, critical care, and global health and travel medicine. These chapters are followed by 97 disease-based chapters that review epidemiology, etiology, pathophysiology, clinical presentation and diagnosis, and nonpharmacologic therapy, followed by an emphasis on clear recommendations for medication selection, desired outcomes, dosing, and patient monitoring. New chapters in this edition include critical care pharmacotherapy; global health and travel medicine; systemic lupus erythematosus; and nose, mouth, and throat disorders. There is also important new chapter content on circulatory shock syndromes, trauma-related anxiety disorder, otic disorders, and antimicrobial stewardship.The following textbook features were designed in collaboration with educational design specialists to enhance learning and retention:

- *Structured learning objectives* at the beginning of each chapter.
- *Key concepts related to the disease, patient assessment,* and *treatment* highlighted with an easily identifiable icon throughout the chapter.
- *Patient encounters*, updated and revised from the previous edition, that facilitate development of critical thinking skills and lend clinical relevance to the scientific foundation provided.
- A *patient care process* section modeling the Joint Commission of Pharmacy Practitioners (JCPP) that provides specific recommendations about the process of care for an individual patient involving five steps: collect information, assess information, develop a care plan, implement the care plan, and follow-up: monitor and evaluate.
- *Up-to-date literature citations* for each chapter to support treatment recommendations.
- *Tables, figures, and algorithms* that enhance understanding of pathophysiology, clinical presentation, medication selection, pharmacokinetics, and patient monitoring.
- *Medical abbreviations and their meanings* at the end of each chapter to facilitate learning the accepted shorthand used in real-world healthcare settings.
- *Self-assessment questions and answers for each chapter* in the Online Learning Center to facilitate self-evaluation of learning.
- *Laboratory values* expressed as both conventional units and Système International (SI) units.
- *Appendices* that contain: (1) conversion factors and anthropometrics; (2) common medical abbreviations; (3) glossary of medical terms (the first use of each term in a chapter appears in bold, colored font); and (4) prescription writing principles.
- *A table of common laboratory tests and reference ranges* appears on the inside covers of the book.

A companion website, *Pharmacotherapy Principles and Practice Study Guide: A Case-Based Care Plan Approach*, is available to further enhance learning by guiding students through the process of applying knowledge of pharmacotherapy to specific patient cases. This study guide contains approximately 100 patient cases that correspond to chapters in the textbook.

The Online Learning Center at www.ChisholmPharmacotherapy.com provides self-assessment questions, grading and immediate feedback on the questions, and reporting capabilities.

We are extremely grateful for the commitment and dedication of more than 190 contributing authors and more than 100 peer reviewers of the chapters in this new edition. We also thank the many educators, schools/colleges, and healthcare institutions that have adopted this textbook in courses or use it as a reference in practice settings. We extend our sincere thanks to the McGraw Hill team for their hard work and commitment to bringing this new edition to our readership.

The Editors
September 2021

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INTRODUCTION

Jack E. Fincham

INTRODUCTION

Health professionals are given significant responsibilities in our healthcare system. These roles may be taken for granted by patients until a pharmacist, nurse practitioner, physician assistant, physician, or others perform assigned tasks that make major positive impacts upon patients and patients' families lives in countless ways. The exemplary manner in which health professionals provide necessary care to patients is a hallmark of health professional practice and delivery of US health care. Patients are thus well served, and fellow health professionals share knowledge and expertise specific to their profession.

However, there are significant problems remaining in the US healthcare system from a structural standpoint. In 2018, the United States spent twice as much as comparative countries on health care, yet the United States ranks 11th in the list that considers increased hospitalization from preventable causes and an increase in avoidable deaths.[1] Keehan and colleagues[2] from the US Centers for Medicare and Medicaid Services (CMS) projected the costs of health care through 2028 and estimate that by 2028, US healthcare expenditures will exceed $6.2 trillion with prescription drug spending estimated to be $560.3 billion. This prescription drug spending amounts to a projected increase in spending of 74% between 2016 and 2028.

A significant issue in the United States is that countless Americans in our midst are uninsured or underinsured. They may have partial coverage after a fashion, but, for these Americans, the high price of deductibles, co-pays, and monthly payments for insurance create an economic dilemma each time they seek care or pay premiums. The Coronavirus Disease (COVID-19) pandemic has amplified the lack of health insurance for many in this country.[3] The swelling of the ranks of the unemployed also means many with prior health insurance through an employer are now not only out of work but also without health insurance. In addition, many other social determinants of care impact who receives health care or not.

The use of medications in the healthcare system provides enormous benefit to many; lives are saved or enhanced, and lifespans are lengthened. Many other uses of medications lead to significant side effects, worsening states of health, and premature deaths. So, how to separate these disparate pictures of drug use outcomes? You, within your practices and within your networks in the healthcare workplace, can help to promote the former and diminish the latter. The authors of the chapters in this book have written informative, current, and superb chapters that can empower you to positively influence medication use.

The following are issues that will impact you as you develop as a healthcare professional or impact your patients as they use medications. These are important issues to consider as you enhance your knowledge concerning medications and how they can impact your patients.

CORONOVIRUS DISEASE 2019 (COVID-19)

The COVID-19 pandemic has wreaked havoc globally upon economic, social, and health structures. Healthcare practitioners have been stressed as never before. Driggin and colleagues[4] have written of the risks heathcare workers are exposed to when providing cardiovascular care and become hosts or vectors of COVID-19 transmission. Much has been written of the fear healthcare workers are experiencing since they fear for their coworkers, their family and friends, and their communities.[5,6] Rose[7] has noted the rapid change of teaching techniques from traditional pre-clerkship course delivery to online learning applications that are now required for health professional curricula during this pandemic.

The general public has experienced significant detrimental emotional impacts due to the COVID-19 pandemic. Pfefferbaum and North[8] have written of the trauma, including post-traumatic stress disorders (PTSD), patients are experiencing due to concerns related to their health, safety, well-being, economic status, and stress disorders. You will have an enormous opportunity to positively impact patients and families in your practices.

DRUG USE IN THE HEALTHCARE SYSTEM

Prescription medications are used daily and problems occurring with the use of drugs can include:

- Medication errors
- Suboptimal drug, dose, regimen, dosage form, and duration of use
- Unnecessary drug therapy
- Therapeutic duplication
- Drug–drug, drug–disease, drug–food, or drug–nutrient interactions
- Drug allergies
- Adverse drug effects, some of which are preventable

Clinicians are often called upon to resolve problems that occur due to undertreatment, overtreatment, or inappropriate treatment. Individuals can purchase medications through numerous outlets. Over-the-counter (OTC) medications can be purchased virtually anywhere. OTCs are widely used by all age groups. Prescription medications can be purchased through traditional channels (community chain and independent pharmacies), from mail-order pharmacies, through the Internet, from physicians, from healthcare institutions, and elsewhere. Herbal remedies and countless cannabidiol (CBD) products are marketed and sold in numerous outlets. The monitoring of the positive and negative outcomes of the use of these drugs, both prescription and OTC, can be disjointed and incomplete. Clinicians and health professionals need to take ownership of these problems and improve patient outcomes resulting from drug use.

Although clinicians are the gatekeepers for patients to obtain prescription drugs, patients obtain prescription medications from numerous sources. Patients may also borrow from friends, relatives, or even casual acquaintances. In addition, patients obtain OTC medications from physicians through prescriptions, on advice from pharmacists and other health professionals, through self-selection, or through the recommendations of friends or acquaintances. Through all of this, it must be recognized that there are both formal (structural) and informal (word-of-mouth) components at play. Health professionals may or may not be consulted regarding the use of medications, and in some cases are unaware of the drugs patients are taking.

External variables may greatly influence patients and their drug-taking behaviors. Coverage for prescribed drugs allows those with coverage to obtain medications with varying cost-sharing requirements. However, many do not have insurance coverage for drugs or other health-related needs.

Self-Medication

Self-medication can be broadly defined as a decision made by a patient to consume a drug with or without the approval or direction of a health professional. The self-medication activities of patients have increased dramatically in the late 20th and early 21st centuries. Many factors affecting patients have continued to fuel this increase in self-medication. There have been many prescription items switched to OTC classification in the last 50 years, which is dramatically and significantly fueling the rapid expansion of OTC drug usage. In addition, patients are increasingly comfortable with self-diagnosing and self-selection of OTC remedies.

Through the rational use of drugs, patients may avoid more costly therapies or expenditures for other professional services. Self-limiting conditions, and even some chronic health conditions (e.g., allergies and dermatologic conditions), if appropriately treated through patient self-medication, allow the patient to have a degree of autonomy in healthcare decisions.

Non-Adherence Issues

Non-adherence is not taking a prescribed medication or not taking it as prescribed and is one of the most understated problems in the healthcare system.[9] Reasons can include not being able to get the medication in a timely manner because of insurance requirements such as a prior approval from the insurance being denied or delayed, the prescribed drug may not be covered under the patient's insurance, the patient cannot afford to pay the drug cost or the copay, regimens are complicated or not understood by the patient, etc. The effects of non-adherence have enormous ramifications for patients, caregivers, and health professionals. Non-adherence is a multifaceted problem with a need for interprofessional, multidisciplinary solutions. Interventions that are organizational (how clinics are structured), educational (patient counseling, supportive approach), and behavioral (impacting health beliefs and expectations) are necessary. Compliant behavior can be enhanced through your actions with the patients for whom you provide care. Sometimes what is necessary is referral to specific clinicians for individualized treatment and monitoring to enhance compliance. The case histories provided in this textbook will allow you to follow what others have done in similar situations to optimally help patients succeed in improving adherence rates and subsequent positive health outcomes.

Drug Use by the Elderly

The major source of payment for prescription drugs for those age 65 years and older in the United States is the Medicare Part D Drug Benefit. Seniors have benefitted tremendously from this component. Estimates place the expenditure for Medicare Part D to be $88 billion in 2020.[10]

A joint effort by health professionals working together is the best approach to aiding seniors in achieving optimal drug therapy. Evaluation of all medications taken by seniors at each patient visit can help prevent polypharmacy from occurring.

IMPACTING THE PROBLEMS OF DRUG USE

Medication Errors

There is a tremendous opportunity in medication use and monitoring to reduce medication errors. Untold morbidity and mortality occur due to the many errors occurring in medication use. The increasing availability of artificial intelligence applications, and increased usage by healthcare professionals can enhance the proper provision of patient care for all patients.[11]

Avoiding Prescribing Cascades

Prescribing cascades occur in healthcare when the side effect from a medication is interpreted as a new condition—and a second drug is prescribed to "treat" the side effect. Prescribing cascades are important because they can be prevented.[12]

Impacting the Opioid Crisis

The use and misuse of prescription opioid analgesic medications are at an all-time high and are increasing, and the negative consequences of this epidemic are many.[13] Health professionals will play a key, vital role in reversing this epidemic and enhancing the health of many and society as well.

SUMMARY

Health professionals are at a crucial juncture facing an uncertain, yet promising future. The skills and knowledge that enable effective practice have never been more daunting among the numerous health professions. Technology can further empower health professionals to play an effective role in helping patients and fellow health professionals to practice safe and effective medicine. Continuing healthcare reforms will have the potential to dramatically impact your practices in the healthcare system for the length of your careers.

The use of this text, which incorporates materials written by the finest minds in pharmacy practice and education, can enable the reader to play a crucial role in improving the drug use process for patients, providers, payers, and society. The thorough analysis of common disease states, discussion of therapies to treat these conditions, and specific advice for patients will help you in your practices. The purpose of this book is to help you make a real improvement in the therapies you provide to your patients. Current and future clinicians can rely on the information laid out here to enhance your knowledge and allow you to assist your patients with the sound advice that they expect you to provide. Use the text, case histories, and numerous examples here to expand your therapeutic skills, and to help positively impact your patients in the years to come.

You can help to reverse medication-related problems, improve outcomes of care both clinically and economically, and enable drug use to meet stated goals and objectives. This text provides a thorough analysis and summary of treatment options for commonly occurring diseases and the medications or alternative therapies used to successfully treat these conditions.

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Part I

Special Populations

1 Geriatrics: Safe Medication Use in Older Adults

Jeannie K. Lee, Damian M. Mendoza, and
Shaun M. Chatelain

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain changing aging population demographics.
2. Discuss age-related pharmacokinetic and pharmacodynamic changes.
3. Identify drug-related problems and associated morbidities commonly experienced by older adults.
4. Describe major components of geriatric assessment.
5. Recognize interprofessional patient care functions in various geriatric practice settings.

INTRODUCTION

The growth of the aging population and increasing lifespan require healthcare professionals to gain knowledge necessary to meet the needs of this patient group. Despite the availability and benefit of numerous pharmacotherapies, older patients commonly experience drug-related problems, resulting in additional morbidities. Therefore, it is essential for clinicians serving older adults across all healthcare settings to understand the epidemiology of aging, age-related physiological changes, drug-related problems prevalent in elders, comprehensive geriatric assessment, and interprofessional approaches to care.

EPIDEMIOLOGY AND ETIOLOGY

As humans age, they are at increasing risk of disease, disability, and death for three reasons: genetic predisposition; reduced immunological surveillance; and the accumulated effects of physical, social, environmental, and behavioral exposures over the life course. Elders experience variably increasing vulnerability (**homeostenosis**) as they age, resulting in heterogeneity in health states and care requirements. While resilient elders can maintain high levels of physical and cognitive functioning, others suffer functional decline, **frailty**, disability, or premature death. There is an urgent need for clinicians to better understand the epidemiology of aging to comprehensively provide high-value services to optimize the function and health-related quality of life of older adults.[1]

Sociodemographics

▶ *Population*

KEY CONCEPT The population is rapidly growing older. In 2020, 56.1 million US residents were 65 years and older, with projections to increase to 94.7 million by 2060.[2] Almost 6.7 million people were 85 years or older (the "oldest-old"), and 100 thousand persons were aged 100 or older.[2] Those 85+ years individuals are projected to grow from 6.4 million in 2016 to 14.4 million in 2040 and further increase to 19 million by 2060.[2] In 2020, older women aged 65 years and above (31 million) outnumbered older men (25 million), with a ratio of 100 to 81; this ratio widens as elders age.[2] Additionally, minority elders are projected to increase to 21.1 million in 2020.[3] With changing aging population demographics, surviving baby boomers will be disproportionally female, more ethnically/racially diverse, better educated, live alone, and have more financial resources than elders in previous generations.

▶ *Economics*

More elders have higher economic prosperity than ever before. In 2017 only 9.2% of Americans of 65 years and older and 11.6% of 80 years and older lived below the poverty line.[4] However, major inequalities persist, with older Blacks (poverty rates of 16.1% for men and 21.5% for women) and those without high school diplomas reporting fewer financial resources.[4,5] Considerable disparities exist and may prevent less advantaged elders from purchasing all prescribed medications.

▶ *Education and Health Literacy*

By 2007, more than 75% of US elders had graduated from high school, and nearly 20% had a bachelor's degree or higher. Still, substantial educational differences exist among racial and ethnic minorities. While more than 80% of non-Hispanic White elders had high school degrees in 2007, 72% of Asians, 58% of Blacks and 42% of Hispanic elders were graduates.[6] Nearly 40% of people 75+ years have low **health literacy**, more than any other age group.[5] Despite these limitations, the Pew Trust reports that 67% of adults aged 65 years and older say they use the Internet,[7] and healthcare systems are increasingly offering online health information to older consumers. These advances are important because communication between healthcare providers and elders is vital in providing quality care, supporting self-care, and navigating care transitions.

Health Status

▶ *Life Expectancy*

Americans are living longer than ever (average of 78.6 years in 2017), and life expectancy has increased (people who survive to age 65 can expect to live an average of 19.3 more years).[5] Yet, US life expectancy lags behind that of many other industrialized nations.[5,8] Disparities in mortality persist; in 2014 life expectancy at birth for the Whites was 3.4 years longer than for the Blacks.[5]

Nearly 35% of US deaths in 2000 were attributed to three risk behaviors: smoking, poor diet, and physical inactivity. Though only 8.4% of Americans 65+ years smoked in 2018, nearly 54% of men and 21% of women were former smokers.[5,9] Overweight elders aged 65 to 74 years increased from 57% to 73% in 2004, largely due to inactivity and a diet high in refined foods, saturated fats, and sugared beverages.[5] Despite proven health benefits of physical activity, 47% of elders 65 to 74 years and 61% of 75+ years reported no physical activity, and only 12% of older adults reported participating in aerobic and muscle-strengthening activities that meet US physical activity guidelines.[5,10]

The 2016 National Health Interview Survey indicated that in 2012 to 2014 older non-Hispanic Whites were more likely to report good to excellent health than non-Hispanic Blacks and Hispanic peers (80% vs 65% and 66%, respectively).[11] Approximately 85% of older adults have at least one chronic condition, and 60% have at least two. The prevalence of certain chronic conditions differs by sex, with women reporting higher levels of arthritis (54% vs 43%), and men reporting higher levels of heart disease (37% vs 26%) and cancer (24% vs 19%).[8] Figure 1–1 specifies the most common chronic conditions of older adults by sex. Frailty is a common biological syndrome in the elderly. Once frail, elders may rapidly progress toward failure to thrive and death. Among US adults 65 years and older, 15.3% were frail according to the National Health and Aging Trends Study.[12]

Healthcare Utilization and Cost

KEY CONCEPT Older Americans use more healthcare services than younger Americans do. Although older adults with one or more hospital stays decreased from 2000 to 2017 (18% vs 15.3%), they accounted for more than half of hospitalizations overall, with longer lengths of stay corresponding to increasing age.[8] Between 2015 and 2016, there were 1.2 million US nursing home residents aged 65+ years, and as the aged live longer, more will require assistance, which will be increasingly performed in the home.[8] Healthcare costs among older Americans are higher than costs for younger Americans. In 2015 older Americans spent 12.9% of their total expenditures on health compared with 7.8% among all consumers.[3] Medicare plays a major role in US healthcare costs, accounting for 20% of total health spending in 2012, 27% of spending on hospital care and 23% on physician services.[13]

Patient Encounter Part 1

CS is an 85-year-old widow who moved to California with her sister 10 years ago to be near their children at the end of life. Though CS has a college degree in art in Japan, she speaks very little English, has limited health literacy, and requires interpretation during health visits. CS comes to the Interprofessional Geriatrics Clinic to receive comprehensive care of her multimorbidity and polypharmacy management. Her past medical history includes depression, diabetes, dyslipidemia, hypertension, hypothyroidism, insomnia, myocardial infarction (14 years ago), and peripheral neuropathy. CS uses 19 medications that include prescription medications for her multiple chronic conditions, vitamins, and herbal supplements for "immune system and sleep." She is underweight, despite eating often to maintain her weight. She walks around her neighborhood with her sister for about 30 minutes every morning, then drinks three to four cups (about 0.75–1 L) of tea while listening to Japanese news.

What information is consistent with epidemiology of aging?

Which of CS's medical conditions are commonly found in older adults?

What additional information do you need before conducting a comprehensive medication review?

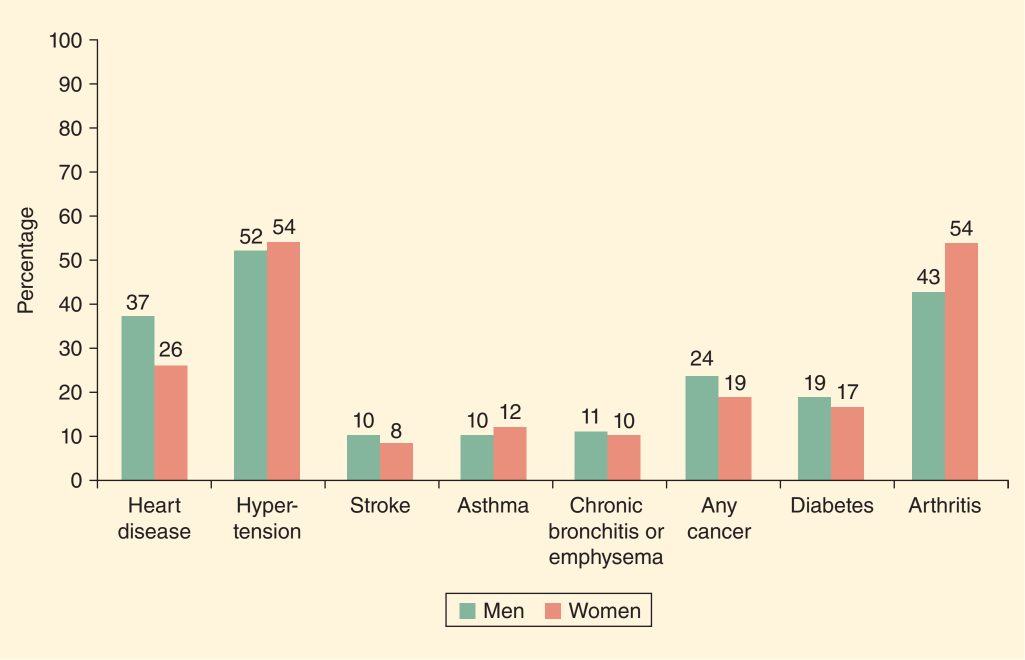


FIGURE 1–1. Percentage of people 65 years and older who reported having selected chronic conditions, by sex, 2005 to 2006. Note: Data are based on a 2-year average from 2005 to 2006. Reference population: These data refer to the noninstitutionalized population. (From Centers for Disease Control and Prevention, National Center for Health Statistics, National Health Interview Survey.)

AGE-RELATED CHANGES

In basic terms, pharmacokinetics is what the body does to the drug, and pharmacodynamics is what the drug does to the body. **KEY CONCEPT** All four components of pharmacokinetics—absorption, distribution, metabolism, and excretion—are affected by aging; the most clinically important and consistent is the reduction of renal elimination of drugs.[14] As people age, they can become frailer and are more likely to experience altered and variable drug pharmacokinetics and pharmacodynamics. Even though this change is influenced by a patient's clinical state more than their chronological age, the older patient is more likely to be malnourished or suffer from diseases that affect pharmacokinetics and pharmacodynamics.[14] Older adults can develop significant drug-related problems when alterations in pharmacokinetics and pharmacodynamics are not appropriately accounted for in prescribing and monitoring medications.[13] Clinicians have the responsibility to use pharmacokinetic and pharmacodynamic principles to improve elder care and avoid adverse effects of pharmacotherapy. Due to the many changes described below, certain chronic medications should be started at 50% of the recommended initial adult dose with doses titrated slowly in older adults. This is a general recommendation for initiating medications, such as antihypertensives and antidepressants, but does not apply to the treatment of acute illness (eg, antibiotics for pneumonia).

Pharmacokinetic Changes

▶ *Absorption*

Multiple changes occur throughout the gastrointestinal (GI) tract with aging, but little evidence indicates that drug absorption is significantly altered. The changes include decreases in overall surface of the intestinal epithelium, gastric acid secretion, and splanchnic blood flow.[14] Peristalsis becomes weaker, and gastric emptying is delayed. These changes slow absorption in the stomach, especially for enteric-coated and delayed-release preparations. Delays in absorption may lead to a longer time required to achieve peak drug effects, but it does not significantly alter the amount of drug absorbed, and drug movement from the GI tract into circulation is not meaningfully changed.[14,15] However, relative **achlorhydria** can decrease the absorption of nutrients, such as vitamin B_{12}, calcium, and iron.[15]

Aging facilitates atrophy of the epidermis and dermis along with a reduction in barrier function of the skin. Tissue blood perfusion is reduced, leading to decreased or variable rates of transdermal, subcutaneous, and intramuscular drug absorption. Therefore, intramuscular injections should generally be avoided in older adults due to unpredictable drug absorption.[14] Additionally, because saliva production decreases with age, medications that need to be absorbed rapidly by the buccal mucosa are absorbed at a slower rate. Yet, for most drugs, absorption is not significantly affected, and the changes described are clinically inconsequential.[15,16]

▶ *Distribution*

The main physiological changes that affect distribution of drugs in older adults are with body fat and water and protein binding. Lean body mass can decrease by 12% to 19% through loss of skeletal muscle in older adults. Thus, blood levels of drugs primarily distributed in muscle increase (eg, digoxin), presenting a risk for overdose.[15] While lean muscle mass decreases, adipose tissue can increase with aging by 18% to 36% in men and 33% to 45% in women. Therefore, fat-soluble drugs (eg, diazepam, amitriptyline, and amiodarone) have increased volume of distribution (V_d), leading to higher tissue concentrations and prolonged duration of action. Greater V_d leads to increased half-life and time required to reach steady-state serum concentration.[14,15]

Total body water decreases by 10% to 15% by age 80. This lowers V_d of water-soluble drugs (eg, aspirin, digoxin, and morphine) leading to higher plasma drug concentrations than in younger adults when equal doses are used.[14,15] Thus lower doses are needed to prevent toxicity. Toxic drug effects may be worsened when dehydration occurs, and when the extracellular space is reduced by diuretic use.

Likewise, plasma albumin concentration decreases by 10% to 20%, although disease and malnutrition contribute more to this decrease than age alone.[14] In patients with an acute illness, rapid decreases in serum albumin can increase drug effects. Examples of highly protein-bound medications include warfarin, phenytoin, and diazepam.[15] For most chronic medications, these changes are not clinically significant because although the changes affect peak level of a single dose, mean serum concentrations at steady state are not altered unless clearance is affected.[15] For highly protein-bound drugs with narrow therapeutic indices (eg, phenytoin), however, it is important to appropriately interpret serum drug levels in light of the older patient's albumin status. In a malnourished patient with hypoalbuminemia, a higher percentage of the total drug level consists of free drug than in a patient with normal serum albumin.[14] Hence, if a hypoalbuminemic patient has a low total phenytoin level, and phenytoin dose is increased, the free phenytoin concentration may reach toxicity.

▶ *Metabolism*

Drug metabolism is affected by age, acute and chronic diseases, and drug–drug interactions. The liver is the primary site of drug metabolism, which undergoes changes with age; though the decline is not consistent, older patients have decreased metabolism of many drugs.[14,16] Liver mass is reduced by 20% to 30% with aging, and hepatic blood flow is decreased by as much as 50%.[15] These changes can drastically reduce the amount of drug delivered to the liver per unit of time, reduce its metabolism, and increase the half-life.[15] Metabolic clearance of some drugs is decreased by 20% to 40% (eg, amiodarone, amitriptyline, and morphine), but it is unchanged for drugs with a low hepatic extraction.[15] Drugs that have high **extraction ratios** have significant first-pass metabolism, resulting in higher bioavailability for older adults. For example, the effect of morphine is increased due to a decrease in clearance by around 33%. Similar increases in bioavailability are seen with propranolol, levodopa, calcium channel blockers, tricyclic antidepressants, and statins. Thus, older patients may respond similarly to younger patients using lower doses of these medications.[14-16]

Aging affects liver enzymes (cytochrome P450 system [CYP450]) that may lead to a decreased elimination rate of drugs that undergo oxidative phase I metabolism, but this is controversial.[14] Originally, it was thought that the CYP450 system was impaired in older adults, leading to decreased drug clearance and increased serum half-life, but studies have not consistently confirmed this. The variations in the CYP450 activity may not be due to aging but lifestyle (eg, smoking), illness, or drug interactions.[14-16] Nutritional status also plays a role in drug metabolism. Frail elders have a more diminished drug metabolism than those with healthy body weight.[14,16] Aging does not affect drugs that undergo phase II hepatic metabolism (eg, lorazepam and temazepam), known as conjugation or glucuronidation, but conjugation is reduced with frailty.[15]

▶ *Elimination*

Clinically, the most important pharmacokinetic change in older adults is decreased renal drug elimination.[14] As people age, renal blood flow, renal mass, glomerular filtration rate, filtration fraction, and tubular secretion decrease. After age 40, the number of functional glomeruli declines, and renal blood flow decreases by approximately 1% yearly. From age 25 to 85 years, average renal clearance declines by as much as 50% and is independent of the effects of disease.[14,15] Still, the impact of age on renal function is variable and not always linear. Longitudinal studies have suggested that a percentage (up to 33%) of older adults do not experience this age-related decline in renal function.[15] Clinically significant effects of decreased renal clearance include prolonged drug half-life, increased serum drug level, and increased potential for adverse drug reactions (ADRs).[14] Special attention should be given to renally eliminated drugs with a narrow therapeutic index (eg, digoxin and aminoglycosides). Monitoring serum concentration and making appropriate dose adjustment for these agents can prevent serious ADRs resulting from drug accumulation.[17] Importantly, despite a dramatic decrease in renal function (creatinine clearance) with aging, serum creatinine may remain fairly unchanged and remain within normal limits. This is because frail older patients have decreased muscle mass resulting in less creatinine production for input into circulation.[14,15] Because chronic kidney disease can be overlooked if a clinician focuses only on the serum creatinine value, overdose and ADR can occur.

Creatinine clearance should be calculated when starting or adjusting pharmacotherapy in older adults. The Cockcroft-Gault equation is the most widely used formula for estimating creatinine clearance (mL/min; or multiply by 0.0167 to express in mL/s) for adjusting drug doses. See Chapter 26 (Table 26–3) for more details.

When serum creatinine is expressed in mg/dL,

$$\text{Creatinine Clearance} = \frac{(140 - \text{Age}) \times \text{Weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} \times (0.85 \text{ if female})$$

When serum creatinine is expressed in μmol/L,

$$\text{Creatinine Clearance} = 1.2 \times \frac{(140 - \text{Age}) \times \text{Weight (kg)}}{\text{Serum creatinine } (\mu\text{mol/L})} \times (0.85 \text{ if female})$$

This equation is also used by most drug manufacturers to determine renal dosing guidelines. The Cockcroft-Gault equation provided the best balance between predictive ability and bias in a comparison study with the Modification of Diet in Renal Disease (MDRD) and Jelliffe "bedside" clearance equations.[15] The Cockcroft-Gault equation can overestimate renal function in obese individuals, so an adjusted body weight should be used in the calculation [AjBW = IBW + 0.4 (ABW − IBW)]. Understand that predictive formulas can also significantly overestimate actual renal function in chronically ill, debilitated older patients.

Pharmacodynamic Changes

Pharmacodynamics refers to the actions of a drug at its target site and the body's response to that drug. Compared to pharmacokinetics, there is less data on age-related pharmacodynamic changes. **KEY CONCEPT** In general, the pharmacodynamic changes that occur in older adults tend to increase their sensitivity to drug effects. Most pharmacodynamic changes in elders are associated with a progressive reduction in homeostatic mechanisms and changes in receptor properties. Although the result of these changes is an increased sensitivity to the effects of many drugs, a decrease in response can also occur. The changes in the receptor site include alterations in binding affinity of the drug, number/density of active receptors at the target organ, structural features, and postreceptor effects (biochemical processes/signal transmission). These include receptors in the adrenergic, cholinergic, and dopaminergic systems, as well as γ-*aminobutyric acid* (GABA) and opioid receptors.[14,15]

▶ *Cardiovascular System*

Decreased homeostatic mechanisms in older adults increase their susceptibility to orthostatic hypotension when taking drugs that affect the cardiovascular system and lower the arterial blood pressure. This is explained by decreased arterial compliance and baroreceptor reflex response, which limits the ability to compensate quickly for postural changes in blood pressure. It has been estimated that 5% to 33% of older adults experience drug-induced orthostasis. Examples, other than typical antihypertensives, that can cause orthostatic hypotension in older patients are antipsychotics, direct vasodilators, loop diuretics, and opioids.[14,15,17] Older people have a decreased β-adrenergic receptor function, and they are less sensitive to β-agonist and β-adrenergic antagonist effects in the cardiovascular system and possibly in the lungs, but their response to α-agonists and antagonists is unchanged.[14,15] Increased hypotensive and heart rate response (to a lesser degree) to calcium channel blockers (eg, verapamil) are reported. Increased risks of developing drug-induced QT prolongation and torsade de pointes are also present.[17] Therefore, clinicians must start medications at low doses and titrate slowly, closely monitoring the patient for any adverse effects.

▶ *Central Nervous System*

Overall, elders exhibit a greater sensitivity to the effects of drugs that gain access to the central nervous system (CNS), especially anticholinergic medications. In most cases, lower doses result in adequate response, and higher incidence of adverse effects may be seen with standard and high doses. For example, lower doses of opioids provide sufficient pain relief for older patients, whereas conventional doses can cause oversedation and respiratory depression.[14,15] The blood–brain barrier becomes more permeable as people age; more medications can cross the barrier and cause CNS effects. Examples include benzodiazepines, antidepressants, antipsychotics, neuroleptics, and antihistamines. There are decreased numbers of cholinergic neurons as well as nicotinic and muscarinic receptors, decreased choline uptake from the periphery, and increased acetylcholinesterase.[14,15] Older adults have a decreased ability to compensate for these imbalances of the neurotransmitters, leading to movement and memory disorders. Older adults have an increased number of dopamine type 2 receptors, making them more susceptible to delirium from anticholinergic and dopaminergic medications. At the same time, they have a reduced number of dopamine and dopaminergic neurons in the *substantia nigra* of the brain resulting in higher incidence of extrapyramidal symptoms from antidopaminergic medications (eg, antipsychotics).[14,15]

▶ *Fluids and Electrolytes*

Fluid and electrolyte homeostatic mechanism is decreased in elders. Older adults experience more severe dehydration with equal amounts of fluid loss compared with younger adults. The multitude of factors involved include decreased thirst and cardiovascular reflexes, decreased fluid intake, decreased ability of the kidneys to concentrate urine, increased atrial natriuretic peptide, decreased aldosterone response to hyperkalemia, and decreased response to antidiuretic hormone.[17] The result is increased incidences of hyponatremia, hyperkalemia, and prerenal azotemia, especially when the older patient is taking a diuretic (eg, hydrochlorothiazide, furosemide). Angiotensin-converting enzyme inhibitors have an increased potential to cause hyperkalemia and acute renal failure in older adults.[14] Thus, these agents need to be started with low doses, titrated slowly with frequent renal function monitoring.

▶ *Glucose Metabolism*

An inverse relationship between glucose tolerance and age has been reported, likely due to reduced insulin secretion and sensitivity (greater insulin resistance). Consequently, hypoglycemia incidences are increased when using sulfonylureas (eg, glyburide, glipizide) from age-related impairment to counter-regulate hypoglycemic responses.[14] Due to an impaired autonomic nervous system, older patients may not distinguish symptoms of hypoglycemia such as sweating, palpitations, or tremors. They still experience neurological symptoms of syncope, ataxia, confusion, or seizures.

DRUG-RELATED PROBLEMS

KEY CONCEPT Comorbidities and polypharmacy complicate health status of older adults, particularly inappropriate medications that lead to drug-related problems. It is estimated that 43.6% of emergency department visits leading to hospitalizations in older adults are due to adverse drug events.[18] Studies indicated that 59% of the older Medicare beneficiaries' sample had at least one medication-related problem, and drug-related morbidity and mortality costed US healthcare system $528.4 billion in 2016.[19,20] Drug-related problems result in poor health outcomes for older adults such as withdrawal effects, therapeutic failure, and adverse drug events.[21] Collaboration among interprofessional providers and older patients can ensure appropriate therapy, minimize adverse drug events, and maximize medication adherence and health outcomes.

Polypharmacy

Polypharmacy is defined as taking multiple medications concurrently (≥ 4–10 medications have been used as criteria in studies). Polypharmacy is prevalent among elders with 39% reporting the use of five or more medications in 2012 compared with polypharmacy use by 24% in 1999, signifying a dramatic increase.[22] In 2011, 67% of older adults used polypharmacy including nonprescription products, an increase from 53% in 2006.[18] The common use of dietary supplements and herbal products in this population adds to polypharmacy. In nursing home settings 50.7% of patients with severe cognitive impairment received polypharmacy (5–9 medications), and 16.9% received excessive polypharmacy (≥ 10 medications).[23] Among various reasons for polypharmacy, an apparent one is an older patient receiving multiple medications from different providers who treat the patient's comorbidities without coordinated care. Hence, medication reconciliation becomes increasingly important as the aging population continues to grow.

A complete evaluation of all medications should be conducted by healthcare providers at each elder's visit to prevent inappropriate polypharmacy. Efforts should be made to reduce polypharmacy by discontinuing any medication without indication. However, clinicians should also understand that appropriate polypharmacy is indicated for older adults who have multimorbidity, and support should be provided for optimal adherence. Drug-related problems associated with polypharmacy can be identified by performing a comprehensive medication review (see Patient Care Process).

Inappropriate Prescribing

Inappropriate prescribing is defined as prescribing medications that cause a significant risk of an adverse event when there is an effective and safer alternative. Potentially inappropriate medications in older adults have been associated with negative outcomes such as confusion, falls, and mortality.[24] At times, medications are continued long after the initial indication has resolved. The clinician prescribing for older adults must understand the rate of adverse reactions and drug–drug interactions, the evidence available for using a specific medication, and patient's use of over-the-counter (OTC) agents and herbal supplements.[21]

Screening tools have been developed to help the clinician identify potentially inappropriate medications in older adults. The most utilized tool in the US is the Beers criteria.[24] The 2019 Beers criteria includes 30 medications and medication classes that are potentially inappropriate in older patients, listed in five categories: medications potentially inappropriate in most older adults, medications that should typically be avoided in older adults with certain conditions, medications to use with caution, drug–drug interactions, and drug dose adjustment based on kidney function.[24]

Examples of medications included in the Beers criteria are as follows[24]:

- Benzodiazepines such as diazepam and alprazolam (risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents)
- First-generation antihistamines such as diphenhydramine and hydroxyzine (risk of confusion, dry mouth, constipation, and other anticholinergic symptoms)
- Tricyclic antidepressants (TCAs) such as amitriptyline and nortriptyline (risk of sedation, orthostatic hypotension, and anticholinergic symptoms)
- Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen (risk of GI bleeding and ulcers)

Practical strategies for appropriate medication prescribing include establishing a partnership with patients and their care partners to enable them to understand and monitor medication effects. Clinicians should perform a comprehensive medication assessment to obtain accurate history of medication use, determine appropriateness of the regimen, conduct drug–drug and drug–disease interaction screenings, use time-limited trials to evaluate the benefits and risks of new medications, and trial off medications to assess continued need.[21]

Undertreatment

Much has been written about the consequences of overmedication and polypharmacy in older adults. However, underutilization of medications is just as harmful, resulting in reduced functioning, and increased morbidity and mortality. There are instances when a drug is truly contraindicated, when a lower dose is indicated, or when prognoses dictate withholding therapy. Outside of these scenarios, many elders do not receive therapeutic interventions that would provide benefit.[21,25] Undertreatment is prevalent across diverse settings in the community, hospitals, and long-term care facilities.[21] Many reasons include multimorbidity, polypharmacy, cost, concerns of nonadherence, fear of adverse effects and associated liability, limited evidence in the age group, starting low and failing to increase to an appropriate dose, skepticism regarding secondary prevention benefits, or ageism.[21,26] Common categories of geriatric undertreatment are listed in Table 1–1.

Table 1–1

Common Categories of Geriatric Undertreatment

Therapy	Concern
Anticoagulation in patients with atrial fibrillation	Overly concerned with risk of bleeding or the risk of falls if anticoagulated
Malignant and nonmalignant pain	Hesitant to prescribe opioids due to possible cognitive and bowel side effects, concerns about addiction; patients may often be hesitant to use opioids
Antihypertensive therapy	Underestimate the benefit on stroke and cardiovascular event prevention and/or fail to add the second or third medication needed to attain control
β-Blocker treatment in heart failure	Concerned about complications in high-risk patients despite the substantial evidence of mortality benefit
Statin treatment for ASCVD	Underestimate benefit or have concerns about adverse events

ASCVD, atherosclerotic cardiovascular disease.

A clinical assessment to weigh the potential benefit versus harm of the older patient's complete medication regimen is required. Once obvious contraindications have been dismissed, the patient's goals and preferences, prognosis or life expectancy, and time to therapeutic benefit should be taken into consideration to determine whether pharmacotherapy meets treatment goals. Underprescribing can best be avoided by using clinical assessment strategies, improving adherence support, and assisting financial coverage of drugs.

Adverse Drug Reaction

ADR is defined by the World Health Organization as a reaction that is noxious and unintended, which occurs at dosages normally used in humans for prophylaxis, diagnosis, or therapy. ADRs increase with polypharmacy use and are the most frequently occurring drug-related problem among older nursing home residents. A brown bag medication review study found that 25% of community-dwelling older adults using at least five medications experienced ADRs.[27] Approximately 9% of hospitalizations among older adults are caused by ADRs.[28] Medication classes causing serious ADRs in older adults include anticoagulants, antidiabetics, and opioids.[29]

Seven predictors of ADRs in elders are[30] taking more than four medications; more than 14-day hospital stay; having more than four active medical problems; general medical unit admission versus geriatric ward; alcohol use history; lower Mini-Mental State Examination score (confusion, dementia); and two to four new medications added during a hospitalization. Similarly, four predictors of severe ADRs in older adults are[31] use of certain medications including diuretics, NSAIDs, antiplatelets, and digoxin; number of drugs taken; age; and comorbidities. Suggested strategies to prevent ADRs in older adults are described in Table 1–2.[31] Particular caution must be taken when prescribing drugs that alter cognition in older adults, including antidepressants, antihistamines, antipsychotics, benzodiazepines, opioids, and muscle relaxants.[31]

One of the most damaging ADRs that frequently occurs in elders is medication-related falls. Falls are associated with a poor prognosis ranging from premature institutionalization to early death, and polypharmacy is a risk factor. Multiple medications included in the Beers criteria are related to falls.[24] For example, benzodiazepine studies found significant association with falls including an increased risk after a new prescription for benzodiazepines and twofold risk with combined use of two or more benzodiazepines.[32] Other agents having strong association with increased fall risk include sedative hypnotics, neuroleptics, antidepressants, and antipsychotics.[32] A comprehensive fall prevention intervention should include deprescribing by slow taper with close monitoring.

Table 1–2

Strategies to Prevent Adverse Drug Reactions in Older Adults

- Evaluating comorbidities, frailty, and cognitive function
- Identifying caregivers to take responsibility for medication management
- Evaluating renal function and adjusting doses appropriately
- Monitoring drug effects
- Recognizing that clinical signs or symptoms can be an ADR
- Minimizing number of medications prescribed
- Adapting treatment to patient's life expectancy
- Realizing that self-medication and nonadherence are common and can induce ADRs

ADR, adverse drug reaction.

Adapted, with permission, from Merle L, Laroche ML, Dantoine T, Charmes JP. Predicting and preventing adverse drug reactions in the very old. Drugs Aging. 2005;22(5):375–392.

Nonadherence

America's other drug problem is the term given to medication nonadherence by the National Council on Patient Information and Education. Nonadherence to chronic medications is prevalent and escalates healthcare costs associated with worsening disease and increased hospitalization. *Medication adherence* describes a patient's medication-taking behavior, generally defined as the extent to which one adheres to an agreed regimen derived from collaboration with their healthcare provider.[33]

KEY CONCEPT Older adults are at greater risk for medication nonadherence due to the high prevalence of multimorbidities, cognitive deficit, polypharmacy use, and financial barriers. Numerous barriers to optimal adherence exist and include patient's lack of understanding, provider's failure to educate, polypharmacy leading to complex regimen and inconvenience, treatment of asymptomatic conditions (such as hypertension and dyslipidemia), and cost of medications.[33] Factors influencing nonadherence are listed in Table 1–3.

Following is a list of six "how" questions to ask when assessing medication adherence[34]:

1. How do you take your medicines?
2. How do you organize your medicines to help you remember to take them?
3. How do you schedule your meal and medicine times?
4. How do you pay for your medicines?
5. How do you think the medicines are working for your conditions?
6. How many times in the last week/month have you missed your medicines?

Table 1–3

Factors Influencing Medication Nonadherence

Three or more chronic medical conditions
Five or more chronic medications
Three times or more per day dosing or 12 or more medication doses per day
Four or more medication changes in past 12 months
Three or more prescribers
Significant cognitive or physical impairments
Recent hospital discharge
Caregiver reliance
Low health literacy
Medication cost
History of medication nonadherence
Living alone in the community

Although no single intervention has found to improve adherence consistently, older person-centered multicomponent interventions, such as combining education, adherence aid, and regular follow-up, have resulted in a positive impact on medication adherence and associated health outcomes.[35] Future research needs include adherence studies evaluating belief-related variables, such as personal and cultural beliefs, in larger and more ethnically/racially diverse samples of older populations.

Patient Encounter Part 2

CS was recently hospitalized after an episode of dizziness and near-fall. Her daughter (interpreter) states that there were several medication changes while CS was in the hospital with some confusion as to what to do at home. CS brought in all medication bottles used at home: (1) amlodipine 10 mg by mouth every morning, (2) aspirin 81 mg by mouth every morning, (3) calcium-vitamin D 600 mg-500 units by mouth every morning and evening, (4) eszopiclone 2 mg by mouth at bedtime, (5) gabapentin 900 mg by mouth three times a day, (6) hydrochlorothiazide 50 mg by mouth every morning, (7) levothyroxine 50 mcg by mouth in the morning, (8) melatonin 3 mg by mouth at bedtime, (9) metformin 500 mg morning and evening, (10) omeprazole 40 mg by mouth every morning, (11) rosuvastatin 5 mg by mouth every evening, (12) valsartan 40 mg by mouth every morning and evening, (13) vitamin B$_6$ 200 mg by mouth every morning and evening, (14) vitamin C 5000 mg by mouth every morning and evening, (15) vitamin E 400 units by mouth every morning and evening, (16) acetaminophen 500 mg two tablets by mouth every 4 hours as needed for pain, (17) ibuprofen 200 mg by mouth three times a day as needed for headaches, (18) pantoprazole 20 mg by mouth in the morning as needed for stomach upset, (19) valerian root 1200 mg by mouth at night as needed for sleep.

She is allergic to sulfa drugs (rash) and intolerant to ramipril (cough).

She does not smoke, has one or two drinks a night, does not use any illicit drug.

VS: BP 122/64 mm Hg, P: 70 beats/min, RR: 12, T: 37.2°C (99°F) Ht: 5 ft (152 cm), Wt: 42 kg, Pain 1/10

Labs: Na 139 mEq/L (mmol/L), K 4.1 mEq/L (mmol/L), Cl 98 mEq/L (mmol/L), CO$_2$ 25 mEq/L (mmol/L), BUN 22 mg/dL (7.9 mmol/L), creatinine 1.5 mg/dL (133 μmol/L), glucose 97 mg/dL (5.4 mmol/L), HgbA$_{1c}$ 6.5% (0.065; 48 mmol/mol Hgb), eGFR 35.1 mL/min/1.73 m^2

What is CS's estimated creatinine clearance?

What drug-related problems are included in CS's medication list?

What steps should be taken to simplify CS's medication regimen?

Patient Encounter Part 3

CS is now 91 years old and has been living at a long-term care facility for a year. She still struggles to maintain her weight, is in pain daily, and has developed a new coccyx ulcer. She is currently on multiple medications including (1) amitriptyline 10 mg by mouth at bedtime, (2) aspirin 81 mg by mouth daily, (3) docusate sodium 100 mg by mouth twice daily, (4) hydrochlorothiazide 25 mg by mouth daily, (5) ibuprofen 600 mg by mouth daily, (6) levothyroxine 25 mcg by mouth daily, (7) lorazepam 1 mg by mouth twice daily, (8) metformin 500 mg by mouth daily, (9) rosuvastatin 5 mg by mouth every evening, (10) vitamin C 500 mg by mouth twice daily, (11) valsartan 40 mg by mouth twice daily.

Today her pain score is 8/10.

Which quality indicators should be of concern in CS?

What recommendations can be made about CS's medication regimen at this time?

GERIATRIC ASSESSMENT

The term *geriatric assessment* is used to describe the comprehensive interprofessional team evaluation of the frail or complex older adult's health including multimorbidity with functional and cognitive status. Such a team may include, but is not limited to, a geriatrician, nurse, pharmacist, case manager/social worker, physical therapist, occupational therapist, speech therapist, psychologist, dietician, dentist, optometrist, and audiologist. Assessment may be performed in various care settings and by a series of evaluations after which the team will conduct an interprofessional case conference to discuss the patient's care plan.

Patient Interview

KEY CONCEPT The clinical approach to assessing older adults frequently goes beyond a traditional "history and physical" used in general internal medicine practice.[36] Functional status must be determined, including the activities of daily living (ADLs) and instrumental activities of daily living (IADLs), see Table 1–4. Cognitive assessment, which may require collateral history from family or care partners, is important in determining the patient's capacity to manage their medications and consent to medical treatment.[37] The mini-cog mental status examination[38] shown in Figure 1–2, is a quick tool to assess patient's cognition. Elders commonly have decreased visual acuity, hearing loss, dysphagia, and impaired dexterity. Decreased skin integrity greatly increases risk for pressure ulcers. Sexual function is a sensitive but important topic and should be specifically addressed. Cardiac, renal, hepatic, and digestive insufficiencies can have significant implications for pharmacotherapy. Inadequate nutrition may lead to weight loss and impaired functioning at the cellular or organ level. See Table 1–5 for common problems experienced by older adults.

It is important to recognize geriatric syndromes such as cognitive decline, functional impairment, polypharmacy, delirium, frailty, falls, osteoporosis, insomnia, and incontinence. In elders, common diseases may present with atypical symptoms, such as thyroid dysfunction or infection presenting as delirium. It is also important to assess for caregiver stress and be aware of older

Table 1–4

Activities of Daily Living and Instrumental Activities of Daily Living

ADLs			
Transfers	Dressing	Mobility	Eating
Bathing	Toileting	Grooming	

IADLs	
Using transportation	If still driving, assess driving ability (including cognitive function, medications that can impair driving ability, vision, neuromuscular conditions that may interfere with reaction time, ability to turn head) at the time of license renewal
Using the telephone	Check for emergency phone numbers located near the telephone
Management of finances	Assess the ability to balance checkbook and pay bills on time
Cooking	Check for safe operation of appliances and cooking tools as well as ability to prepare balanced meals
Housekeeping	Check for decline in cleanliness or neatness
Medication administration	Assess organization skills and adherence

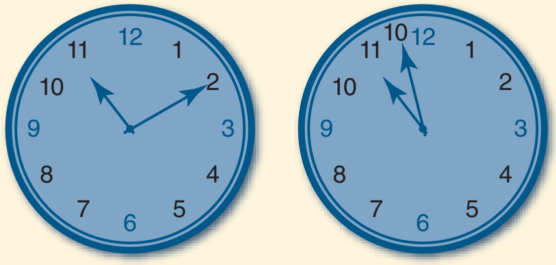
ADL, activity of daily living; IADL, instrumental activity of daily living.

Three item recall

1. Ask the patient if you may test his or her memory.
2. Give the patient 3 words (eg. apple, table, penny) to repeat and remember.
3. Have the patient repeat the 3 words from memory later (eg. after the clock drawing test).

Clock drawing test

1. Have the patient draw the face of a clock, including numbers.
2. Instruct the patient to place the hands at a specific time, such as 11:10.



Correct

Incorrect hands and inserted number

A positive dementia screen

1. Failure to remember all 3 words.
2. Failure to remember 1–2 words plus an abnormal clock drawing.

FIGURE 1–2. The mini-cog mental status examination. (Adapted from Borson S, Scanlan J, Brush M, Vitaliano P, Dokmak A. The mini-cog: a cognitive "vital signs" measure for dementia screening in multi-lingual elderly. Int J Geriatr Psychiatry. 2000;15(11):1021–1027.)

Table 1–5

The *Is* of Geriatrics: Common Problems in Older Adults

Immobility
Isolation
Incontinence
Infection
Inanition (malnutrition)
Impaction
Impaired senses

Instability
Intellectual impairment
Impotence
Immunodeficiency
Insomnia
Iatrogenesis

From Hajjar ER, Hersh LR, Gray SL. Prescribing in the older adult. In: DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V, eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020. Available from: https://accesspharmacy.mhmedical.com/content.aspx?bookid=2577&sectionid=233054609. Accessed September 1, 2020.

patients' support systems that may include family, friends, social or religious networks, home health agencies, and hired caregivers. Such networks may facilitate older individuals to continue living independently. Safety should be assessed and includes a home safety assessment and a driving assessment for patients with cognitive or functional limitations. In addition, look for signs and symptoms of elder abuse, neglect, or exploitation. Health professionals are mandatory reporters of elder mistreatment to Adult Protective Services.[39]

Drug Therapy Monitoring

Geriatric patients often have multiple medications, comorbidities, and prescribers. It is essential that there be a single provider who oversees the patient's pharmacotherapy. Particularly challenging in elders is identifying the cause(s) of medication nonadherence. Providers assessing older patients' medication regimens should keep the following questions in mind:

- Are medications skipped or reduced due to cost?
- Can the patient benefit from sample drugs? Starting a patient on a free drug sample may increase patient costs in the long term because samples typically are newer, expensive medications.[40]
- Is there an educational barrier such as low health literacy?
- Does the patient speak English but only read in another language?
- Can the patient see labels and written instructions?
- Does the patient have hearing problems? Patients might not admit they cannot hear instructions.
- Can the patient manipulate pill bottles, syringes, inhalers, eye/ear drops?
- Has the patient's cognitive functioning worsened over time such that they can no longer follow the medication regimen?

Regarding cost, the providers need to be aware of the patient's Medicare Part C or D plan, and what type of coverage these plans afford. What is the copayment for generic, formulary, and nonformulary drugs? Is the patient responsible for all drug costs during the Medicare "donut hole" period? (In basic part D plans, patients pay increasing percentages of drug costs up to $7425 per year.[40]) Many Medicare patients, especially the socioeconomically challenged, have limited understanding of the complex Medicare drug benefit. This problem is compounded when the prescriber also does not understand the patient's insurance program.[41] Providers can assist patients by prescribing generic medications that are offered through community pharmacy discount plans ($4 retail pharmacy programs do not bill insurance, thus are not counted toward their Medicare part D deductible) and help patients apply for the medication assistance programs offered by drug manufacturers.

Documentation

A clear, current, and accurate medication list must be available to the patient and all individuals involved in their care. It is particularly important for older adults to bring medication containers for reconciliation by a clinician. Medication adherence may require verification with the pharmacist, caregivers, or family. Transitions in care, such as hospital to subacute nursing facility or home, lead to medication errors because medications may have been deleted or added.[42] It is standard of care to conduct medication reconciliation upon hospital admission and discharge to ensure that the medication list is up to date.

Patient Education

Geriatric patients often have difficulty understanding and retaining provider instructions. "Ask me 3" cues the patient to ask three important questions of their providers to improve health literacy[43]:

1. What is my main problem?
2. What do I need to do?
3. Why is it important for me to do this?

The provider can assess patient grasp of medication instructions by asking the patient to repeat instructions initially and again in 3 minutes (teach-back method).

KEY CONCEPT Addressing deficits in vision, hearing, swallowing, cognition, motor impairment, and health literacy can lead to enhanced medication adherence. Specific drug formulations, such as inhalers, ophthalmic/otic drops, nasal sprays, and subcutaneous injections, will require detailed education and practice. Patients who cannot swallow tablets/capsules need instructions on which tablets are safe to crush and which capsules safe to open and sprinkle on food. Patients and/or caregivers need to be advised of potential ADRs and when to notify the provider.

GERIATRIC PRACTICE SITES

Some say geriatrics has become a nonspecialty due to the aging population. Clinicians with geriatric certification or training practice in nearly all settings of healthcare, primary care to wide spectrums of specialty care and long-term care. A few interprofessional practice sites are highlighted here. See Chapter e3 for information on palliative care practices.

Ambulatory Care Clinic and Home-Based Primary Care

Geriatric clinics are established to provide a multitude of primary care needs specifically tailored to older adults. Home-based primary care is delivered in the home or independent living facility of homebound patients to facilitate independent living. Patients are usually referred by their primary care providers to increase access to services, meet complex care needs due to multimorbidity and polypharmacy, and offer a comprehensive geriatric assessment. It is common for the onset of cognitive impairment to be the catalyst for a referral to geriatric services. Interprofessional team care is the norm in these settings, which benefits patients with multifaceted needs. The interprofessional teams hold regular meetings to discuss care plans of involved patients. Geriatricians, who specialize in elder care, assess and treat physical, medical, emotional, and social needs. Nurses provide medical triage and day-to-day patient care activities such as obtaining vitals, providing wound care, educating and ensuring adherence. Clinical pharmacists focus on medication regimen optimization, evidence-based disease state management, drug-related problem resolution, and patient, caregiver, and healthcare team education about pharmacotherapy and monitoring parameters. Social workers address social and structural needs, in addition to assessing mood and cognitive status, facilitating completion of advance directives and obtaining placement in higher levels of care. Physical/occupational therapists work to improve the patient's functional status, provide fall prevention interventions, and maintain a safe home environment. They provide adaptive equipment such as grab bars, raised toilet seats and shower benches for the bathroom, and cane/walker for ambulation. Dieticians evaluate the patient's nutritional status and educate on proper diet and weight management. Using these team collaborations, specialty settings have been developed including a multidisciplinary geriatric oncology clinic[44] and PACE centers (Programs of All-inclusive Care for the Elderly) that incorporate the interdisciplinary team and adult day healthcare in one center.[45]

Long-Term Care

Long-term care provides support for people who are dependent to varying degrees in ADLs and IADLs, numbering about 9 million people 65+ years in 2008.[46] Care is provided in the patient's home, in community settings such as adult care homes or assisted living facilities, and in nursing homes. Long-term care is expensive, typically several thousand dollars per month. Most care is provided at home by unpaid family members or friends. Medicare covers all or part of the cost of skilled nursing care for a limited-period posthospitalization.[46] Medicare does not cover long-term care. Financing of long-term care comes from patients' and family savings and/or private long-term care insurance. When a patient's assets have been depleted, Medicaid provides basic nursing home care under long-term care insurance coverage.[46] However, this care is heavily discounted, often resulting in economizing such as lower caregiver-to-patient ratios and higher number of patients per room. Nursing homes are highly regulated by state and federal government through the Center for Medicare and Medicaid Services.[47] Initial and continuing certification of the facility depends on periodic state and federal review of the facility. Auditors' ratings are available to consumers in an online Nursing Home Report Card.[47] **Quality indicators** are used by facility administrators and government overseers to identify the following problem areas[48]:

- Use of more than nine medications in a single patient
- Prevalence of indwelling catheters
- Prevalence of antipsychotic, anxiolytic, and hypnotic use
- Use of physical restraints
- Prevalence of depression in patients without antidepressant therapy
- Clinical quality measures such as pressure ulcers
- Moderate daily pain or excruciating pain

Long-term care practices emphasize the interprofessional team approach. The medical director leads regular meetings with care providers. The pharmacist conducts a monthly drug review of

Patient Care Process

1. Collect Information:

- Perform a comprehensive medication reconciliation and review.
- Have the patient bring all medication bottles, including prescriptions, OTC agents, vitamins, supplements, and herbal products.
- Review medical history and physical assessment.
- Ask about allergies/intolerance.
- Inquire about ADRs (Table 1–2).
- Collect adherence information using combination of methods (eg, self-report, refill history, dosage form count, demonstration of nonoral agent use).
- Ask about prevention including vaccinations.
- Collect vital signs and laboratory results.
- Inquire about functional status (Table 1–4).
- Measure cognitive status (Figure 1–2).

2. Assess the Information:

- Identify indication(s) for all medications.
- Assess for potential inappropriate medications using Beers criteria.[24]
- Assess medication doses to determine underdose/overdose.
- Screen for drug–drug/disease/supplement/herbal/food interactions.
- Check against allergies/intolerance.
- Identify ADRs.
- Assess medication adherence (Table 1–3).
- Identify untreated indication/undertreatment (Table 1–1).
- Evaluate vital signs, including pain, and laboratory.
- Assess medication needs based on cognitive and functional status.
- Recognize common problems in older adults (Table 1–5).

3. Develop a Care Plan:

- Discontinue unnecessary medications.
- Tailor regimen: simplify dosing frequency, modify time of dosing based on ADRs and drug interactions, and tie medication taking to individuals' daily routine to improve adherence.
- Develop educational materials, keeping in mind health literacy and cognitive status.
- Create solutions to any functional barriers (eg, non–child-resistant caps, tablet cutters).
- Draft referral plan to target nonpharmacological strategies (eg, diet, physical therapy, behavioral health, integrative health approaches).

4. Implement the Care Plan:

- Educate about medications and disease states in health literacy-sensitive manner.
- Highlight any medication changes and tailored regimen.
- Educate on the use of nonoral agents (eg, inhalers, insulin, ophthalmic/otic drops).
- Provide a medication chart/list to include generic/brand names, indication, dose, directions for use, timing of dose, etc.
- Teach about medication storage, expiration date, and refill status.
- Emphasize adherence and what to do when a dose is missed/forgotten.
- Use medication organizers (eg, pillbox, blister pack) or other adherence aids (eg, alarm, phone reminder) when indicated.
- Implement solutions to any physical/functional barriers (eg, non-childproof caps).
- Refer for nonpharmacological interventions.

5. Follow-up: Monitor and Evaluate:

- Provide a list of future appointments and follow-up.
- Promote self-monitoring (eg, recognize and report ADRs, use blood pressure monitor or glucometer).
- Encourage therapeutic lifestyle modifications including diet, exercise, and smoking cessation.
- Endorse prevention including immunizations, wellness visits, eye examinations, and dental care.
- Formulate a patient-centered and interprofessional team-based follow-up plan to track patient response, adverse events, adherence, and health outcomes.

each patient's medication list.[46] The physician is alerted to medication concerns and approves the patient's orders every 60 days. Such a team approach is vital to coordinate care for the typical frail, complex long-term care patient.

CONCLUSION

By applying the principles of geriatrics, clinicians can better intervene with pharmacotherapy to postpone disease, disability, and mortality, and promote health, functioning, and health-related quality of life. In addition, interprofessional geriatric care improves health outcomes.

List of Abbreviations

ADL	Activities of daily living
ADR	Adverse drug reaction
GABA	γ-Aminobutyric acid
$HgbA_{1c}$	Hemoglobin A_{1c}
IADL	Instrumental activities of daily living
LDL-C	Low-density lipoprotein-cholesterol
MDRD	Modification of diet in renal disease
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over-the-counter
V_d	Volume of distribution

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2 Pediatrics Pharmacotherapy

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Define different age groups within the pediatric population.
2. Identify factors that affect selection of safe and effective drug therapy in pediatric patients.
3. Explain general pharmacokinetic and pharmacodynamic differences in pediatric versus adult patients.
4. Develop strategies for appropriate and effective medication administration to infants and young children.
5. Determine approaches to effectively communicate with patients and caregivers about appropriate medication use including expected outcomes, possible adverse effects, and appropriate administration.

INTRODUCTION

Pediatric clinical practice involves care of infants, children, and adolescents with the goal of optimizing health, growth, and development toward adulthood. Clinicians serve as advocates for this unique and vulnerable patient population to optimize their well-being. Care for pediatric patients is relevant in both inpatient and outpatient settings and requires additional considerations with regard to selection and monitoring of drug therapy.

KEY CONCEPT Despite the common misconception of pediatric patients as "smaller adults" where doses are scaled only for their smaller size, there are multiple factors to consider when selecting and providing drug therapy for patients in this specific population. Pediatric patients significantly differ within their age groups and from adults regarding drug administration, psychosocial development, and organ function development, which affect the efficacy and safety of pharmacotherapy.

FUNDAMENTALS OF PEDIATRIC PATIENTS

Classification of Pediatric Patients

Pediatric patients are those younger than 18 years, although some pediatric clinicians may care for patients up to age 21. Unlike an adult patient, whose age is commonly measured in years, a pediatric patient's age can be expressed in days, weeks, months, and years. Patients are classified based on age and may be further described based on other factors, including birth weight and prematurity status (Table 2–1).[1–3]

Growth and Development

Children are monitored for physical, motor, cognitive, and psychosocial development through clinical recognition of timely milestones during routine well-child visits. As a newborn continues to progress to infant, child, and adolescent stages, different variables are monitored to assess growth compared with the general population of similar age and size. Growth charts are used to plot head circumference, weight, length or stature, weight-for-length, and body mass index for a graphical representation of a child's growth compared with the general pediatric population. These markers of growth and development are both age- and gender-dependent; thus, the use of the correct tool for measurement is important. For children younger than 2 years, one should use the World Health Organization's (WHO) growth standards (Figure 2–1).[4] For children 2 years and older, the Centers for Disease Control and Prevention (CDC) Growth Charts (Figure 2–2) are used.[5,6] These tools assess whether a child is meeting the appropriate physical growth milestones, thereby allowing identification of nutritional issues such as poor weight and height gain (eg, failure to thrive). Failure to thrive is defined as inadequate physical growth with weight that falls below the fifth percentile or decreases over time, crossing two or more major percentile lines. **Body habitus** is often evaluated at routine checkups or well-check visits, with definitions of underweight as body mass index (BMI) less than the 5th percentile for age, overweight as BMI between 85th to 94th percentile for age, and obese as BMI greater than 95th percentile.[7] Since these charts were developed based on a general, healthy population, growth charts may not be accurate evaluation of physical development in children with congenital diseases. Growth charts specific to disease states (eg, Turner syndrome or cystic fibrosis) with regard to expected growth trajectory and/or nutritional goals may be utilized by clinicians as part of care.

Differences in Vital Signs

Normal values for heart rate and respiratory rate vary based on age. Normal values for blood pressure vary based on gender and age for all pediatric patients and height percentile for patients older than 1 year. Respiratory rates are also higher in neonates and infants (30–60 breaths/min), decreasing with age to adult rates around 15 years of age (12–20 breaths/min).[8–10] (Table 2–2).

Normal values for blood pressure in pediatric patients are found in various national guidelines and other pediatric diagnostic references. In general, blood pressure increases with age, with average blood pressures of approximately 70/50 in neonates, increasing throughout childhood to approximately

Table 2–1

Pediatric Age Groups, Age Terminology, and Weight Classification[1-3]

Age Group	Age
Neonate	≤ 28 days (4 weeks) of life
Infant	29 days to < 12 months
Child	1–12 years
Adolescent	13–17 years (most common definition)
Age Terminology	**Definition**
GA	Age from date of mother's first day of last menstrual period to date of birth
Full term	Describes infants born at 37-weeks' gestation or greater
Premature	Describes infants born before 37-weeks' gestation
Small for GA	Neonates with birth weight below the 10th percentile among neonates of the same GA
Large for GA	Neonates with birth weight above the 90th percentile among neonates of the same GA
Chronological or postnatal age	Age from birth to present, measured in days, weeks, months, or years
Corrected or adjusted age	May be used to describe the age of a premature child up to 3 years of age: Corrected age = Chronological age in months – [(40 – GA at birth in weeks) × 1 month ÷ 4 weeks]. For example, if a former 29-week GA child is now 10 months old chronologically, his corrected age is approximately 7 months: 10 months – [(40–29 weeks) × 1 month ÷ 4 weeks] = 7.25 months
Weight Classification	**Definition**
LBW infant	Premature infant with birth weight between 1500 and 2500 g
VLBW infant	Premature infant with birth weight 1000 g to < 1500 g
ELBW infant	Premature infant with birth weight < 1000 g

ELBW, extremely low birth weight; GA, gestational age; LBW, low birth weight; VLBW, very low birth weight.

110/65 in adolescents.[8,9] Heart rates are highest in neonates and infants, ranging from 90 to 205 beats/min and decrease with age, reaching adult rates (60–100 beats/min) around 10 years of age.[8-10]

Another vital sign commonly monitored in children by their caregivers is body temperature, especially when they seem "warm to the touch." The American Academy of Pediatrics (AAP) supports the use of rectal measurement of body temperature as it is most accurate when appropriate technique is used; however, for other routes, the AAP offers an age-specific guideline on routes of measurement.[11,12] For patients younger than 3 months, rectal measurement using a digital thermometer is recommended. For those 3 months and older, use of temporal artery is an available option. The use of tympanic measurement is appropriate for patients who are 6 months and older. Axillary measurement is not considered first-line in all these age groups, as proper technique is important for accurate measurement, and other accurate options are available. For patients age 4 or 5 years and older, oral measurement is reliable. Generally, fever is defined as temperature 100.4°F (38°C) and greater measured via rectal, otic, or temporal artery technique. For oral and axillary measurement, fever is defined as temperature 100°F (37.8°C) and 99°F (37.2°C) and greater, respectively.[12] Low-grade fevers range from 100° to 102°F (37.8°–38.9°C), with antipyretic treatment (eg, acetaminophen) considered by most pediatricians in cases of temperature greater than 38.3°C (101°F, any measurement route) accompanied by patient discomfort. Formal definition of fever, like other vital signs, is also age dependent, with a lower temperature threshold for neonates (38°C or 100.4°F) and infants (38.2°C or 100.7°F).[11,12]

Pain assessment is more challenging in neonate, infants, and young children due to their inability to communicate symptoms. Indicators of possible pain include physiological changes, such as increased heart rate, respiratory rate, and blood pressure, decreased oxygen saturation, as well as behavior changes such as prolonged, high-pitched crying, and facial expressions.[13] Such indicators are used in validated assessment scales, such as the FACES scale and FLACC behavioral tools.[14,15] The FACES scale is a visual analog scale, where patients age 3 years and older can select a face that best associates with their current pain level.[14] The FLACC scale, intended for patients of age 2 months to 7 years or those patients unable to communicate pain, is a scale in which a clinician scores a patient based on series of criteria (facial expression, leg movement, activity, crying, and consolability).[15]

Fluid Requirements

Fluid requirement and balance are important to monitor in pediatric patients, especially in premature neonates and infants. Maintenance fluid requirement can be calculated based on body surface area for patients greater than 10 kg, with a range of 1500 to 2000 mL/m^2 per day. However, a weight-based method of determining normal maintenance fluid requirement for children is often used (Table 2–3).[16]

Patient Encounter Part 1

HM is a 33-week GA premature newborn boy weighing 1.6 kg (3.5 lb), length 39 cm (15.4 in), born to a 25-year-old woman today. HM is currently admitted to the neonatal intensive care unit.

What is HM's weight classification as a neonate?

Calculate HM's corrected age for 6 months from today.

How much maintenance fluid per day (mL) and overall rate (mL/hour), is appropriate at this time for HM?

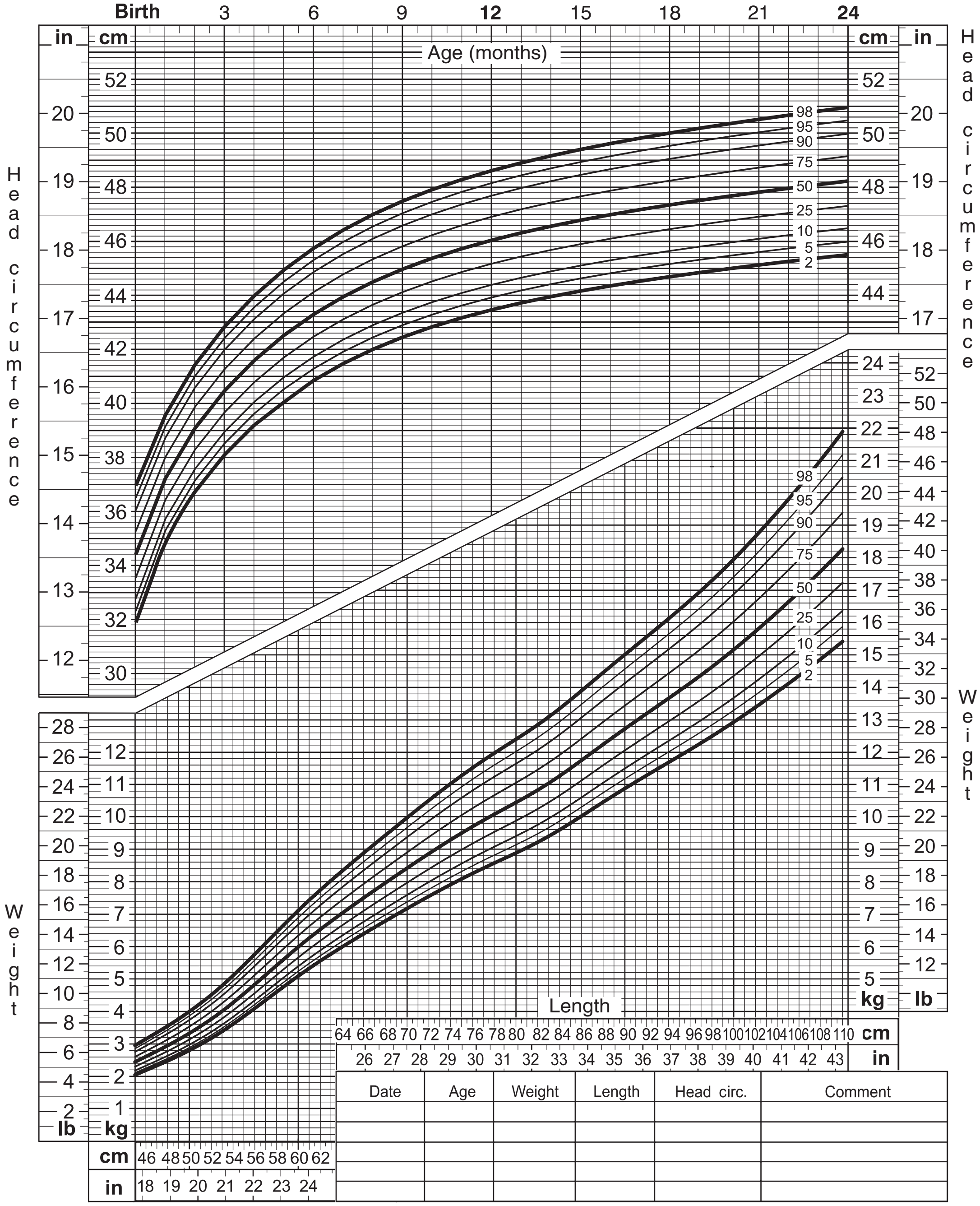
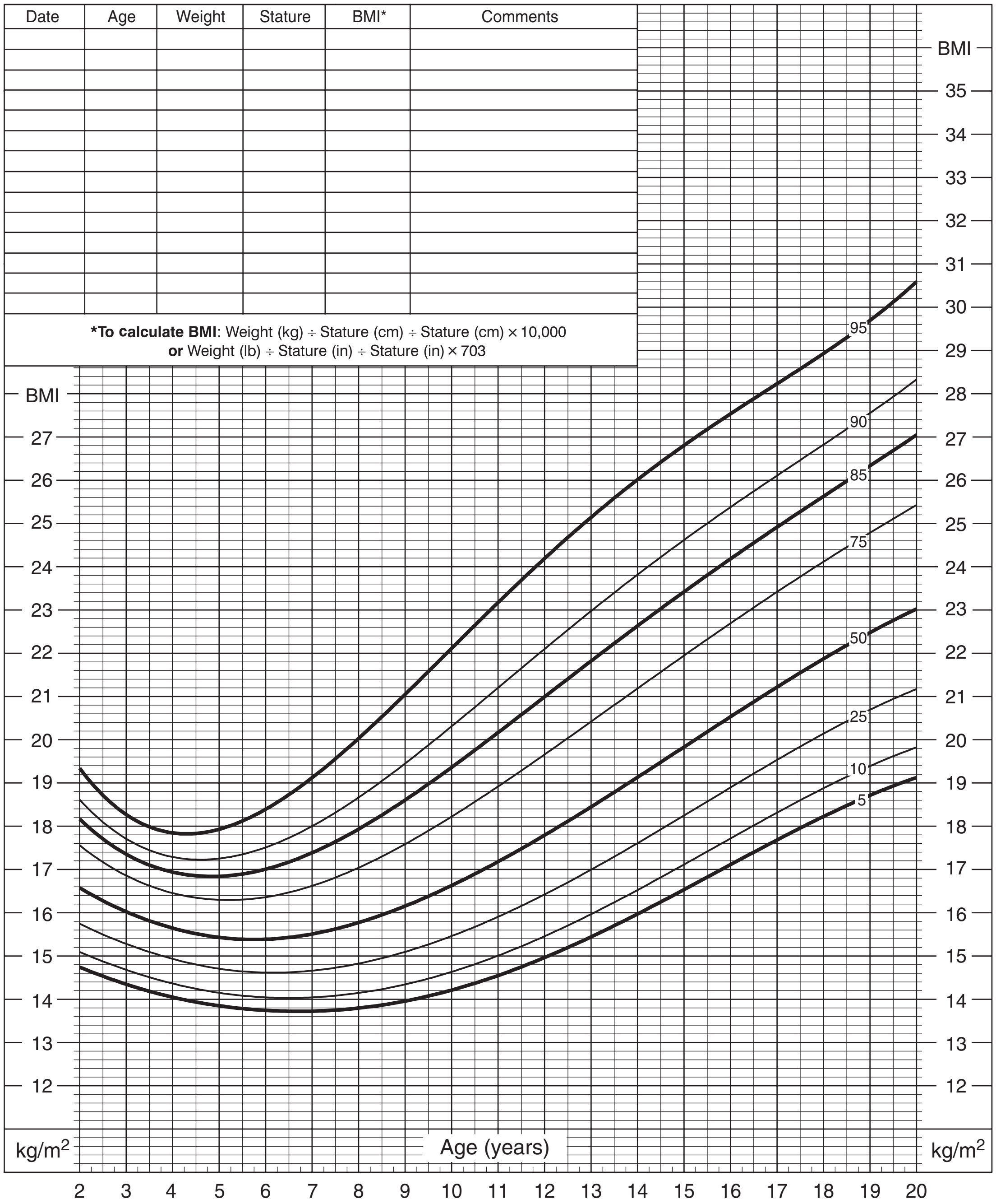


FIGURE 2–1. Example of WHO growth chart of girls, birth to 24 months: Head circumference-for-age and weight-for-length percentile, 2000. (From Centers for Disease Control and Prevention from the WHO Growth Standards. World Health Organization [WHO] Growth Standards are recommended for use in the U.S. for infants and children 0 to 2 years of age. [updated 2010 Sept 9; cited 2020 Nov 16]. Available from: http://www.cdc.gov/growthcharts/who_charts.htm.)

EFFECTS OF PHARMACOKINETIC AND PHARMACODYNAMIC DIFFERENCES ON DRUG THERAPY

Drug selection strategy may be similar or different depending on age and disease state, as a result of differences in pathophysiology of certain diseases and pharmacokinetic and pharmacodynamic parameters among pediatric and adult patients. It is noteworthy that pediatric patients may require different medications from those used in adults affected by certain diseases. For example, phenobarbital is commonly used for treatment of neonatal seizures, but seldom used for seizure treatment in adults, due to differences in seizure etiology and availability of extensive data regarding its use in neonates compared with newer antiepileptic medications. There also exist commonalties between pediatric and adult patients, such as therapeutic serum drug concentrations required to treat certain diseases. For example, target vancomycin serum concentrations needed for treatment of a given infection are often similar between children and adults. Appropriate selection and dosing of drug therapy for a pediatric patient depends on a number of specific factors, such as



***To calculate BMI**: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) × 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) × 703

FIGURE 2–2. Example of CDC growth chart of boys, 2 to 20 years: Body mass index for age percentile, 2000. (From Centers for Disease Control and Prevention. CDC Growth Charts. [updated 2016 Dec 7; cited 2020 Nov 16]. Available from: https://www.cdc.gov/growthcharts/cdc_charts.htm.)

age, weight, height, disease, comorbidities, developmental pharmacokinetics, and available drug dosage forms. Pediatric drug doses are often calculated based on body weight (eg, mg/kg/dose) compared with uniform dosing (eg, mg/day or mg/dose) for adult patients. Thus, accurate weight should be available while prescribing or dispensing medications for this patient population. Pediatric doses may exceed adult doses by body weight for certain medications due to differences in pharmacokinetics and pharmacodynamics; hence, the use of pediatric drug dosing guides is recommended.

KEY CONCEPT Due to multiple differences, including age-dependent development of organ function in pediatric patients, the pharmacokinetics, efficacy, and safety of drugs often differ between pediatric and adult patients; thus, pediatric dosing should not be calculated based on a single factor of difference. Equations proposed to estimate pediatric doses based on adjusted age or weight, such as the Clark's, Fried's, or Young's rule, should not be routinely used to calculate pediatric doses because they account for only one factor of difference (eg, age or weight) and lack integration of the effect of growth and development on drug pharmacokinetics and pharmacodynamics in this population. For **off-label** medication dosing, when no alternative treatment is available and limited dosage guidelines have been published, clinicians

Table 2–2

Normal Ranges of Vital Signs (Heart Rate, Respiratory Rate, Blood Pressure) by Age Group[8-10]

Age Group	Heart Rate (Sleep)[a]	Heart Rate (Awake)[a]	Respiratory Rate[b]	Systolic Blood Pressure[c,d]	Diastolic Blood Pressure[c,d]
Neonate (< 28 days)	90–160	100–205	30–60	67–84	31–45
Infant (1–12 months)	90–160	100–190	30–53	72–104	37–56
Toddler (1–2 years)	80–120	98–140	22–37	86–106	42–63
Preschool (3–5 years)	65–100	80–120	20–28	89–112	46–72
School–Age (6–11 years)	58–90	75–118	18–25	97–115	57–76
Adolescent (12–15 years)	50–90	60–100	12–20	102–131	61–83

Note: prematurity can affect values. Values listed are average ranges.

[a] Beats per minute

[b] Breaths per minute

[c] mm Hg

[d] Exact normal values will vary based on age, height, and sex.

may estimate a pediatric dose based on body surface area ratio.

$$\textbf{Approximate pediatric dose} = \textbf{Adult dose} \times [\textbf{BSA (in m}^2\textbf{)} \div \textbf{1.73 m}^2]$$

Limitations for this dose-estimating approach include the need for the patient to be of normal height and weight for age and lack of incorporation of exact pharmacokinetic differences regarding each medication.[17]

Absorption

Oral absorption may be different in premature infants and neonates due to differences in gastric acid secretion and pancreatic and biliary function. Neonates and infants have increased gastric pH (eg, pH 6–8) due to lower gastric acid output by body weight, reaching adult values by approximately 2 years of age.[18] Low gastric acid secretion can result in increased serum concentrations of weak bases and acid-labile medications, such as penicillin, and decreased serum concentrations of weak acid medications, such as phenobarbital, due to increased ionization. Additionally, gastric emptying time and intestinal transit time are delayed in premature infants, increasing drug contact time with the gastrointestinal (GI) mucosa and drug absorption.[18,19] Diseases, such as gastroesophageal reflux, respiratory distress syndrome, and congenital heart disease may further delay gastric emptying time. Pancreatic exocrine and biliary function are also reduced in newborns, with about 50% less secretion of amylase and lipase than adults, reaching adult values as early as the end of the first year and as late as 5 years of age. Deficiency in pancreatic secretions and bile salts in newborns can decrease bioavailability of prodrug esters, such as erythromycin, which requires solubilization or intraluminal hydrolysis.[18] Due to limited data on oral bioavailability of medications in infants and children for newer agents, some drug dosing recommendations may be extrapolated from adult safety and efficacy studies and case reports.

Table 2–3

Maintenance Fluid Calculations by Body Weight[16]

Patient Body Weight	Maintenance Fluid Requirement
< 10 kg	100 mL/kg/day
11–20 kg	1000 mL + 50 mL/kg over 10 kg
> 20 kg	1500 mL + 20 mL/kg over 20 kg

Reproduced with permission from Holiday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. Pediatric. 1957;19(5):823–832, by the AAP.

Topical or percutaneous absorption in neonates and infants is increased due to a thinner stratum corneum, increased cutaneous perfusion, and greater body surface-to-weight ratio. Hence, application of topical medications, such as corticosteroids, should be limited to the smallest amount possible. Limiting exposure can help minimize serum concentrations of active as well as inactive drugs, yet potentially harmful additives such as propylene glycol.

Intramuscular absorption in premature and full-term infants can be erratic due to variable perfusion, poor muscle contraction, and decreased muscle mass compared with older patients.[18] Intramuscular administration may be appropriate for some medications; however, use of this route of administration can be painful and is usually reserved when other routes are not accessible, for example, initial intravenous (IV) doses of ampicillin and gentamicin for neonatal sepsis.

Intrapulmonary absorption and distribution are largely due to anatomical size of the lungs and drug delivery. The smaller airways of neonates and lower inspiratory volume can result in greater drug concentrations in the upper and central airways. Particle size, breathing pattern, and route (eg, oral vs nasal) can impact the amount of drug absorbed and should be considered when utilizing pulmonary drug delivery devices such as nebulizers or inhalers.[20]

Rectal absorption can also be erratic due to increased peristalsis causing early expulsion of the dosage form in younger patients (ie, infants and young children).[21] Thus it is not commonly recommended if other routes are available. This route is useful in cases of severe nausea and vomiting or seizure activity. For medications that undergo extensive first-pass metabolism, bioavailability increases as the blood supply bypasses the liver from the lower rectum directly to the inferior vena cava. Availability of rectal dosage forms varies and use of oral medications or other dosage forms rectally is based on limited studies and case reports. High osmolality and large volume of a liquid dosage form may present as a limitation to using an oral liquid formulation for rectal use.

Volume of Distribution

In pediatric patients, apparent volume of distribution (V_d) is normalized based on body weight and expressed as L/kg. Extracellular fluid and total body water per kilogram of body weight are increased in neonates and infants, resulting in higher V_d for water-soluble drugs, such as aminoglycosides, and decrease with age. Therefore, neonates and infants often require higher individual doses by weight (mg/kg) than older children and adolescents to achieve the same therapeutic serum concentrations.[18] Fluid overload and diuresis can affect V_d and should be assessed for when evaluating drug dosing and pharmacokinetics. The use of extracorporeal membrane oxygenation (ECMO) can further affect V_d of medications in patients due to the added volume from the circuit and potential fluid changes (eg, edema) while on the circuit. Thus, the use of additional clinical and, when available, therapeutic drug monitoring is recommended for those patients requiring ECMO.[22] Neonates and infants have a lower normal range for serum albumin (2–4 g/dL, 20–40 g/L), reaching adult levels after 1 year of age. Highly protein-bound drugs, such as sulfamethoxazole-trimethoprim and ceftriaxone, are not typically used in neonates due to theoretical concern for bilirubin displacement. This displacement may result in a complication known as **kernicterus**, from bilirubin encephalopathy.[23]

Although neonates have lower body adipose composition compared with older children and adults, their overall V_d for many lipid-soluble drugs (eg, lorazepam) is similar to infants and adults. Some medications (eg, vancomycin, phenobarbital) may also reach higher concentrations in the central nervous system (CNS) of neonates due to an immature blood–brain barrier.[24]

Metabolism

Hepatic drug metabolism is slower at birth in full-term infants compared with adolescents and adults, with further delay in premature neonates. Phase 1 reactions and enzymes, such as oxidation and alcohol dehydrogenase, are impaired in premature neonates and infants and do not fully develop until later childhood or adolescence. Accordingly, the use of products containing ethanol (eg, elixirs) can cause toxicities such as respiratory depression and thus should be avoided, whenever possible, in neonates and infants. Age at which cytochrome P450 isoenzymes (eg, CYP3A4, CYP2C19) activity reaches adult values varies, depending on the isoenzyme, with delayed development in premature infants. Increased dose requirements by body weight (eg, mg/kg) for some hepatically metabolized medications (eg, phenytoin, valproic acid) in young children (ie, ages 2–4 years) is theorized due to an increased liver mass to body mass ratio.[23] This increase in metabolism slows to adult levels as the child goes through puberty into adulthood.[18]

Among phase 2 reactions, sulfate conjugation by sulfotransferases is well developed at birth in term infants. Glucuronidation by the uridine diphosphate glucuronosyltransferases, in contrast, is immature in neonates and infants, reaching adult values at 2 to 4 years of age. In neonates, this deficiency results in adverse effects including cyanosis, ash gray color of the skin, limp body tone, and hypotension, also known as "gray baby syndrome" with use of chloramphenicol.[18] Products containing benzyl alcohol or benzoic acid should be avoided in neonates due to immature glycine conjugation, resulting in accumulation of benzoic acid. This accumulation can lead to "gasping syndrome," which includes respiratory depression, metabolic acidosis, hypotension, seizures or convulsions, and gasping respirations. Similarly, due to limited metabolic capacity, propylene glycol, a solvent found in some dosage forms, should be avoided, as toxicity results in serum hyperosmolality, seizures, and respiratory distress.[25] Acetylation via *N*-acetyltransferase reaches adult maturation at around 1 year of life; however, overall activity is dependent on genotypic variability.[18]

Elimination

Nephrogenesis completes at approximately 36 weeks gestation; thus, premature neonates and infants have compromised glomerular and tubular function that may correlate with a glomerular filtration rate (GFR). This reduction in GFR affects renal drug clearance, thereby necessitating longer dosing intervals for renally cleared medications, such as vancomycin, to prevent accumulation. GFR increases with age and exceeds adult values in early childhood, after which there is a gradual decline to approximate adult value during adolescence. For example, vancomycin is often given every 18 to 24 hours in a low-birth-weight (LBW) premature neonate, every 6 hours in children with normal renal function, and every 8 to 12 hours in adult patients with normal renal function. Children with cystic fibrosis also present with greater renal clearance of drugs such as aminoglycosides, compared with children without the disease, requiring higher doses by weight and more frequent dosing intervals.[26]

Creatinine clearance is used as a surrogate marker for GFR; however, there are equations available to estimate GFR in the pediatric population. Pediatric GFR is often calculated to mL/min/1.73 m^2. The Cockroft-Gault, Jelliffe, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, or Modification of Diet in Renal Disease (MDRD) equations for estimating creatinine clearance or GFR in adults should not be used for evaluating patients younger than 18 years. This is due to potential for significant overestimation of GFR and/or lack of validation of these equations in pediatric age ranges, even adolescents. For example, past attempts for proposed application of equations, such as Cockroft-Gault, demonstrated that lack of agreement with measured GFR (via renal scan) in adolescents as young as 13 years of age.[27] The Schwartz's equation was previously used method of estimating pediatric GFR from infancy up to 21 years of age (**Figure 2–3**). This equation uses patient length (cm), serum creatinine (mg/dL) (or µmol/L × 0.0113), and a constant, *k*, which depends on age (including low-birth-weight status for infants).[28] This "original" Schwartz equation is no longer used by many clinicians, due to a change in measurement of serum creatinine methods with calibration traceable to isotope dilution mass spectrometry (IDMS), invalidating the original

"Original Schwartz" Equation

$$GFR = kL/SCr$$

Age	K
Low birth weight < 1 year	0.33
Full term < 1 year	0.45
1–12 years	0.55
13–21 years (female)	0.55
13–21 years (male)	0.70

K = proportionality constant
L = length in cm
SCr = serum creatinine in mg/dL
GFR = estimated glomerular filtration rate in mL/min/1.73 m^2

FIGURE 2–3. "Original" Schwartz equation for estimation of glomerular filtration rate (GFR)in pediatric patients up to 21 years of age. (From Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am. 1987;34(3):571–590.)

“Bedside Schwartz” Equation

$$GFR = [0.413 \times h]/SCr$$

H = height in cm
SCr = serum creatinine (in mg/dL)
GFR = estimated glomerular filtration rate in mL/min/1.73 m^2

FIGURE 2–4. Bedside Schwartz equation for estimation of glomerular filtration rate (GFR)in pediatric patients ages 1 to 18 years old. (From Staples A, LeBlong R, Watkins CW, Brandt J. Validation of the revised Schwartz estimating equation in a predominantly non-CKD population. Pediatr Nephrol. 2010;25:2321–2326.)

equation’s clinical application and can overestimate GFR by up to 40%.[27–31] The preferred method to estimate GFR in children (ages 1–18 years) is the “bedside” Schwartz as it was devised for use with creatinine methods traceable to IDMS (Figure 2–4).[29–31]

Urine output is also a parameter used to assess renal function in pediatric patients. Infants and children with acute kidney injury are likely to present with oliguria or anuria with urine output less than 1 mL/kg/hour.

SPECIFIC CONSIDERATIONS IN DRUG THERAPY

In addition to differences in pharmacokinetics and pharmacodynamic parameters, other factors, including dosage formulations, medication administration techniques, and parent/caregiver education, should be considered when selecting drug therapy.

Off-Label Medication Use

Currently, there is a lack of pediatric dosing, safety, and efficacy information; thus, many drugs remain off-label for children.[32] Off-label use of medications occur in both outpatient and inpatient settings. Off-label use of medication is the use of a drug outside of its approved labeled indication. This includes the use of a medication in the treatment of illnesses not listed on the manufacturer’s package insert, use outside the licensed age range, dosing outside those recommended, or use of a different route of administration.[32] **KEY CONCEPT** It is appropriate to use a drug off-label when no alternatives are available; however, clinicians should refer to published studies and case reports for available safety, efficacy, and dosing information. Food and Drug Administration (FDA) regulatory changes provide incentives for a pharmaceutical manufacturer to study and market new drugs for pediatric patients. However, such incentives are not available for generic drugs.

Patient Encounter Part 2

RG is a 1-week-old (weight 3.5 kg [7.7 lb], length 50 cm (19.7 in), no known drug or food allergies), full-term newborn male child admitted to the NICU now presenting lethargy, poor oral intake, and temperature instability. A neonatal sepsis and meningitis rule-out is started. Blood samples, cerebral spinal fluid, and urine were collected for Gram stain and culture, still pending results. Other laboratory results (complete blood count, complete metabolic panel) are still pending. The team requests the consultation regarding empiric antibiotic selection.

The medical resident asks you whether ceftriaxone (highly protein binding) or cefotaxime (low protein binding) should be used as part of the antibiotic regimen to treat RG. Which is the most appropriate and why?

Routes of Administration and Drug Formulations

Depending on age, disease, and disease severity, different routes of administration may be considered. The rectal route of administration is reserved for cases where oral administration is not possible and IV route is not necessary. Topical administration is often used for treatment of dermatologic ailments. Transdermal routes are not often used due to limited product availability. The injectable route of administration is used in patients with severe illnesses or when other routes of administration are not possible. As done with adult patients, IV compatibility and access should be evaluated when giving parenteral medications. Dilution of parenteral medications may be necessary to measure smaller doses for neonates. However, a higher concentration of parenteral medications may be necessary for patients with fluid restrictions, such as premature infants and patients with cardiac anomalies and/or renal disease. Appropriate stability and diluent selection data should be obtained from the literature.

When oral drug therapy is needed, one must also consider the dosage form availability and child’s ability to swallow a solid dosage form. Children younger than 6 years are often not able to swallow oral tablets or capsules and may require oral liquid formulations. Not all oral medications, especially those unapproved for use in infants and children, have a commercially available liquid dosage form. Use of a liquid formulation compounded from a solid oral dosage form is an option when compounding and stability data are available. Factors such as drug stability, suspendability, dose uniformity, and palatability should be considered when compounding a liquid formulation.[33] Commonly used suspending agents include methylcellulose and carboxymethylcellulose (eg, Ora-Plus). Palatability of a liquid formulation can be enhanced by using simple syrup or OraSweet. If no dietary contraindications or interactions exist, doses can be mixed with food items such as pudding, fruit-flavored gelatin, chocolate syrup, applesauce, or other fruit puree immediately before administration of individual doses. There may be instances when clinicians may elect to prescribe tablets or capsules that are to be crushed or opened, respectively, and mixed in soft foods. This should be limited to instances when a commercial or compounded liquid dosage form is not appropriate. Additionally, it is important in this scenario, to avoid use of sustained or extended formulations of tablets or capsules. Use should also be limited to wide therapeutic index medications (eg, β-lactam antibiotics) as they have a wide margin of safety, and dose rounding to a certain extent (eg, 10%) is likely feasible to fit an available tablet or capsule strength. To help with palatability of oral medication, some clinicians pair bitter tasting medications (eg, clindamycin) with chocolate flavoring and metallic tasting medications (eg, ferrous sulfate drops) with fruit (eg, citrus) flavoring. Honey, although capable of masking unpleasant taste of medication, may contain spores of *Clostridium botulinum* and should not be given to infants younger than 1 year due to increased risk for developing botulism. Most hospitals caring for pediatric patients compound formulations in their inpatient pharmacy. Limited accessibility to compounded oral liquids in community pharmacies poses a greater challenge. A list of community pharmacies with compounding capabilities should be maintained and provided to the parents and caregivers before discharge from the hospital.

Common Errors in Pediatric Drug Therapy

Prevention of errors in pediatric drug therapy begins with identification of possible sources. Unfortunately, medication errors are common in pediatrics with up to 27% of all pediatric medication orders resulting in an error.[34] Off-label use of medications increases risk of medication error and has been attributed to difference in frequency of errors compared with adults. One of the most common reasons for medication errors in this specialized population is incorrect dosing such as calculation error.[35] **KEY CONCEPT** Medication errors among pediatric patients are possible due to differences in dose calculation and preparation; it is important to identify potential errors through careful review of orders, calculations, dispensing, and administration of drug therapy to infants and children. It is crucial to verify accurate weight, height, and age for dosing calculations and dispensing of prescriptions because pediatric patients are a vulnerable population for medication error. Consistent units of measurements in reporting patient variables, such as weight (kg) and height (cm), should be used. Dosing units such as mg/kg, mcg/kg, mEq/kg, mmol/kg, or units/kg should also be used accurately. Given the age-related differences in metabolism of additives, such as propylene glycol and benzyl alcohol, careful consideration should be given to the active and inactive ingredients when selecting a formulation.

Decimal errors, including trailing zeroes (eg, 1.0 mg misread as 10 mg) and missing leading zeroes (eg, .5 mg misread as 5 mg) in drug dosing or body weight documentation, are possible, resulting in several-fold overdosing. Strength or concentration of drug should also be clearly communicated by the clinician in prescription orders. Similarly, labels that look alike may lead to drug therapy errors (eg, mistaking a vial of heparin for insulin). Dosing errors of combination drug products can be prevented by using the right component for dose calculation (eg, dose of sulfamethoxazole-trimethoprim is calculated based on the trimethoprim component).

Use of standardized concentrations and programmable infusion pumps, such as smart pumps with built-in libraries, is encouraged to minimize errors with parenteral medications, especially those for continuous infusions such as inotropes. Electronic health records (EMR) with clinical decision support systems and barcoding technology, with ability for dose range checks by weight for pediatric medication orders and accurate matching of correct ordered medication to patient, respectively, have decreased medication errors.[34]

Prevention of medication errors is a joint effort between healthcare professionals, patients, and parents/caregivers. Obtaining a complete medication history, including over-the-counter (OTC) and complementary and alternative medicines (CAMs), simplification of medication regimen, clinician awareness for potential errors, and appropriate patient/parent/caregiver education on measurement and administration of medications, are essential in preventing medication errors.

Complementary/Alternative and Over-the-Counter Medication Use

Between 30% and 70% of children with a chronic illness (eg, asthma, attention deficit hyperactivity disorder, autism, cancer) or disability use CAMs. CAMs can include mind-body therapy (eg, imagery, hypnosis), energy field therapies (eg, acupuncture, acupressure), massage, antioxidants (eg, vitamins C and E), herbs (eg, St. John's wort, kava, ginger, valerian), prayer, immune modulators (eg, echinacea), or other folk/home remedies. It is important to encourage communication about CAM use, including interdisciplinary discussion between CAM providers and pediatric healthcare providers.[36] It is critical to appreciate that there are limited data establishing efficacy of various CAM therapies in children. For example, colic is a condition of unclear etiology in which an infant cries inconsolably for over a few hours in a 24-hour period, usually during the same time of day. Symptoms of excessive crying usually improve by the third month of life and often resolve by 9 months of age. No medication has been approved by the FDA for colic; however, parents may be advised by family and friends to use products that may have harmful additive ingredients. Gripe water is an oral solution containing a combination of ingredients, such as chamomile and sodium bicarbonate, and is not regulated by the FDA. Some gripe water products may contain alcohol, which is not recommended for infants due to their limited metabolism ability (ie, alcohol dehydrogenase). Further, some CAM products (eg, St. John's wort) can interact with prescription drugs and produce undesired outcomes. It is important to assess OTC product use in pediatric patients. For example, treatment of the common cold in children is similar to adults, including symptom control with adequate fluid intake, rest, use of saline nasal spray, and acetaminophen (10–15 mg/kg/dose every 6–8 hours) or ibuprofen (4–10 mg/kg/dose every 8 hours) for relief of discomfort and fever. Other products, such as a topical vapor rub or oral honey, have demonstrated some potential for alleviation of symptoms, such as cough, based on survey studies of parents for children of 2 years and older.[37,38] Unlike adults, symptomatic relief through the use of pharmacologic agents, such as OTC combination cold remedies, is not recommended for pediatric patients younger than 4 years. Currently, the FDA does not recommend the use of OTC cough and cold medications (eg, diphenhydramine and dextromethorphan) in children younger than 2 years; however, the Consumer Healthcare Products Association, with the support of the FDA, has voluntarily changed product labeling of OTC cough and cold medications to state "do not use in children under 4 years of age." This is due to increased risk for adverse effects (eg, excessive sedation, respiratory depression) and no documented benefit in relieving symptoms. It has also been noted that these medications may be less effective in children younger than 6 years compared with older children and adults.[39,40] Also noteworthy is the potential for medication error with use of OTC products in older children, such as cold medications containing diphenhydramine and acetaminophen. A parent/caregiver may inadvertently overdose a child on one active ingredient, such as acetaminophen, by administering acetaminophen suspension for fever and an acetaminophen-containing combination product for cold symptoms. The use of aspirin in patients younger than 18 years with viral infections is not recommended due to the risk of Reye syndrome. Signs or symptoms of Reye syndrome, usually appearing several days after start of a viral infection, are relatively nonspecific, including diarrhea, persistent vomiting, increased respiratory rate, increasing lethargy, and seizure. While making an appropriate recommendation for an OTC product for a pediatric patient, the parent/caregiver should always be referred to their pediatrician for further advice and evaluation when severity of illness is a concern.

Clinicians should respect parents'/caregivers' beliefs in the use of CAM and OTC products and encourage open discussion with the intention of providing information regarding their risks and benefits to achieve desired health outcomes as well as optimize medication safety.

Medication Administration to Pediatric Patients and Caregiver Education

Considering the challenges in cooperation from infants and younger children, medication administration can become a difficult task for any parent or caregiver. One should also consider factors that may affect adherence to prescribed therapy including caregiver's and/or patient's personal beliefs, socioeconomic limitation(s), and fear of adverse drug effects. One common factor to consider is ease of measurement and administration when selecting and dosing pediatric drug therapy. Clinicians should check concentrations of available products and round doses to a measurable amount. For example, if a patient were to receive an oral formulation, such as amoxicillin 400 mg/5 mL suspension, and the dose was calculated to be 4.9 mL, the dose should be rounded to 5 mL for ease of administration. Rounding the dose by 10% to the closest easily measurable liquid amount or available tablet/capsule strength is commonly practiced for most medications (eg, antibiotics); however, drugs with narrow therapeutic indices (eg, anticoagulants) are exceptions to this guideline.

The means or devices for measuring and administering medications should also be closely considered. Special measuring devices as well as clear and complete education about their use are essential. Oral syringes are accurate and offered at most community pharmacies for the measurement of oral liquid medications. Studies have demonstrated less error in dose measurement using an oral syringe compared to other devices (eg, dosing cup, dropper, dosing spoon) and that in addition to appropriate device caregiver health literacy contributes to potential for medication dose measurement error.[41] Due to inconsistencies and risk for possible inaccuracy of measuring smaller doses, dosing or measuring spoons, oral droppers, and medicine cups are not recommended for measuring doses for infants and young children. Household dining or measuring spoons are not accurate or consistent and should not be used for the administration of oral liquids. Additionally, consistency in dosing units used for liquid formulation (eg, milliliters instead of teaspoons or ounces) is necessary to minimize further medication dosing errors.[42] Individuals in supervision of infants and children attending daycare and schools should also be educated about medication administration. Guidelines with regard to medication use in school settings are available.[43–45]

KEY CONCEPT Comprehensive and clear parent/caregiver education improves medication adherence, safety, and therapeutic outcomes and is essential in care of infants and young children. Information about the drug, including appropriate and safe storage away from children, possible drug interactions, duration of therapy, importance of adherence, possible adverse effects, and expected therapeutic outcomes should be provided. Parent/caregiver education is important in both inpatient and outpatient care settings and should be reviewed at each point of care.

Because parents/caregivers are often sole providers of home care for ill children, it is important to demonstrate appropriate dose preparation and administration techniques to the caregivers before medication dispensing. First, a child should be calm for successful dose administration. Yet, calming a child is often a challenge during many methods of administration (eg, otic, ophthalmic, rectal). Parents/caregivers should explain the process in a simple and understandable form to the child because this may decrease the child's potential anxiety. In addition, it is also recommended to distract younger children using a favorite item such as toy or to reward cooperative or "good" behavior during medication administration. Helpful tips regarding administration of selected dosage forms in pediatric patients are listed in Table 2–4.[46]

Table 2–4

Helpful Tips for Medication Administration for Selected Dosage Forms[46]

Dosage Form	Recommendations
Ophthalmic drops or ointment	• Wash hands thoroughly prior to administration • Position child laying down in supine position • Avoid contact of applicator tip to surfaces, including the eye • Drops should be placed in the pocket of the lower eyelid • Ointment strip should be placed along the pocket of the lower eyelid

Otic drops	• Wash hands thoroughly prior to administration
	• Position child laying down in prone position
	• Tilt head to expose treated ear, gently pull outer ear outward, then due to age-dependent change in angle of eustachian tube:
	  • If child < 3 years of age, gently pull downward and back; apply drops
	  • If child is > 3 years of age, gently pull upward and back; apply drops

Nasal drops	• Wash hands thoroughly prior to administration • Position child laying down in supine position • Slightly tilt head back; place drops in nostril(s) • Remain in position for appropriate distribution of medication
Rectal suppository	• Similar to adult administration; challenging route for administration • For younger patients (ie, < 3 years), a smaller finger (eg, pinky finger) should be used to insert suppository
Metered-dose inhalers	• Use a spacer • For younger children, use one with a mask, be sure the mask is secured/placed closely up against the child's face, avoiding gaps between face and mask and creating a seal to ensure medication delivery • Child should take slow breaths in with each dose • Wait at least 1 minute between doses

From Buck MI, Hendrick AE. Pediatric Medication Education Text, 5th ed. American College of Clinical Pharmacy, 2009; Sec1: xvii–xxvii.

Patient Encounter Part 3

DD is a 13-year-old adolescent boy who is brought to the clinic with a weeklong history of productive cough, rhinorrhea, and congestion. The child's temperature last night was 39°C (102.2°F) by electronic axial thermometer. Mom reports to have given the child several doses of acetaminophen, but symptoms did not improve and thus she brought him to be seen. Patient has history of allergic rhinitis and eczema. The pediatrician diagnoses DD with community-acquired pneumonia requiring antibiotic treatment and asks you to develop a treatment care plan for DD including use of cefdinir 14 mg/kg/dose by mouth divided twice a day for 10 days.

What additional information would you need to develop an appropriate treatment care plan for DD?

Mom asks you if acetaminophen was the right choice for DD's fever and pain and if other options such as aspirin could be used instead. What would you recommend for pain and fever for DD? Why?

The medical assistant provides you DD's weight as 85.8 lb (39 kg). Mom states that DD would prefer a liquid form as he is still working on swallowing pills. Cefdinir is available as a 125 mg/5 mL or 250 mg /5 mL suspension. What is the most appropriate dosage strength and calculated dose of cefdinir for DD?

Two days later, Mom calls the clinic stating that DD did not like the taste of cefdinir and would like to change to a capsule or tablet. Cefdinir comes as a 300-mg capsule. Explain whether or not this change is appropriate.

Accidental Ingestion in Pediatric Patients

Pediatric accidental ingestions most often occur in the home. Various factors account for incidence of accidental ingestions in young children, including hand-to-mouth behaviors as well as new and increased mobility resulting in easier access areas where harmful substances are stored (eg, medication cabinets). Indeed, caregivers are encouraged to use "child-safe" devices to lock closets and cabinets to reduce risk of accidental ingestions; however, this is not a substitute for appropriate caregiver supervision.

Ingested substances can vary, from household cleaning solutions to prescription and nonprescription medications. The most common exposures in children younger than 5 years were cosmetics/personal care products, analgesics, household cleaning substances, foreign bodies (eg, small toys), and topical preparations.[47] Unintentional or accidental ingestions are the most common type in younger children (ie, younger than 5 years) with fatalities possible with as little as one to two tablets/capsules of medications such as calcium channel blockers, tricyclic

Patient Care Process

Collect Information:

- For patients up to 2 years of age, review birth history, including gestational age, birth weight, medical complications, postnatal age, and corrected age.
- Review patient's past medical history, comorbidities.
- Review patient's available laboratory data (eg, serum creatinine, liver function tests).
- Review all current medication therapy, including CAM and OTC.
- Review patient's medication allergies and/or intolerances.

Assess the Information:

- Assess appropriateness of therapy. Is patient on appropriate drug therapy for current diagnoses? Are current medication doses appropriate (ie, for age, weight, etc.)? Any medications without indication?
- Evaluate patient's organ function (renal and hepatic), including use of appropriate equations (eg, bedside Schwartz).
- Assess current therapy for safety and efficacy. Is the medication effective for this patient? Is the patient experiencing any adverse effects?
- Consider available data regarding safe and effective dosing of selected drug.
- Assess patient's (or patient's caregiver) history of medication adherence and health care beliefs.

Develop a Care Plan:

- Consider available routes of administration. What is the most appropriate route? If IV medication is needed, what types of IV accesses are available? For example, does the patient have a central or peripheral line? Determine if IV medication needs to be further diluted or concentrated based on patient's comorbidities and fluid status.
- Consider ease of administration for the patient and/or caregiver. Is the dose easily measurable? Is the dosing frequency reasonable for their family schedule?
- Verify accuracy of dose calculations. Verify current weight and dosing units (e.g., mg/kg/day, mg/kg/dose). Is the dosing interval appropriate?
- Determine what drug-drug/drug-food interactions are possible with this new therapy. How can they be managed?

Implement the Care Plan:

- Communicate plan for care with patient care team.
- Educate parent/caregiver/patient regarding selected drug therapy including purpose, dose, administration, duration therapy, possible side effects, etc.

Follow-up: Monitor and Evaluate:

- Monitor signs and symptoms of clinical outcomes (improvement and decline). Measure drug serum concentrations when appropriate. Monitor for possible adverse drug events.
- Reinforce patient/caregiver education.

antidepressants, or opioids. For those age between 13 and 19 years and older, intentional exposures outnumber those classified as unintentional/accidental and include recreational and self-harm attempts.[47] Management of accidental ingestions varies depending on the ingested substance, the amount, and the age and size of the child. The American Academy of Clinical Toxicology and the AAP do not recommend the use of ipecac syrup for treatment of accidental ingestion; thus, inducing emesis is not a recommended approach for any type of ingestion.[48] Clinicians receiving calls regarding management of accidental ingestions, depending on severity of case, should direct them to the emergency department for evaluation and/or the local or regional poison control center for specific recommendations, which can reached via a universal contact number (1-800-222-1222), with additional information located through the American Association of Poison Control Centers (*www.aapcc.org*).[49]

Abbreviations Introduced in This Chapter

AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
bpm	Beats per minute
CAM	Complementary and alternative medicine
CDC	Centers for Disease Control and Prevention
CPOE	Computer physician order entry
ELBW	Extremely low birth weight
GA	Gestational age
GFR	Glomerular filtration rate
LBW	Low birth weight
MDI	Metered-dose inhaler
OTC	Over-the-counter
V_d	Volume of distribution (apparent)
VLBW	Very low birth weight

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3 Palliative Care Management

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the philosophy of palliative care including hospice care and its impact on medication therapy management.
2. Discuss the therapeutic management of palliative care patients and how it differs from and is similar to traditional patient care at the end of life.
3. List the most common symptoms experienced by the terminally ill patient.
4. Explain the pathophysiology of the common symptoms experienced in the terminally ill patient.
5. Describe the pharmacologic rationale of medication therapy used for symptom management in the terminally ill patient.
6. Recommend nonpharmacologic and pharmacologic management of symptoms in a terminally ill patient.
7. Develop a patient-specific palliative care management plan.
8. Educate patients and caregivers regarding palliative care management plan, including rationale of treatment, importance of medication adherence, and assessment and monitoring of desired outcomes.

INTRODUCTION

KEY CONCEPT According to the World Health Organization (WHO), "Palliative care is an approach that improves the **quality of life** of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual." The goal of palliative care is to achieve the best quality life for patients and their families.[1] "Palliate" literally means "to cloak." The WHO goal of achieving high quality life depends on a team approach to manage disease-related symptoms while honoring the patient's care goals.[2] Palliative care focuses on patients and their families and the challenges associated with life-threatening illness.[3] The goal is to prevent and relieve suffering by means of early identification, assessment, and treatment of pain and other physical symptoms, including associated psychosocial, emotional, and spiritual concerns.[1] Palliative medicine is rapidly becoming a well-recognized medical specialty[4] and is much needed due to the increased number of patients with chronic, slowly debilitating diseases.[2]

The term *palliative care* is frequently used synonymously with hospice and, although hospice programs provide palliative care, palliative care has a much broader application. In the United States, hospice is defined by Medicare and other third-party payers as a benefit available to individuals who have less than or equal to 6 months life expectancy if the disease runs its typical course.[2] Hospice care guidelines and regulations are primarily defined by federal regulations. Palliative care outside of the umbrella of hospice care, in contrast, is not currently regulated nor has the same reimbursement structure. Palliative care services may be provided at any point during the disease process and are not limited to the last 6 months of life; therefore, patients and families may receive palliative care services beginning at the time of diagnosis of life-limiting illness. Palliative care may be delivered in all care settings.[5] The foundation for providing quality palliative care centers around active participation of an interdisciplinary team working closely to meet patient and family goals.[6] Team members include representatives from medicine, nursing, social work, pastoral or related counseling, pharmacy, nutrition, rehabilitation, and other professional disciplines providing a holistic approach to the patient's care. KEY CONCEPT The goals of palliative care include enhancing quality of life while maintaining or improving functionality.[6,7] Palliative care should be delivered to patients from the onset of any chronic, life-altering disease. Before many of our modern medical and therapeutic advancements were developed, curative treatments were not normally available.[8] Provision of comfort was considered the mainstay for patient care. Advances in medical care, nutrition, public health, and trauma care resulted in fewer patient deaths, and medical management shifted focus from comfort to a death-denying approach, with prolonging life as the primary goal. With this shift, palliative care became less emphasized until 1967 when the first modern hospice was established in London, England. Today the palliative care philosophy attempts to combine enhanced quality of life, compassionate care, and patient and family support with modern medical advances.

EPIDEMIOLOGY AND ETIOLOGY

Currently, approximately 6100 hospice agencies care for patients across the United States.[9] In 2013, approximately 59% of hospice patients were cared for in the home, and 84% of hospice patients were older than 65 years.[9]

Palliative care for advanced lung cancer is positively correlated with increased survival and reduced risk of death in acute care settings.[10] Lung cancer patients receiving early palliative care survived 23% longer than those with delayed palliative care.[11] Early referrals to hospice appear to improve overall care of the patient and offer prolonged survival in some. The integration of palliative care prior to the patient's eligibility for hospice care may even further improve survival and quality of life and care of patients.

Because healthcare providers have an increasing recognition of palliative care benefit for patients with all life-limiting illness, increased integration of this care model has extended to other disease states beyond cancer.

PATHOPHYSIOLOGY

Understanding the pathophysiology of multiple end-stage disease states is daunting, yet in palliative care, the emphasis is less on disease state management than on assessment and appropriate treatment of associated physical, psychological, social, and spiritual symptoms. Palliative care focuses on symptom management for patients with progressive life-limiting illnesses from diagnosis through death where the pathophysiological impact of disease on a patient's symptoms may vary greatly. **KEY CONCEPT** Palliative care is appropriate for all life-limiting diseases including cancer, chronic obstructive pulmonary disease, dementia, including Alzheimer's disease, Parkinson's disease, chronic cardiac disease, stroke, renal failure, hepatic failure, multiorgan failure, diabetes mellitus, etc.

For the purpose of this chapter, pathophysiology is not a primary focus. Rather, the philosophy of managing physical, psychological, social, and spiritual symptoms to maintain quality of life and prevent suffering is discussed within the context of progressively incurable illnesses. Although palliative may coexist with aggressive disease state management to extend life, as the patient approaches the end of life, philosophy and management generally moves away from principles related to disease state management of patients where prolonging life is the goal.

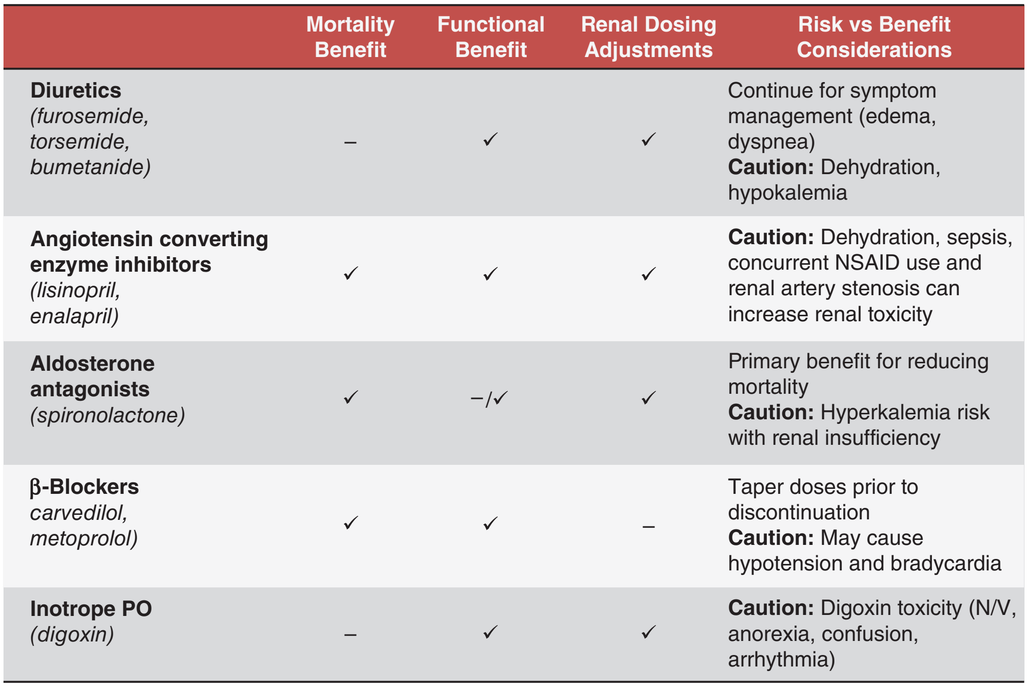
CLINICAL PRESENTATION AND DIAGNOSIS

Cancer

Palliative care is commonly associated with cancer patients. Regardless of whether or not the cancer is curable, most patients have various degrees of physical, psychological, social, and spiritual symptoms that arise once a diagnosis is confirmed. Once a cancer patient has failed curative and life-prolonging therapy, prognosis and disease trajectory are easier to determine than in patients with other life-limiting diseases. The change in focus from cure to symptom control becomes apparent and therefore more acceptable. Cancer symptoms depend on both the primary tumor site and the location of metastatic spread. Symptoms may also result from the effects of cancer treatments, such as chemotherapy and radiation. (See Chapters 88–99 for specific cancers and their treatments.)

End-Stage Heart Failure

Many forms of heart disease result in sudden death; however, disease progression of heart failure is protracted, yet unpredictable. Advanced heart failure (class III–IV or stage C or D) is characterized by persistent symptoms that limit activities of daily living despite optimal drug therapy. Common symptoms include fatigue, breathlessness, anxiety, fluid retention, and pain. In heart failure, standard medication management intends to reduce progression of cardiac remodeling and is considered disease modifying. However, as patients approach the final months of life, with the exception of cholesterol-lowering agents, these same cardiac medications are also palliative and should not be discontinued prematurely without cause (Figure 3–1). Exacerbations of heart failure symptoms should be aggressively treated as long as the patient is responsive to therapy and wishes to receive treatment. In hospice, this can often be accomplished through medication



	Mortality Benefit	Functional Benefit	Renal Dosing Adjustments	Risk vs Benefit Considerations
Diuretics *(furosemide, torsemide, bumetanide)*	–	✓	✓	Continue for symptom management (edema, dyspnea) **Caution:** Dehydration, hypokalemia
Angiotensin converting enzyme inhibitors *(lisinopril, enalapril)*	✓	✓	✓	**Caution:** Dehydration, sepsis, concurrent NSAID use and renal artery stenosis can increase renal toxicity
Aldosterone antagonists *(spironolactone)*	✓	–/✓	✓	Primary benefit for reducing mortality **Caution:** Hyperkalemia risk with renal insufficiency
β-Blockers *carvedilol, metoprolol)*	✓	✓	–	Taper doses prior to discontinuation **Caution:** May cause hypotension and bradycardia
Inotrope PO *(digoxin)*	–	✓	✓	**Caution:** Digoxin toxicity (N/V, anorexia, confusion, arrhythmia)

FIGURE 3–1. Drugs, their use in Class III-IV heart failure, and their effects on mortality, hospital admissions, and functional status. Checkmark, indicating a positive impact on specified parameter, and — indicating no significant impact on specified parameter.[7,31]

manipulation in the patient's home without the need for hospitalization (see Chapter 7).

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) has a prolonged and variable course. COPD Patients have numerous physician visits and hospital admissions. Palliative care treatment is directed at reducing symptoms, reducing the rate of decline in lung function, preventing and treating exacerbations, and maintaining quality of life. In end-stage COPD, bronchodilators and anti-inflammatory agents become less effective. As patients decline, the ability to appropriately use inhalers becomes more difficult. Utilizing a nebulizer to administer bronchodilators allows for more reliable drug delivery to the site of action. Symptoms of late-stage disease include wheezing, chronic sputum production, cough, frequent respiratory infections, dyspnea with exertion progressing to dyspnea at rest, fatigue, pain, hypoxia, and weight loss. Pulmonary hypertension may also occur and can lead to cor pulmonale or right-sided heart failure (see Chapter 16).

End-Stage Kidney Disease

Chronic kidney disease is progressive and leads to renal failure. In end-stage kidney disease, the only life-sustaining treatments are dialysis or renal transplant. Without treatment, kidney failure causes uremia, oliguria, hyperkalemia and other electrolyte disorders, fluid overload and hypertension unresponsive to treatment, anemia, hepatorenal syndrome, and uremic pericarditis. Symptoms associated with chronic kidney disease (stage 5) include fatigue, pruritus, nausea, vomiting, constipation, dysgeusia, muscle pain, agitation, and bleeding abnormalities. Palliative care in these patients includes the minimization of these symptoms; however, because many options for drug therapy will be cleared through the kidneys, agents should be chosen cautiously to avoid other complications (see Chapter 27).

End-Stage Liver Disease

Like kidney disease, the only treatment to prolong life in advanced liver disease is transplant. Patients with end-stage liver disease typically present with ascites, jaundice, pruritus, or encephalopathy, and, frequently, all four symptoms. Additionally, bleeding disorders are common, and bleeding esophageal or gastric varices are the cause of death in about one-third of those who die from liver disease. Palliative care in these patients focuses on the symptom management of end-stage liver disease complications.

Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome

Pharmacologic advances have changed prognosis and progression of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS). Palliative care is predominantly directed toward patients without access to drug therapy in early stages of disease. Patients with progressed HIV/AIDS are susceptible to opportunistic infections and cancer that may hasten death. Common symptoms in individuals with HIV/AIDS at the end of life include fatigue, profound weight loss, breathlessness, nausea, gastrointestinal (GI) disturbances, and pain. The goal of palliative care in these patients is to minimize common AIDS-related symptoms (see Chapter 87).

Stroke/Cerebral Vascular Accident

Stroke results from hemorrhage or ischemia. The prognosis of cerebral vascular accident (CVA) patients is unpredictable and may be extended, resulting in caregiver fatigue. Approximately one-third of patients who have a stroke will die within 2 years. Patients with stroke deal with loss of physical and cognitive function, poststroke pain, and frequent depression. Incontinence, aphasia, **dysphagia**, and seizures are also common. Patients with dysphagia have a high incidence of aspiration pneumonia, which often is the cause of death (see Chapter 12).

Parkinson Disease

Parkinson disease is a degenerative neurologic disease with a long chronic, progressive course evidenced by akinesia, rigidity, and tremor. The goal of therapy is to reduce symptoms and maintain or improve quality of life. Palliative care provides support to both patients and caregivers as patients become more disabled, and neuropsychiatric problems arise. Frequent symptoms are skin infections and breakdown, constipation, pain, depression, hallucinations, and confusion. Individuals with Parkinson disease often die from bronchial pneumonia due to dysphagia or complication from falls (see Chapter 34).

Amyotrophic Lateral Sclerosis (Lou Gehrig Disease)

Amyotrophic lateral sclerosis (ALS) is a chronic neurodegenerative disorder characterized by progressive loss of motor neurons. The median survival is approximately 3 years from the symptom onset with less than 15% of patients surviving 10 years. Initially, symptoms of ALS present as limb weakness, with other symptoms developing in no particular order including cramps, spasticity, pain, dysarthria, sialorrhea, fatigue, insomnia, depression, fear and anxiety, involuntary emotional expression disorder, constipation, aspiration, and laryngospasm. Many patients do not have cognitive impairment; however, one-fourth to one-half of patients with ALS may have associated frontal lobe dementia. Disease progression eventually involves all systems except sphincter control and eye movement. Unless the individual has long-term mechanical ventilation, the cause of death is typically respiratory failure.

Alzheimer Disease and Other Dementia

Dementia is a progressive, nonreversible deterioration in cognitive function with associated behavioral dysfunction. Alzheimer disease accounts for most dementia cases; vascular, Parkinson disease, dementia with Lewy body, and frontotemporal dementias are less prevalent. Drug therapy targets slowing progression of cognitive symptoms and preserving patient function. As patients progress toward end-stage dementia, in addition to memory loss and personality and behavioral changes, they require assistance in basic activities of daily living such as feeding, dressing, and toileting. At this point they may not respond to their surroundings, may not communicate, or have impaired movements and dysphagia. Depression, agitation, delusions, compulsions, confusion, hallucinations, incontinence, and disruption of sleep/wake cycles are all common symptoms in end-stage dementias. Symptom assessment is challenging due to the cognitive impairment and frequent aphasia. Palliative care is not only directed toward the patient but also emotional support for those close to them (see Chapter 30).

TREATMENT

KEY CONCEPT Following a complete assessment of the patient, developing a comprehensive therapeutic plan that utilizes the fewest number of medications to achieve the highest quality of life is essential. Many times, one drug may relieve multiple symptoms, resulting in better patient care, lower costs, and decreased medications. Cost-effective drug recommendations are essential to control costs. Avoiding polypharmacy will reduce adverse drug events related to drug interactions, excessive side effects, and therapy duplication. The following list of symptoms includes common symptoms observed in palliative and end-of-life care; however, it is not comprehensive. **KEY CONCEPT** Palliative care is more than just pain management. It includes treatment of symptoms resulting in discomfort for the patient, which may include nausea and vomiting, agitation, anxiety, depression, **delirium**, dyspnea, anorexia and cachexia, constipation, diarrhea, pressure ulcers, and edema.

Note that many drugs used to treat symptoms in palliative and end-of-life care are often prescribed for unapproved uses, administered by unapproved routes or in dosages higher than recommended by the package insert. Conducting large-scale, rigorous drug studies that supply necessary information for an approved drug indication poses ethical difficultly due to the delicate nature of patients receiving palliative and/or hospice care.

Anxiety

A comprehensive review of anxiety disorders is found in Chapter 41.

▶ *Palliative Care Considerations*

- Anxiety is "characterized by apprehensive anticipation of future danger or misfortune accompanied by psychological symptoms such as worrying, vigilance, and rumination as well as by physical feelings such as tension, jitters, dyspnea, chest discomfort, or abdominal stress."[7]
- Anxiety is closely related to fear, but fear has an identified cause or source (eg, fear of death). Fear may respond more to counseling than anxiety that the patient cannot attribute to a particular fearful stimulus. Anxiety disorders are the most prevalent class of mental disorders, so it is not surprising that anxiety is a common cause of distress at life's end.

In addition to anxiety disorders, a variety of conditions can cause, mimic, or exacerbate anxiety.[12,13] **Delirium**, particularly in its early stages, can easily be confused with anxiety. Physical complications of illness, especially dyspnea and undertreated pain, are common precipitants. Significant anxiety is present in most patients with advanced lung disease and is closely related to periods of oxygen desaturation. Medication side effects, especially akathisia from older antipsychotics and antiemetics (including metoclopramide), can present as anxiety. Interpersonal, spiritual, or existential concerns can mimic and exacerbate anxiety. Patients with an anxious or dependent coping style are at high risk of anxiety as a complication of advanced illness. Short of making a diagnosis of a formal anxiety disorder, differentiating normal worry and apprehension from pathologic anxiety requires clinical judgment.

Behaviors indicative of pathological anxiety include intense worry or dread, physical distress (eg, tension, jitteriness, or restlessness), maladaptive behaviors and diminished coping, and inability to relax.[12]

Pathological anxiety may be complicated by insomnia, depression, fatigue, GI upset, dyspnea, or dysphagia.[14] Anxiety can also worsen these conditions, if they are already present. Untreated anxiety may lead to numerous complications, including withdrawal from social support, poor coping, limited participation in palliative care treatment goals, and family distress. Reassess the patient for anxiety with any change in behavior or any change in the underlying medical condition. Assessment for formal anxiety disorders or other contributing factors is key to management. A comprehensive review of insomnia may be found in Chapter 42.

▶ *Nonpharmacologic Treatment*

Regardless of treatment approach, the following principles apply. Ask questions and listen to patients' concerns and fears. Offer emotional support and reassurance when appropriate. Err on the side of treatment—be willing to palliate anxiety. Assess treatment response and side effects frequently. Aim to provide maximum resolution of anxiety and educate patients and families about anxiety and its treatments.

Psychotherapies can help manage anxiety, although availability of trained therapists willing to make home visits, and limited stamina and attention span of seriously ill patients, typically make such therapies impractical in the hospice setting. Cognitive and behavioral therapies can be beneficial, including simple relaxation exercises or distraction strategies (ie, focusing on something pleasurable or at least emotionally neutral). Encourage pastoral care visits, especially if spiritual and existential concerns predominate.

When an underlying cause of anxiety can be identified, treatment is initially aimed at the precipitating problem, with monitoring to see if anxiety improves or resolves as the underlying cause is addressed.[14]

▶ *Pharmacotherapy*

In most cases, management of pathological anxiety in the hospice setting involves pharmacologic therapies. Benzodiazepines are standard treatment; however, selective serotonin reuptake inhibitors (SSRIs), typical and atypical antipsychotics, may be appropriate based on the patient's life expectancy.[14] The primary goal of therapy for anxiety in hospice is patient comfort. Aim to prevent anxiety, not just treat it with as needed medications. Think of pain management as an analogy. As with all medications that act in the central nervous system (CNS), anxiolytics, such as benzodiazepines, should be dosed at the lower end of the dose range to prevent unnecessary sedation, particularly in the frail and elderly. However, recognize that standard or higher doses may be required. Avoid use of bupropion and psychostimulants for anxiety. Although effective for depression, they are ineffective for anxiety and may make anxiety worse. Many patients have difficulty swallowing as they approach the end of life. Lorazepam, alprazolam, and diazepam tablets are commonly crushed and placed under the tongue with a few drops of water if the liquid formulations are not readily available. Low-dose haloperidol is also used to treat anxiety in palliative care, particularly if delirium is present.[15] Chapter 41 provides more detailed information on appropriate use of anxiolytic agents.

Delirium

▶ *Palliative Care Considerations*

Delirium is very common in hospice, occurring in more than 80% of terminally ill patients, most often in the last few days of life.[11] Potential causes in the hospice setting include medical illness, dehydration, hypoxia, sleep deprivation, metabolic disturbances, sepsis, medication side effects (particularly anticholinergic agents, benzodiazepines, opioids, corticosteroids, tricyclic antidepressants), urinary retention, urinary tract infection, constipation or impaction, uncontrolled pain, or alcohol or drug withdrawal.[7,15]

A classic delirium symptom is clouding of consciousness. This can be manifested by an inability to either maintain or shift attention. Patients also have impaired cognitive functioning, which may or may not include memory disturbances. "Sundowning" is very common phenomenon at the end of life, especially in the presence of delirium. It presents as daytime sleepiness and nighttime agitation and restlessness. Another common characteristic is fluctuation in severity of delirium symptoms during the day. This can even occur within the course of a single hour or also from day to day. Patients exhibiting agitation from their delirium are easy to identify, but those who present as withdrawn and with diminished responsiveness ("quiet" delirium) are more difficult to diagnose. It is not uncommon for patients to exhibit both quiet and agitated delirium. Treatment is the same for both types. Delirium is difficult to distinguish from dementia. Delirium more commonly presents as a sudden onset (eg, hours to days), with an altered level of consciousness and a clouded sensorium. However, dementia more commonly presents gradually and with an unimpaired level of consciousness.[15]

▶ *Nonpharmacologic Treatment*

Establishing a safe, soothing environment including familiar objects such as photographs and familiar music can be helpful to calm the patient. Minimizing injury risk is important when the patient is agitated. Providing education to families and caregivers about the causes of delirium, signs and symptoms, and how to best manage it will help reduce their anxiety and distress when it occurs.

▶ *Pharmacotherapy*

The most important initial step is to determine the care goal. If possible, reverse the underlying cause of delirium to restore the patient to a meaningful cognitive status.[7,11] If the precipitating factors cannot be reversed, initiate symptom treatment. If the patient is irreversibly delirious and agitated, drug therapy is generally indicated.

Antipsychotic (neuroleptic) drugs (conventional or atypical antipsychotics) are the drugs most used to treat confusion and agitation associated with delirium. However, treatment of delirium with these drugs is "off-label." Atypical antipsychotics including risperidone, olanzapine, quetiapine, ziprasidone, paliperidone, and aripiprazole are also an option.[16]

Haloperidol, in doses less than 2 mg/day, is well tolerated and nonsedating. Doses greater than 4.5 mg/day are associated with increased extrapyramidal symptoms.[16,17] Cumulative doses of 35 mg or single intravenous (IV) doses greater than 20 mg have been associated with QTc prolongation.[18] When sedation is beneficial for terminal aggressive, agitated delirium, quetiapine provides more sedation as compared with low-dose haloperidol. When patients are bedbound and in the final stages of life, excess sedation common with quetiapine is not a concern. Haloperidol is commonly given sublingually or rectally if swallowing becomes difficult, although these are not approved administration routes. Haloperidol, but not quetiapine, can be given subcutaneously.[19]

Administering benzodiazepines alone in a patient with delirium can make the delirium and confusion worse. While addition of benzodiazepines with antipsychotics is not routinely used, delirium induced by withdrawal or untreated anxiety may benefit from addition of a benzodiazepine.[13]

Dyspnea

▶ *Palliative Care Considerations*

Dyspnea is described as an uncomfortable awareness of breathing. It is a subjective sensation, and patient self-report is the only reliable indicator. Respiratory rate or Po_1 may not correlate with the feeling of breathlessness.[20] Respiratory effort and dyspnea are not the same. While opioids do not address bronchoconstriction or bronchospasm, patients may report substantial relief of dyspnea from opioids with no change in respiratory rate. The prevalence of dyspnea varies from 12% to 74%, worsening during the last week of life in terminally ill cancer patients to between 50% and 70%. History and physical examination should be taken and reversible causes of dyspnea should be identified and treated, if present.[21–23]

Patient Encounter 1

SF is an 89-year-old woman diagnosed with metastatic breast cancer with left nodal involvement and sternal bone. Past medical history: hypertension, atrial fibrillation, asthma, depression with anxiety, and glaucoma. No known allergies. SF reports sternal pain rating 7/10 (visual analog pain scale, 0–10). Pain: deep, constant, aching, and limits movement. Breathing pain is 6/10 (visual analog pain scale, 0–10) and located in the left middle quadrant. Pain: sharp, spasmodic, worsens with deep breathing and movement. SF reports constipation, dizziness, and worsening depression and anxiety. She recently fell, and her "feet feel heavy" with 3+ pitting edema.

VS: BP 101/70 mm Hg, RR 32 breaths/min, P 88, wt 60 kg (132 lb), ht 5 ft 3 in (160 cm)

Medications: amlodipine 10 mg by mouth daily, albuterol sulfate inhaler: inhale 1 to 2 puffs by mouth every 6 hours as needed for asthma symptoms, amiodarone 200 mg by mouth daily, furosemide 20 mg by mouth twice daily for ankle edema, multivitamin by mouth once daily, latanoprost ophthalmic drops: instill one drop into both eyes once daily, hydrocodone/acetaminophen 5–325 1 tablet by mouth every 4 hours as needed, polyethylene glycol 17 g in 120 mL of water once daily, calcium carbonate 600 mg by mouth twice daily.

What are the two types of pain that SF is experiencing?

What are the other symptoms that SF is reporting during your patient encounter?

What potential drug–drug interactions may exist, and how would you monitor the patient for interactions?

What may be contributing to SF's report of dizziness and leading recent fall?

What medications should be added, changed, or discontinued?

List nonpharmacologic interventions that the practitioner could make to improve the care of SF.

▶ *Nonpharmacologic Treatment*

Provide information, anticipate and proactively prepare the patient and family for worsening symptoms. Identify and attempt to minimize triggers that cause episodes of dyspnea. Educate patient and family regarding treatment of dyspnea, including the use of opioids and benzodiazepines for dyspnea-associated anxiety. Prevent isolation and address spiritual issues that can worsen symptoms. Encourage relaxation and minimize the need for exertion.

Reposition to comfort, usually to a more upright position or with the compromised lung down. Avoid strong odors, perfumes, and smoking in the patient's presence or in proximity. Improve air circulation/quality: provide a draft, use fans, or open windows and adjust temperature/humidity with air conditioner or humidifier.

▶ *Pharmacotherapy*

If no treatable causes can be identified, or when treatments do not completely alleviate distressing symptoms, opioids are first-line agents for treating dyspnea.[21,23,24] Opioids suppress respiratory awareness, decrease response to hypoxia and hypercapnia, vasodilate, and have sedative properties. Low-dose opioids (eg, starting oral dose of morphine ~5 mg) have been shown to be safe and effective in the treatment of dyspnea. Opioid doses should be titrated judiciously. Once an effective dose of an opioid has been established, converting to an extended-release preparation may simplify dosing. When using opioids, anticipate side effects and prevent constipation by initiating a stimulant laxative/stool softener combination.

Nebulized opioids for treatment of dyspnea are controversial. Study results have been inconsistent.[22,23] Nonrandomized studies, case reports, and chart reviews describe anecdotal improvement in dyspnea using nebulized opioids; however, several controlled studies using nebulized opioids have provided inconclusive or negative results.[21,22]

Nebulized furosemide appears effective for dyspnea refractive to other conventional therapies.[24] The hypothesized mechanism of action of nebulized furosemide is its ability to enhance pulmonary stretch receptor activity, inhibition of chloride movement through the membrane of the epithelial cell, and its ability to increase the synthesis of bronchodilating prostaglandins.[24]

Because anxiety can exacerbate dyspnea, benzodiazepines and antidepressants having anxiolytic properties are frequently beneficial. Not all dyspnea is caused by low oxygen saturation. However, oxygen therapy is useful and beneficial for dyspnea if hypoxia is present.

For known etiologies of dyspnea, consider the following:

Bronchospasm or COPD exacerbation: Albuterol, ipratropium, and/or oral steroids are effective for symptom management. Nebulized bronchodilators are more effective than handheld inhalers in patients who are weak and have difficulty controlling breathing.

Thick secretions: If cough reflex is strong, loosen secretions by increasing fluid intake. Guaifenesin may thin secretions; however, its efficacy in the absence of hydration is controversial. Nebulized saline may also help loosen secretions. If the patient is unable to cough, hyoscyamine, glycopyrrolate, or scopolamine patch can effectively dry secretions.[21,23] Oral glycopyrrolate is preferred since it has less propensity to cause the anticholinergic side effect of confusion.

Anxiety associated with dyspnea: Consider benzodiazepines (eg, lorazepam, diazepam).

Effusions: Thoracentesis may be necessary.

Low hemoglobin: Red blood cell transfusion (controversial) or erythropoietin (rarely used in hospice but might have larger role in palliative care).

Infections: Antibiotic therapy as appropriate.

Pulmonary emboli: Anticoagulants for prevention and treatment or vena cava filter placement (rarely used in hospice but might have a larger role in palliative care).

Rales due to volume overload: Reduction of fluid intake or diuretic therapy as appropriate.

Patient Encounter 2

KP is a 74-year-old man admitted to the palliative care service with a diagnosis of moderate Alzheimer disease. Comorbidities include type 2 diabetes mellitus and hyperlipidemia. KP is widowed, resides in the community. He smokes one ppd and consumes two to four beers per day. No known drug allergies. Related symptoms: disorientation to time and place with repeated questioning, difficulty performing, and withdrawal from daily tasks, complex actions and social engagements. Recent weight loss of 25 pounds (11 kg) over 3 months.

VS: BP 125/50 mm Hg, RR 20 breaths/min, P 88, wt 54.5 kg (120 lb), ht 5 ft 6in (168 cm)

Medications: metformin 1000 mg by mouth twice daily, glimepiride 2 mg by mouth once daily, atorvastatin 10 mg by mouth daily, psyllium 1 teaspoonful by mouth dissolved in 8 oz (240 mL) of water twice daily for constipation, donepezil 5 mg by mouth daily.

What parameters should be assessed prior to making changes to or adding additional interventions for KP's current situation?

What medication(s) could be added, changed, or discontinued?

What are some nonpharmacologic interventions for treating KP's symptoms of disorientation, frequent questioning, difficulty with daily tasks, and decline in social engagement?

Nausea and Vomiting

A comprehensive review of nausea and vomiting may be found in Chapter 21.

▶ *Palliative Care Considerations*

Up to 71% of palliative care patients will develop nausea and vomiting with approximately 40% experiencing these symptoms in the last 6 weeks of life. Chronic nausea can be defined as lasting longer than a week and without a well-identified or self-limiting cause, such as chemotherapy, radiation, or infection.[3] Four major mechanisms are correlated with stimulation of the vomiting center (Figure 3–2). Potentially reversible causes of nausea and vomiting should not be overlooked. Causes of chronic nausea in end-of-life patients may include autonomic dysfunction, constipation, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), other drugs, infection, bowel obstruction, metabolic abnormalities (eg, renal or hepatic failure, hypercalcemia), increased intracranial pressure, anxiety, radiation therapy, chemotherapy, or untreated pain.[23,25,26]

▶ *Nonpharmacologic Treatment*

Relaxation techniques may prove beneficial. Strong foods or odors should be avoided and eliminate offending medications.

▶ *Pharmacotherapy*

Clinical features of nausea and vomiting should guide the choice of antiemetics used (for a more comprehensive review, see Chapter 21).

Chemoreceptor trigger zone (CTZ)-induced nausea and vomiting are caused by chemotherapeutic agents, bacterial toxins, metabolic products (eg, uremia), and opioids. Dopamine (D_2),

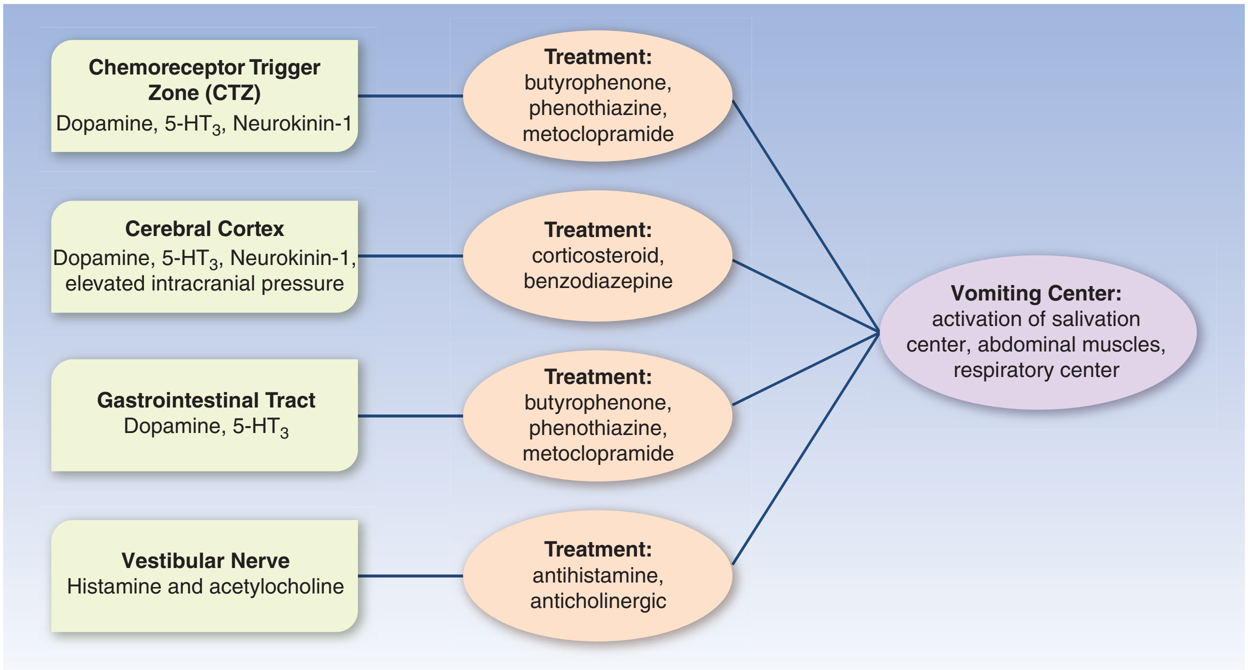

Chemoreceptor Trigger Zone (CTZ)
Dopamine, 5-HT3, Neurokinin-1
Cerebral Cortex
Dopamine, 5-HT3, Neurokinin-1, elevated intracranial pressure
Gastrointestinal Tract
Dopamine, 5-HT3
Vestibular Nerve
Histamine and acetylocholine
Treatment: butyrophenone, phenothiazine, metoclopramide
Treatment: corticosteroid, benzodiazepine
Treatment: butyrophenone, phenothiazine, metoclopramide
Treatment: antihistamine, anticholinergic
Vomiting Center: activation of salivation center, abdominal muscles, respiratory center

FIGURE 3–2. Mechanisms and associated neurotransmitters involved in nausea and vomiting.[7,25,28]

serotonin (5-HT), and neurokinin-1 are the primary neurotransmitters involved in this process. Therapy is based on blocking D_2 with D_2-antagonists including butyrophenones (eg, haloperidol), phenothiazines, and metoclopramide.

Due to receptor specificity, serotonin_3 (5-HT_3) antagonists such as ondansetron, granisetron, dolasetron, and palonosetron have limited usefulness in nausea and vomiting at the end of life.[7,25] They are typically indicated with emetogenic chemotherapy and up to 10 to 14 days posttreatment. Aprepitant is a neurokinin-1 antagonist indicated for the treatment of nausea due to highly emetogenic chemotherapy in combination with a 5-HT_3 antagonist and corticosteroid. Aprepitant should not be used as monotherapy.[23]

Cerebral cortex–induced nausea and vomiting can be caused by anxiety, taste, and smell, and also secondary to increased intracranial pressure. Corticosteroids decrease intracranial pressure due to tumor involvement. Corticosteroids can be effective in nonspecific nausea and vomiting. The mechanism of action is unknown. Anxiolytics, such as benzodiazepines, are used to treat anxiety and "anticipatory" gustatory and olfactory stimulation.[23]

Vestibular nausea and vomiting is triggered by motion. Opioids can sensitize the vestibular center, resulting in movement-induced nausea. Since histamine and acetylcholine are the predominant neurotransmitters, antihistamines and anticholinergics are the drugs of choice in movement-induced nausea and vomiting.

GI tract stimulation occurs through vagal and sympathetic pathways. These pathways are triggered by stimulation of mechanoreceptors or chemoreceptors located in the gut. Gastric stasis, GI obstruction, drugs, metastatic disease, bacterial toxins, chemotherapeutic agents, and irradiation may cause nausea and vomiting. Glossopharyngeal or vagus nerve stimulation in the pharynx by sputum, mucosal lesions, or infection (eg, *Candida*) can also evoke nausea. The major neurotransmitters in the upper GI tract are D_2, acetylcholine, and 5-HT. Metoclopramide is a 5-HT_4 agonist and increases gastric motility above the jejunum, whereas anticholinergics decrease GI spasticity and motility in nausea induced by gut hyperactivity. In high doses, metoclopramide also acts as a 5-HT_3 antagonist.[7,23]

Autonomic failure causes gastroparesis resulting in anorexia, nausea, early satiety, and constipation. Delayed gastric emptying occurs in patients with diabetes mellitus, chronic renal failure, and neurological disorders. Malnutrition, cachexia, lung and pancreatic cancers, HIV, radiotherapy, and drugs such as opioids, anticholinergics, antidepressants, and vasodilators have been associated with autonomic failure and resulting chronic nausea, poor performance, tachycardia, and malnutrition. Evaluate underlying causes, including multiple drugs that may cause gastroparesis. If drug therapy is indicated, metoclopramide is effective in improving gastric emptying.[7]

GI irritation can cause nausea and vomiting due to generalized gastritis, gastroesophageal reflux disease (GERD), or peptic ulcer disease. Histamine_2 (H_2) antagonists or proton pump inhibitors (PPIs) are considered the drugs of choice for ongoing gastritis.

Refractory cases of nausea and vomiting often require judiciously selected combinations of medications from different classes (eg, various combinations of haloperidol, metoclopramide, lorazepam, and dexamethasone).

Pain

A comprehensive review of pain management may be found in Chapter 35.

► *Palliative Care Considerations*

According to the SUPPORT study, 74% to 95% of very ill or dying patients still experience uncontrolled pain.[26] Conducting a comprehensive pain assessment is key to choosing appropriate interventions. Palliative care patients must be evaluated for anxiety, depression, delirium, and other neurological influences that may heighten a patient's awareness or response to pain.

▶ Nonpharmacologic Treatment

Nonpharmacologic treatment is essential. Physical, complementary, and cognitive behavioral interventions reduce the perception of pain and decrease the dose requirements of medications. Examples of such strategies may include providing education, massage, ice, heat, physical therapy, music therapy, imagery, pet therapy, and psychotherapy.

▶ Pharmacotherapy

Pain should be assessed thoroughly and frequently, especially at the onset of treatment. The WHO approach to pain management addresses nociceptive pain (see Chapter 35). Although opioid analgesics are not always necessary or appropriate for all types of pain, most patients with cancer-related pain require opioids. For chronic, constant pain, around-the-clock dosing of analgesics (preferably long-acting agents) is usually necessary and preferred.[27] When titrating opioid doses, increase daily maintenance doses by 25% to 50% if patients routinely require three or more breakthrough doses per 24 hours as a result of around-the-clock maintenance dose failure. The around-the-clock maintenance doses should not be increased if breakthrough doses are used only for incident pain, such as increased activity or dressing changes.

Fentanyl transdermal patches may be appropriate in some; however, many end-of-life patients experience fat and muscle wasting and dehydration, resulting in reduced and variable absorption. Fentanyl transdermal patches have a slow onset of action, contributing to difficulty in dose titration.[7]

Only short-acting opioids should be used for breakthrough pain (eg, immediate-release morphine, oxycodone, and hydromorphone are common examples). The dose of short-acting opioids for the treatment of breakthrough pain should be equal to 5% to 20% of the total daily maintenance dose. Frequencies for breakthrough dosing should not exceed the following:

- **Oral:** Every 1 to 2 hours
- **Subcutaneous:** Every 20 to 30 minutes
- **IV:** Every 8 to 20 minutes

Monitor for and appropriately treat common side effects of opioids, including constipation, nausea and vomiting, itching, and transient sedation. Because constipation occurs with all chronic opioid therapy, prevention is imperative. Stimulant laxatives (senna or bisacodyl) with or without a stool softener (docusate) are the drugs of choice.[7] Myoclonus, delirium, hallucinations, and hyperalgesia are possible signs of opioid-induced neurotoxicity and require rotation to another opioid or dose reduction. Respiratory depression is uncommon with the appropriate opioid dose. However, if dangerous opioid-induced respiratory depression does occur, small doses (0.1 mg) of the μ receptor antagonist naloxone are appropriate and can be repeated as necessary. The goal is to increase respirations to a safe level while preventing the patient from experiencing a loss of pain control.

Different types of pain may require specific types of analgesics or adjuvant medications. Identification and treatment of these separate pain types will help avoid unnecessary opioid dose escalations and opioid side effects. Examples of pain types commonly seen in patients with advanced illness are as follows. See Figure 3–3 for medication options.

Visceral pain (nociceptive pain induced by stretching or spasms of visceral organs including the GI tract, liver, and pancreas) should be treated with an adjuvant such as an anticholinergic agent or, if inflammation is associated with the pain, corticosteroids.

Bone pain (metastatic site of cancer) is best treated with NSAIDs or corticosteroids in addition to standard opioid therapy.

Neuropathic pain (pain caused by damage to the afferent nociceptive fibers) can be managed with tricyclic antidepressants, antiepileptic drugs, tramadol, tapentadol or *N*-methyl-D-aspartate antagonists, such as ketamine. Methadone is an opioid μ-agonist that has a role in neuropathic pain given its added *N*-methyl-D-aspartate antagonist activity. Methadone has a very long half-life compared to most other opioids, except buprenorphine. It should be used with caution and under the close supervision of clinicians experienced in its use for pain management.

Terminal Secretions

▶ Palliative Care Considerations

Terminal secretions, or death rattle, is the noise produced by the oscillatory movements of secretions in the upper airways in association with the inspiratory and expiratory phases of respiration.[28,29] As patients lose their ability to swallow and clear oral secretions, accumulation of mucus results in a rattling or gurgling sound produced by air passing through mucus in the lungs and air passages. The sound does not represent any discomfort for the patient. However, the sound is sometimes so distressing to the family that it should be treated. Terminal secretions are typically seen only in patients who are obtunded or are too weak to expectorate. Drugs that decrease secretions are best initiated at the first sign of death rattle because they do not affect existing respiratory secretions. These agents have limited or no impact when the secretions are secondary to pneumonia, pulmonary congestion, or edema.[30]

▶ Nonpharmacologic Treatment

Position the patient on their side or in a semiprone position to facilitate drainage of secretions. If necessary, place the patient in the Trendelenburg position (lowering the head of the bed); this allows fluids to move into the oropharynx, facilitating an easy removal. Do not maintain this position for long due to the risk of aspiration. Oropharyngeal suctioning is another option but may be disturbing to the patient and visitors. Fluid intake can also be decreased, as appropriate.[23,30]

▶ Pharmacotherapy

Anticholinergic drugs remain standard therapy for prevention and treatment of terminal secretions due to their ability to effectively reduce future production of secretions.[28–30] Drugs used for this indication are similar pharmacologically, and one can be selected by anticholinergic potency, onset of action, route of administration, alertness of patient, and cost. The most used anticholinergic agents are atropine, hyoscyamine, scopolamine, and glycopyrrolate.

Anticholinergic side effects include blurred vision, constipation, urinary retention, confusion, delirium, restlessness, hallucinations, dry mouth, and heart palpitations. Unlike the other anticholinergics, glycopyrrolate does not cross the blood–brain barrier and is associated with fewer CNS side effects, and it is often preferred if the use of anticholinergic intervention is prolonged for more than 7 to 10 days. Glycopyrrolate is a potent drying agent when compared with other agents and has the potential to cause excessive dryness.[30]

Advanced Heart Failure

▶ Palliative Care Considerations

Heart failure symptoms at the end of life may include hypotension, volume overload, edema, and fatigue. Patients should be

Pharmacologic Adjuvants: Nociceptive Pain	
Bone Pain *(inflammatory)*	
Nonsteroidal anti-inflammatory drug (NSAID)	
Ibuprofen (Motrin)[a] Naproxen (Naprosyn)[a] Celecoxib (Celebrex)[b] Meloxicam (Mobic)[b]	- Often first line for untreated diffuse bone pain - Similar efficacy among NSAIDs; however, the risks of GI bleeding, GI ulcers, renal toxicity, and cardiovascular concerns are higher among the nonselective NSAIDs - Selective NSAIDs have less GI effects, but retain risk of renal toxicity
Bisphosphonates	
Zolendronic acid (Zometa) Pamidronate (Aredia) Ibandronate (Boniva)	- Role in treating diffuse bone pain - Intravenous administration with renal monitoring - Monitor: osteonecrosis of the jaw, follow-up with dental evaluation
Steroids	
Dexamethasone (Decadron) Methylprednisolone (Medrol) Prednisone (Deltasone)	- May be preferred over NSAIDs for diffuse bone pain in patients experiencing anorexia and fatigue - Burst and taper recommended for rapid pain control - Monitor: edema, glucose, insomnia, GI upset - Less edema with mineralcorticosteroid - Administer doses earlier in the day with food to avoid insomnia and GI upset
Visceral Pain	
Anticholinergic/Antispasmodics	
Dicyclomine (Bentyl) Glycopyrolate (Robinul IV) Hyoscyamine (Levsin) Scopolamine (Transderm Scop)	- Monitor: *(especially in elderly)* constipation, dry mouth, confusion, dizziness, urinary retention - Steroids may also be used concurrently for visceral pain with associated inflammatory processes (ie, pleuritic pain, capsular organ pain, diffuse intestinal cancer) - Often used short term for treatment of terminal secretions “death rattle”
[a]Nonselective NSAID [b]COX-II selective NSAID	

FIGURE 3–3. Pharmacologic adjuvants for the treatment of bone pain and inflammatory pain.[7,23,26]

assessed to confirm that symptoms are related to heart failure rather than other disease states to ensure appropriate treatment.[31]

Goals for advanced heart failure treatment differ from traditional heart failure management. Drug therapy focuses on symptom management rather than improving mortality. Prevention of cardiovascular disease through cholesterol reduction is no longer necessary.

▶ *Nonpharmacologic Treatment*

Patients should maintain a comfortable position with feet elevated to minimize lower leg fluid accumulation. Minimizing high-salt foods and limiting fluid intake can help reduce fluid accumulation. At this stage in heart failure, comfort becomes the primary initiative.

▶ *Pharmacotherapy*

As patients approach the end of life, it is difficult to determine when certain medications for heart failure should be dose reduced or discontinued. The following general principles may help serve as a guide. However, patient history, prognosis, and current condition should be evaluated to determine appropriateness.

If a patient becomes symptomatic due to hypotension, angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and/or β-adrenergic blocker doses should be reduced or discontinued. For β-adrenergic blockers, in particular, this should be done gradually to avoid significant clinical deterioration. If volume overload occurs or persists while taking β-adrenergic blocker therapy, consider tapering off the medication. Likewise, for patients experiencing fatigue while taking a β-adrenergic blocking agent, consider tapering the dose *only if* their heart rate does not increase with exertion. Consider discontinuing the ACE inhibitor (or the angiotensin receptor blocker) if the patient’s renal function deteriorates (eg, cardiorenal syndrome).

In patients with excessive fluid overload where sodium and water intake restrictions are not effective or not possible, consider increasing the diuretic dose. However, vascular dehydration can occur in some patients with end-stage heart failure if the dose of diuretic is excessive.

Digoxin toxicity is common; therefore, patients should be carefully monitored and therapy adjusted or discontinued as appropriate. The symptoms of digoxin toxicity include complaints of anorexia, nausea and vomiting, visual disturbances, disorientation, confusion, or cardiac arrhythmias.[31]

Hydroxymethylglutaryl coenzyme-A (HMG-CoA) reductase inhibitors (and other cholesterol-lowering medications) are likely to have a long-term effect rather than a palliative effect.

Figure 3–1 provides a list of agents that improve functional status in advanced heart failure patients.

OUTCOME EVALUATION

KEY CONCEPT Involving the patient, family, and caregivers in the development of the therapeutic plan demonstrates responsible palliative care. Before implementation of drug therapy, the patient, family, and caregiver should be involved with decision making. The practitioner should provide information about all reasonable options for care so that the patient, family, and caregivers can collaborate with the healthcare team to meet their combined goals. **KEY CONCEPT** Positive therapeutic outcomes include resolution of symptoms while minimizing adverse drug events. When treating symptoms pharmacologically, adverse drug events must be avoided or minimized to prevent negative outcomes.

Patients with life-limiting diseases have emotional and spiritual issues deserving attention by trained professionals. Addressing these concerns and providing support and coping skills can dramatically reduce medication requirements for symptom control. Psychosocial and spiritual support is not only directed toward the patient in palliative care but also supports the family during the time of the illness and after the death of their loved one.

KEY CONCEPT Patient and caregiver education is vital to ensuring positive outcomes. If the patient and caregiver are unaware of the purpose and goals for interventions used in palliative medicine, adherence to regimens will be hindered and outcomes compromised. Education regarding the role and value of the palliative care team will allow the patient and family to understand why palliative care is important to their overall quality of life. Patients will achieve the best possible outcomes when practitioners incorporate the interdisciplinary palliative care approach to care early in the disease progression of patients with life-limiting illnesses.

Patient Encounter 3

JM is a 45-year-old man diagnosed with colon cancer. He received palliative chemotherapy with localized radiation for a few months with the last chemotherapy and radiation administered 4 weeks ago. The interventions were unsuccessful in limiting tumor growth, which has now metastasized to liver and brain. JM has jaundice with mild ascites with no pruritus. JM's chief complaint today is uncontrolled nausea and vomiting, which worsens upon awakening and is unresponsive to antiemetics. The nausea improves throughout the day. The oncologist prescribed ondansetron 8 mg by mouth every 8 hours as needed. JM has taken six doses over 3 to 4 days without improvement in his morning nausea. Comorbidities: hypertension, depression with recent uncontrolled anxiety. Allergy: codeine (reaction unknown). Medications: tramadol 50 mg 1 to 2 tablets by mouth every 4 to 6 hours as needed for pain, ibuprofen 200 mg 1 to 2 tablets by mouth every 4 to 6 hours as needed for pain, ondansetron 8 mg by mouth every 8 hours as needed for nausea.

What are potential causes of JM's nausea and vomiting? Based on this differential list, what questions would you ask JM during your assessment of his nausea and vomiting?

What potential drug–drug interactions and side effects exist in this patient?

What medications could be added, changed, and/or discontinued?

How does the patient's reported allergy to codeine impact potential treatment options?

Patient Care Process

Collect Information:

- Evaluate physical examination, review of systems and relevant laboratory findings and assess for symptoms related to or worsened by their current hospice diagnosis.
- Perform medication reconciliation (prescription, OTC medications, herbal).
- Determine goals as related to the hospice care plan.
- Identify cultural, spiritual, or ethnic traditions that impact patient care and incorporate those aspects into the plan of care.

Assess the Information:

- Ensure medications confer functional status benefit rather than only survival (see Figure 3–1) and that this supports the patient's goals.
- Establish realistic medication outcomes prior to initiating or titrating a medication for palliative care.
- Verify prescription coverage or institutional formulary when adding medications.
- Provide preventative care recommendations (ie, immunization, annual health screening, etc.) and discuss health benefits.

Develop a Care Plan:

- Based on prognosis of a health condition, determine if continuing medication for preventative or long-term management is appropriate.
- If laboratory monitoring is discontinued, medications with a narrow therapeutic index may be discontinued.
- Ensure medications are appropriate for the patient's functional status.
- Evaluate adherence strategies and monitor for side effects.
- Before adding a medication to treat symptoms, ensure that the symptom is not attributable to current medications.

Implement the Care Plan:

- Involve the patient, family, and caregivers in development of pharmacologic/nonpharmacologic strategies based on patient's goals.
- Share patient preferences, priorities, and goals with healthcare providers.
- Communicate resuscitation preferences with caregivers and healthcare providers.

Follow-up: Monitor and Evaluate:

- Monitor results following initiation of drug therapy, and discuss findings in context to symptom prioritization, goals, and outcomes.
- Continuous evaluation of therapy as functional status (ie, ambulation, swallowing, continence) changes, and ensure safe and effective medication use.
- Encourage the patient, family, and caregivers to contact the hospice or palliative team with questions.
- Bimonthly reviews of the patient's medical condition, medications, and goals occur during hospice interdisciplinary meetings.

Abbreviations Introduced in This Chapter

5-HT	5-Hydroxytriptophan (serotonin)
ACE	Angiotensin-converting enzyme
ALS	Amyotrophic lateral sclerosis
ARB	Angiotensin receptor blocker
CHF	Chronic heart failure
COPD	Chronic obstructive pulmonary disease
CTZ	Chemoreceptor trigger zone
CVA	Cerebrovascular accident
ESRD	End-stage renal disease
GERD	Gastroesophageal reflux disease
HMG-CoA	Hydroxymethylglutaryl coenzyme-A
NSAID	Nonsteroidal anti-inflammatory drug
PEG	Percutaneous endoscopic gastrostomy
PPIs	Proton pump inhibitors
SSRI	Selective serotonin reuptake inhibitor
WHO	World Health Organization

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4 Critical Care Pharmacotherapy

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Understand the function and role of an intensive care unit (ICU).
2. List the healthcare members that comprise a critical care or intensive care unit team.
3. Differentiate components that comprise an intensive care unit not seen on general floor.
4. Identify key areas in which critical care healthcare providers have impact in patient care.
5. Explain the differences in types of vascular access utilized in critically ill patients for administration of fluids and medications.
6. Formulate a recommendation for nutrition as well as subsequent glycemic control management in the ICU.
7. Discuss indications for neuromuscular blockade in the critically ill patients.
8. Contrast mechanical ventilation modes and parameters of invasive mechanical ventilation.
9. Identify risk factors and prevention strategies for stress ulcers.
10. Design a pain management plan for the critically ill patients.

INTRODUCTION

KEY CONCEPT The intensive care unit (ICU) is a designated place within an institution that is highly specialized and sophisticated, dedicated to managing critically ill patients with potentially recoverable diseases who would benefit from close observation and treatment. There are various types of ICUs including those dedicated to the management of patients with, but not limited to, medical, surgical, traumatic, pediatric, cardiac, or neurological conditions. Typically, the ICU is staffed and equipped for the highest level of acuity possible, given the illness of patients, with designated teams trained in **critical care medicine**.

Patients within the ICU typically have more invasive indwelling devices (eg, intravenous catheters) and procedures, require higher levels of respiratory support than patients on general floors, and have a higher severity of illness. The illness of these patients often leaves them immobile, more **obtunded**, at risk for increased multiorgan failure, and malnourished, requiring frequent monitoring and, often, more nutritional support. Overall, the main functions of an ICU and critical care team are to provide optimal therapies and adequate monitoring for those who may have a high risk of sudden death.

While each specialized ICU may have some slight variations, they all will be equipped to handle mechanical ventilation, circulatory support, renal replacement therapies, and management of shock. The specialized services offered in the ICU are staffed for continuous service, 24 hours a day, should a patient's condition decline. Additionally, there are times a patient may not require the equipment listed above but have disease states or be placed on pharmacologic therapies that necessitate close monitoring, that is not possible on general wards. Each ICU will have different criteria for admission and the realization that patients have high acuity, need for close monitoring, and have a reversible disease state.

Since ICUs are staffed with continuous complex equipment, services, and personnel, they often can incur the highest financial burden on institutions. Therefore, patients are often prioritized for ICU admission to ensure they are not so sick that their care would be futile and, conversely, they are sick enough to have resources allocated toward their recovery that could not be provided elsewhere.[1] Admissions to the ICU can be planned or emergent. For example, a patient undergoing a coronary artery bypass grafting is often a planned admission, whereas, a patient suffering from a traumatic brain injury will require an emergency admission. Formal criteria for admission will likely be institution specific but should be at the discretion of the ICU, general floor, and hospital administration team to ensure patients are being treated at the optimal level of care. Similarly, there are no formal discharge criteria. Given the greater cost associated with ICU beds, patient needs are constantly evaluated to identify those who no longer require the higher intensity of care. Once the acute illness has stabilized and strenuous monitoring or therapy is no longer required, patients are often transitioned to a lower level of care. Similarly, once a patient reaches the point of medical futility, they may be transferred from the ICU into a palliative or comfort care unit.

While the immediate illness of a patient who has been discharged from the ICU may subside, the long-term effects of critical illness has been a focus of clinicians in recent years. **Post-intensive care syndrome** (PICS) describes the disability that is noted after discharge from the ICU and critical illness.[2] Impairments which have been described include, but are not limited to, issues with cognition, mental health disabilities, and recurring physical ailments, specifically neuromuscular weakness. Since PICS has been reported to occur in up to 25% of all ICU survivors, clinician's efforts are aimed at mitigating not only death and morbidity in the short term but also how best to prevent ailments associated with ICU admission long term.

EPIDEMIOLOGY AND ETIOLOGY

It is estimated that over 5 million patients are admitted to the ICU within the United States annually with this number expected to rise.[3] The majority of admissions that require ICU care are adult patients with respiratory failure requiring ventilator support, acute myocardial infarction, intracranial hemorrhage or acute ischemic stroke, patients requiring cardiovascular procedures, and sepsis with shock.

The American Hospital Association Hospital Statistics system 2015 survey reported there are 2862 acute care registered hospitals with 2814 of these institutions having at least one ICU bed.[4] In the decade between 2000 and 2010 annual critical care medicine costs increased by 92% from $56.6 billion to $108 billion which represented 0.72% of the entire US gross domestic product.[5] Multiorgan failure, cardiovascular compromise, and sepsis are the leading causes of death within the ICU in the United States.[6] The pharmacotherapies offered within the ICU oftentimes contribute a large percentage of an institution's budget.

ROLES OF VARIOUS HEALTHCARE PROFESSIONALS IN ICUs

The management of critically ill patients requires a robust pool and broad range of healthcare providers who have developed a skill set to aid in the treatment of this subset of patients. Historically, paternalistic medicine, where the physician is regarded as the ultimate authority on the care of the patient, has since been shifted to allow for a team approach while also promoting more autonomy to patients in the decisions of their care. While physicians can often be seen as the "coach" of the team, each member serves a unique role utilizing their highly trained skill set. **KEY CONCEPT** While each ICU team will be constructed differently, the Society of Critical Care Medicine (SCCM) recommends the team that consists of an intensivist, physician assistant or advanced practice registered nurse, critical care nurse, pharmacist, registered dietitian, respiratory therapist, occupational and physical therapist, chaplain, and support staff.[7]

The intensivist is a physician who is trained to care for critically ill patients; they often have subspecialty training in surgery, internal medicine, neurology, pediatrics, nephrology, pulmonary/critical care, or anesthesiology. As the head of the care team the intensivist is responsible for overseeing all aspects of patient care while relying on the rest of their healthcare providers to maximize therapies in each respective area. Their primary role includes, but is not limited to, obtaining medical histories, ordering, and interpreting different diagnostic tests and performing various medical procedures in caring for critically ill patients. In addition to patient care duties, the intensivist often is responsible for the training of younger physicians including interns, residents, and fellows dedicated to the care of critically ill patients.

A physician assistant or advanced practice registered nurse within the ICU acts as an extension of the intensivist. Under intensivist supervision, these midlevel practitioners can perform many of the same functions as the intensivist. Many institutions do not have 24-hour intensivist support, and physician assistants and nurse practitioners can provide their skill sets in the hours an intensivist may not be present. In recent years, advances in technology have allowed for electronic ICU coverage for smaller institutions who may not have an intensivist present during the day, as well as coverage at night.

The critical care nurse is the most visible bedside healthcare provider serving as a liaison between the patient, family, and ICU team. The nurse skill set includes, but is not limited to, obtaining and monitoring samples for laboratory tests, placement of intravenous lines, administration of medications, assessing vital signs, and executing the daily plans developed by the ICU team. Critically ill patients are hyperdynamic requiring extensive monitoring and treatments which necessitate nurse to patient ratios that are lower compared to general floors.

The critical care pharmacist provides pharmacotherapeutic expertise to the ICU team. The scope of what a critical care pharmacist entails has been outlined by the American Society of Health-System Pharmacists, SCCM, and American College of Clinical Pharmacy.[8] The critical care pharmacist is responsible for all aspects of drug therapy management including interpreting test and diagnostic data to recommend therapeutic options, dose optimization, medication reconciliation, monitoring for drug–drug or drug–disease interactions, and education to healthcare providers or patients. Additionally, as many members of the ICU team constantly rotate on or off the critical care service, the pharmacist often is the member who is able to provide key information on the history or management of the patient. Lastly, the critical care pharmacist has a tremendous role in managing pharmacological therapies as it relates to transitions of care, such as transitioning patients from parenteral to oral treatments. Patients are initiated on medications during the acute illness that may not be appropriate once the process has subsided; therefore, the pharmacist's perpetual review of the medication profile can be crucial to prevent inappropriate therapies from reaching the patient or medication errors.

During critical illness, patients often have complex caloric and other nutritional needs that are evaluated by a registered dietitian. Nutritional needs are assessed not only for the appropriate caloric totals but appropriate combination of macro- and micronutrients. In conjunction with a critical care pharmacist, dietitians work to provide patients with enteral or parenteral feeding goals. The registered dietitian interprets laboratory results and diagnostic tests to ensure appropriate caloric needs are met.

Frequently, patients with critical illness develop respiratory distress or failure that requires various forms of oxygenation or ventilator support. A respiratory therapist works in conjunction with the critical care team to support these needs with various forms of supplemental oxygen, noninvasive mechanical ventilation, or invasive forms of mechanical ventilation. The respiratory therapist, in conjunction with the intensivist or nurse, will follow protocols to adjust or support the oxygenation or ventilatory needs of the patient.

A large portion of the management of critical illness is to ensure survival; however, the quality of life post illness is just as important. Physical therapists work to ensure appropriate muscle, bone, tissue, and nerve function to improve daily life activities. Occupational therapists work with patients to help regain life skills to ensure that their activities of daily living are maximized. Early mobility, with physical therapists, and continued focus on living as independently as possible, by occupational therapists, has been a growing area of research in critical care. Speech pathologists are trained specialists who work with patients in the management of communication and swallowing disorders secondary to critical illness.

During critical illness there is a tremendous amount of emotional support needed for the patient, family, and ICU team.

Patient Encounter Part 1

A 62-year-old man presents to the neurological ICU after experiencing a massive ischemic stroke to his middle cerebral artery. In the emergency department, the patient received intravenous thrombolytic therapy as well as endovascular thrombectomy of the clot. While unable to speak due to his stroke, his previous admissions showed his wife was his surrogate and did not have advanced directives in place.

What information presented would warrant this patient to have an ICU admission?

Which healthcare providers do you believe should be a part of this patient's neurological ICU team?

Emotional and spiritual support is often provided by a chaplain or, at a minimum, organized so that the patient's or family's spiritual needs are met during the time of critical illness. The chaplain has a large role during end-of-life care to support the needs of the patient, family, and those involved in the care of the patient.

Lastly, there are numerous support staff that aid the ICU team during the management of critical illness. Environmental services, child life specialists, hospital informatics, and many more are needed to have a functioning ICU.

INTRAVENOUS ACCESS

KEY CONCEPT Establishment of intravenous (IV) access is essential for care of critically ill patients. Venous access is a direct route into the bloodstream for administration of medications, fluid resuscitation, delivery of parental nutrition, to administer nonpharmacologic treatments such as dialysis, or to obtain blood for analysis or noninvasive hemodynamic monitoring. Types of venous access devices (VADs) include peripheral IV lines, midline peripheral lines, peripherally inserted central catheters (PICCs), and central catheters.[9] Peripheral lines are most often placed in the arm or hand as well as in the foot. Guidelines recommend rotating these sites every 72 to 96 hours to prevent phlebitis.[9] Central catheters terminate in the veins within the thoracic cavity and are indicated for the administration of medications which may cause harm if administered peripherally, such as vesicants (examples include calcium chloride, hypertonic saline, and vasopressors or chemotherapy). Further, central catheters are placed for administration of intravenous products in large quantity or over a longer period of time, for long-term access for procedures, or when peripheral access cannot be obtained.

Midline peripheral catheters are alternatively placed within the antecubital vein and extend roughly 20 cm long, allowing for a longer duration of retention (1–4 weeks) as they are at less risk of failure from displacement compared to shorter peripheral lines. However, as the tips of these catheters terminate prior to the central veins, their use has fallen out of favor secondary to an increase in PICCs. While central venous catheters are typically placed within the internal jugular, subclavian, or femoral vein, a PICC is a central line that is placed peripherally in the basilica, brachial, or cephalic vein but terminates in a central vein. A PICC can be in place up to 6 months. While skin-tunneled catheters and implanted ports are considered types of central access, most patients in the ICU receive nontunneled catheters given they are intended for more short-term use. Catheters range in length and diameter, ranging typically from 14 gauge (2.1 mm diameter and 45 mm length) to 26 gauge (0.6 mm diameter with 19 mm length) and are color coded. Selection of catheter is determined based on patient anatomy, provider preference/expertise, overall desired use of the catheter, and device risk. Wider diameters are necessary for faster or large infusion volumes but can be at higher risk of complications.[10,11] Complications of VAD include infection, thrombosis, **pneumothorax**, **hematoma**, among others.[11]

An alternative access site is intraosseous (IO). This catheter is placed directly into the bone marrow using a drill, providing a noncollapsible venous entry. This mode should only be used when IV access is not obtainable. Locations for access include the proximal femur, proximal humerus, and the tibial tuberosity. All medications can be administered via IO; however, **pharmacodynamics** and **pharmacokinetics** can be altered.

PHARMACOKINETICS AND PHARMACODYNAMICS

KEY CONCEPT Multiple pharmacokinetic aspects may be altered within the ICU population. Within critical illness, decreased subcutaneous or gastrointestinal perfusion may occur secondary to shock or vasopressor use.[12] Because of altered perfusion, in combination with the use of enteral nutrition, decreases in area under the curve (AUC) for some medications are seen. Drug distribution can be altered within the critically ill for a variety of reasons. Decreases in cardiac output from shock or mechanical ventilation can decrease drug distribution. Poor peripheral perfusion can result in a reduction in free drug concentration at local tissues. Fluid resuscitation can increase volume of distribution for hydrophilic medications, decreasing peak concentration.[12] Reductions in serum albumin and increases in α1-acid glycoprotein can result in alterations in free drug concentrations (eg, phenytoin). Hepatic blood flow can be reduced while hepatic enzymes can be inhibited and/or induced by critical illness or commonly administered medications, resulting in potential for both reduction and increase of low extraction ratio medications. Regarding elimination, roughly 25% of patients with critical illness present in acute kidney injury (AKI), decreasing the clearance of renally eliminated drugs.[12] Alternatively, patients can present with augmented renal function that increases clearance. The use of renal replacement therapies for AKI can have a variable effect on clearance depending on type of therapy and drug (see Chapter 26).

Regarding pharmacodynamics, doses of medications are titrated or monitored based on clinical parameters, such as blood pressure, sedation, and pain. Most studies of pharmacodynamics in this population have centered on antimicrobials as they do not have a an effect that can be visually monitored clinically and are often prescribed within the ICU.[13] An increasing amount of evidence supports prolonged versus standard interval administration of time-dependent antibiotics (such as 3-hour cefepime or meropenem infusions vs 30-minute infusions).[13] Further, increasing evidence supports the use of vancomycin continuous infusion given the potential increase in AUC/minimum inhibitory concentration (MIC) ratio. Aminoglycosides or other purely concentration-dependent antibiotics rely on high maximum concentration/MIC ratios. Given the pharmacokinetic alterations in critically ill patients, these anti-infectives may require higher empiric dosing than a noncritically ill population.

INVASIVE AND NONINVASIVE VENTILATION

KEY CONCEPT Mechanical ventilation, the provision of an external source of ventilation and often oxygenation, is used frequently within the ICU for patients presenting in respiratory failure and can be either noninvasive or invasive.[14] Noninvasive ventilation, such as bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP), is oxygen supplementation administered without placement of an endotracheal tube (ETT). BiPAP, when worn continuously, requires ICU level of care for risk of aspiration. Alternatively, nighttime BiPAP can be worn on general medical floor. Noninvasive ventilation can decrease invasive ventilation (endotracheal intubation), decreasing complications, such as ventilator-associated pneumonia as well as death, and decreasing overall duration of stay.[14] Noninvasive ventilation can be provided via a nasal mask, helmet, or an oronasal mask (facial mask), with the latter being the most common. Guidelines currently recommend noninvasive ventilation for patients with hypercapnia secondary to an exacerbation of chronic obstructive pulmonary disease, cardiogenic edema, immunocompromised, postoperative, palliative care, trauma, postextubation in high-risk patients, and weaning in hypercapnia, all in the setting of acute respiratory failure.[15]

Invasive ventilation can be performed via an ETT or tracheostomy tube. The ETT allows for ventilator support while also providing airway protection. Breaths on the mechanical ventilator are administered via triggering, defined as the initiation of a breath, and cycling, which is simply defined as the end of a breath. Breaths are classified as volume, pressure, or time cycled. Volume breaths end after a certain volume is delivered; pressure breaths end after a certain pressure is reached; and time cycles end dependent on a prespecified duration.[16] Mechanical ventilation can be either full support, delivering all ventilatory needs, or partial support, acting as a supplement to the patient's own respiratory effort. Important parameters for the mechanical ventilator can be found in Table 4–1. A full review of mechanical ventilation is beyond the purpose of this chapter. Endotracheal intubation also uniquely provides an additional route of drug administration for medications. Medications that can be administered via the ETT include naloxone, atropine, vasopressin, epinephrine, lidocaine, and others. Inhalation solutions and metered-dose inhalers (MDIs) can be administered via the ventilation circuit but not dry powder inhalers.

After initial noninvasive airway approaches have been exhausted, clinicians may consider endotracheal intubation for invasive ventilation that will likely require **rapid sequence intubation** (RSI). RSI is an airway procedure that aims to reduce the incidence of complications of placing an endotracheal tube. During the procedure agents are utilized to induce an amnestic state while also causing muscle relaxation to allow for easier passage of the tube to the lungs. Commonly utilized medications for RSI include propofol, ketamine, etomidate, midazolam, fentanyl for induction, and rocuronium, vecuronium, and succinylcholine for paralysis.

Table 4–1

Common Ventilator Parameters

Parameter	Definition	Normal Range
Tidal volume	Volume of air inhaled or exhaled during a normal respiratory cycle	6–8 mL/kg
Respiratory rate	Breaths given per minute	8–12 breaths/min
Fio$_2$	Fraction of inspired oxygen	21% room air
I/E ratio	Ratio of inspiratory to expiratory time	1:2
PEEP	Pressure within the lungs after exhalation phase to increase alveoli diffusion	5 cm H_2O (0.5 kPa)
Peak pressure	Pressure at end of inspiration	40 cm H_2O (3.9 kPa)
Plateau pressure	Pressure in alveoli between inspiration and expiration	< 30 cm H_2O (2.9 kPa)

I/E, inspiratory: expiratory ratio; PEEP, positive end expiratory pressure.

While listed as paralysis with induction, it is important to note that paralysis without induction should never occur. When deciding the appropriate agents for RSI, the healthcare provider must take into consideration numerous confounders including patient's vital signs, comorbidities, medication pharmacokinetics, and pharmacodynamics. Table 4–2 gives an overview of the commonly utilized medications for paralysis and induction during RSI. Understanding appropriate pharmacokinetic, pharmacodynamic, and adverse events profiles can aid clinicians at selecting the ideal agent for their patient.

PAIN, AGITATION, DELIRIUM, AND SLEEP

Pain, agitation, delirium, immobility, and sleep (PADIS) management in patients within the ICU is complex. Each modality is highly individualized to the patient and is determined by a multitude of factors including, but not limited to, illness severity, comorbidities, concurrent medications, and patient demographics. Practice guidelines have continued to evolve as the understanding of the pathophysiology of critical illness changes with the approach to PADIS.[17]

Patients experience pain in a highly individualized manner. Acute, chronic, or acute-on-chronic pain can manifest in different ways, and understanding that the source of pain, whether it be somatic, visceral, or neuropathic pain (see Chapter 35), also produces phenotypically separate patterns can be quite challenging for management. Pain itself, can be considered as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[17] ICU clinicians will rely on a patient's self-reported pain; however, if a patient is unable to communicate the experience to providers, this does not negate the fact they may still be experiencing pain and can be assessed by other objective tools such as the Critical Care Pain Observation Tool or Behavioral Pain Scale. There are negative consequences associated with untreated pain, therefore, the PADIS guidelines attempt to standardize the treatment of pain with a multimodality pharmacological approach. The utilization of opioids, such as fentanyl, morphine, and hydromorphone, remains the cornerstone of treatment for pain in the ICU for mechanically ventilated and nonmechanically ventilated patients. However, as opioids have known adverse drug events, like oversedation, respiratory depression delirium, hypotension, and decreased gastrointestinal (GI) motility, the guidelines have promoted the use of a multimodal approach to pain. Concurrent treatments such as acetaminophen, nonsteroidal anti-inflammatory drugs, lidocaine, ketamine, and neuropathic pain medications (eg, gabapentin, pregabalin) have roles in select patients at reducing daily **morphine equivalents**. Patients often will receive combinations of these therapies via the intravenous, oral, rectal, or even transdermal routes. **KEY CONCEPT** The practice of analgesia-first sedation, or **analgosedation**, is a sedative-sparing technique which has shown improved ventilator-free days as well as reductions in ICU length of stay. Fentanyl is the most common opioid used in the United States for analgesic sedation. In addition to pharmacologic management of pain there are recommendations for nonpharmacologic therapies such as music, pet,

Table 4–2

Commonly Utilized Induction and Paralysis Agents

Agent	Utilized for Induction or Paralysis	Dosing	Adverse Reactions
Midazolam	Induction	0.2–0.3 mg/kg IV	Respiratory depression, hypotension
Etomidate	Induction	0.3 mg/kg IV	Adrenal suppression
Propofol	Induction	1–2 mg/kg IV	Hypotension, bradycardia, respiratory depression
Ketamine	Induction	0.5–1.5 mg/kg IV	Increased secretions, nystagmus, laryngospasm
Succinylcholine	Paralysis	1–1.5 mg/kg IV	Hyperkalemia, bradycardia, malignant hyperthermia
Vecuronium	Paralysis	0.1 mg/kg IV	Caution with hepatic or renal dysfunction
Rocuronium	Paralysis	0.6–1.2 mg/kg IV	Caution with hepatic or renal dysfunction

massage, temperature control, and relaxation techniques, which are beyond the scope of this chapter.

Anxiety is quite prevalent within the ICU, especially in mechanically ventilated patients, and sedatives are often needed to reduce the stress associated with routine ICU care. As previously discussed, patients within the ICU often have an analgesia-first approach to sedation but, if anxiety is not relieved by this approach, agents like benzodiazepines, propofol, or dexmedetomidine are utilized in the mechanically ventilated patient. Validated scales, such as the Richmond Agitation-Sedation Scale (RASS) or Riker Sedation-Agitation Scale (SAS), are utilized to assess the degree of sedation. A paradigm shift has occurred in the management of critically ill mechanically ventilated patients from utilizing deep levels of sedation, considered to be comatose, to lighter levels, or arousable levels, of sedation which has improved clinical outcomes. However, deep levels of sedation are needed for refractory status epilepticus, paralysis, or refractory elevations in intracranial pressures. The PADIS guidelines recommend utilizing nonbenzodiazepines, such as propofol or dexmedetomidine, to maintain a light goal of sedation and to minimize delirium.

Delirium is a clinical diagnosis that is detected utilizing the Confusion Assessment Method for the ICU scale (CAM-ICU) and is associated with worse outcomes, such as increased associated healthcare costs, hospital, ICU length of stays, and mortality. At this time there are no Food and Drug Administration (FDA)-approved treatments for delirium, and management strategies include trying to prevent delirium by reducing benzodiazepine utilization, patient reorientation, improving sleep hygiene, early mobilization, and lighter sedation strategies.

Proper sleep and sleep hygiene within the ICU can serve an important role. Patients in the ICU can experience sleep disturbances, including disruptions in normal circadian rhythms, from their critical illness as well as being in a noisy environment, not conducive to sleep due to disruption, light patterns, and patient monitoring. By minimizing noise and light disturbances, ICU clinicians may improve sleep patterns. Currently, the PADIS guidelines provide no pharmacotherapy recommendations for improving sleep patterns.

GLYCEMIC CONTROL

KEY CONCEPT Optimal glycemic control within the critically ill patients has been an evolving concept for decades. Hyperglycemia is common in the setting of the stress response. Endogenous inflammation and corticosteroids can result in elevation of blood glucose values. The consequences of poor glucose control are infection and poor wound healing. Studies that signaled potential benefit of tighter glucose control (< 110 mg/dL [6.1 mmol/L]), however, were contradicted by a much larger study that demonstrated higher mortality with glucose goals less than 100 mg/dL (5.6 mmol/L) compared to a target of less than 180 mg/dL (10 mmol/L).[18–20] This is likely attributed to the higher incidence of hypoglycemia with intensive glucose control in the larger study. Hypoglycemia has the potential to worsen autonomic function, alter blood flow and composition, while also altering immune cell mediation and release as well as vasoconstriction. Moderate hypoglycemia (41–70 mg/dL [2.3–3.9 mmol/L]) is associated with a 40% increase in mortality, while severe hypoglycemia (< 41 mg/dL [2.3 mmol/L]) has been associated with a doubled risk of death.[21]

Of growing interest is the concept of glycemic variability, or glucose fluctuations, within the critically ill patients rather than set values for hyper- and hypoglycemia. Glycemic variability has yet to be definitively defined, and its causative role in outcomes is unknown.[22] For this reason, guidelines currently recommend initiation of insulin therapy after two consecutive blood glucose values greater than 180 mg/dL (10 mmol/L) to reach a goal of less than 180 mg/dL (10 mmol/L), with glucose checks every 1 to 2 hours.[23] Guidelines also recommend the utilization of an insulin infusion over subcutaneous dosing while cautioning against the use of point-of-care capillary glucose testing over plasma testing given potential inaccuracy given physiologic changes in this population.

STRESS ULCER PROPHYLAXIS

Upper gastrointestinal bleeding is a known consequence of acute illness secondary to changes to the gastroduodenal mucosa. Inflammatory changes, splanchnic hypoperfusion, and altered microcirculation result in an altered mucosal barrier, increasing potential for gastrointestinal bleeding.[24] The significance of these changes is less clear. While historic cohorts demonstrated an incidence of overt bleeding, defined as hematemesis, frank blood or coffee-grounds in aspirate, or melena, between 5% and 25%, the incidence of clinically important bleeding (CIB) is between 0% and 5%. CIB is overt bleeding with the addition of one or more of the following:

1. Blood pressure drop of 20 mm Hg or more in 24 hours.
2. An orthostatic increase in pulse of at least 20 beats/min and decrease in systolic blood pressure of 10 mm Hg.
3. A decrease in hemoglobin of 2 g/dL (20 g/L; 1.24 mmol/L) or moreover a 24-hour period or transfusion or 2 units of red blood cell transfusion within 24 hours.
4. An invasive intervention required, such as vasopressors or endoscopy.

Critically ill patients are at the highest risk of CIB with two risk factors independently associated with gastrointestinal bleeding:

Table 4–3

Risk Factors for Stress-Related Mucosal Changes

Independent	Relative
Coagulopathy, defined as platelet count < 50,000 /mm^3 (50×10^9/L, INR > 1.5, or PTT > 2 × control value	Spinal cord injury Multiple trauma Hepatic failure
Respiratory failure requiring mechanical ventilation ≥ 48 hours	Thermal injury > 35% body surface area Partial hepatectomy Head injury with Glasgow coma score < 11 History of gastric ulcer or bleed within 1 year Sepsis/septic shock ICU stay exceeding 1 week Occult or overt bleeding for 1 week Corticosteroids

ICU, intensive care unit; INR, international normalized ratio; PTT, partial thromboplastin time.

mechanical ventilation for 48 hours or longer and coagulopathy. Other relative risk factors can be found in Table 4–3.[25]

Guidelines recommend the initiation of prophylaxis against CIB in the presence of an independent risk factor or two other risk factors within the ICU. Notably, these guidelines were established over two decades ago, with growing concern for overutilization of prophylactic regimens and potential for harm in the setting of low incidence of CIB. Stress ulcer prophylaxis has been shown to decrease the incidence of overt bleeding with mixed evidence on impact for CIB. Choices for prophylaxis include histamine-2 receptor antagonists and proton pump inhibitors. Previously evaluated choices, including antacids and sucralfate, have fallen out of favor secondary to administration difficulties or lack of efficacy. Studies evaluating these agents show a slight benefit of proton pump inhibitors therapy over histamine-2 receptor antagonists for decreasing incidence of bleeding overall.[26] No difference in adverse events has been routinely found between groups.

Increasing attention has been given to the usefulness of enteral nutrition in preventing bleeding of patients receiving enteral nutrition. Early studies of CIB were performed prior to data demonstrating benefit of early feeding in this population. As standards of care have evolved to include early enteral nutrition, recent evidence has sought to evaluate its use over pharmacologic prophylaxis. In patients receiving enteral nutrition, current data support continuing pharmacologic prophylaxis at the time to decrease incidence of CIB; however, it is unclear if this has any impact on clinical outcomes such on clinically important events or mortality.[27]

THROMBOPROPHYLAXIS

Disruption in normal hemostatic functions occur regularly in the critically ill patient populations. Venous thromboembolism (VTE) is a general term where patients experience inappropriate clot formation causing deep vein thrombosis (DVT) or pulmonary embolisms (PEs). A PE typically occurs after embolization of a lower extremity DVT but can occur even without the presence of a DVT. The incidence rate of VTE is largest in those with the highest acuity, specifically in patients with traumatic injuries or septic shock.[28,29] The prophylaxis against VTE development is vital to the critically ill patient as it can reduce mortality. KEY CONCEPT Risk factors for the development of DVT or PE may be stratified by modifiable or nonmodifiable risk factors (Table 4–4). A risk assessment tool that has been validated to predict VTE in medical patients, the Padua Score, is often utilized to help stratify patients at low and high risk for inappropriate clot formation.[30] The score assesses factors which place patients at higher risks for VTE development such as reduced mobility, advanced age (≥ 70 years), obesity, previous VTE, recent trauma or surgery, known hematological conditions, heart or respiratory failure, acute coronary syndrome, acute ischemic stroke, active infection, and ongoing treatment with hormonal pharmacologic therapies.

Heparinoids, such as low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH), are the most widely utilized thromboprophylaxis agents administered in critically ill patients. Multiple factors are utilized when deciding on whether to utilize LMWH or UFH in the critically ill patient population and which dose to administer. Type of critical illness, renal function, and body habitus are just a few of the deciding factors when selecting a heparinoid for VTE prophylaxis.[31] For patients in the surgical or trauma setting LMWH, such as enoxaparin, is preferred over UFH and typically dosed as enoxaparin 30 mg subcutaneously every 12 hours. Dose adjustment is based on body habitus or anti-Xa levels. Medical patients or those with renal dysfunction primarily receive 5000 units of UFH subcutaneously every 8 hours, however, may be dose adjusted again for body habitus or enoxaparin 40 mg subcutaneously once daily.

In addition to heparinoids, there is an increased interest in utilizing the direct oral anticoagulants (DOACs) in the critically ill patient population including their use for VTE prophylaxis. However, when compared to the heparinoids, the DOACs have shown no difference in VTE occurrence while increasing bleeding risk.[32] At this time DOACs should not be utilized instead of heparinoids for thromboprophylaxis in critically ill patient populations while in the inpatient setting.[31,32]

Fondaparinux at 10 mg administered subcutaneously or a continuous infusion of IV argatroban are at times utilized in clinical scenarios where heparinoids are contraindicated such as heparin-induced thrombocytopenia.

In addition to chemical VTE prophylaxis, patients should also receive mechanical prophylaxis with agents such as sequential compression devices (SCDs). An SCD is an inflatable sleeve that primarily rests on the patient's lower legs and is then inflated, which promotes blood perfusion rather than venous stasis, a known risk factor for VTE development. In addition to mechanical motion the inflation provides, the increased blood velocity decreases tissue factor release, increases fibrinolysis, and releases endogenous heparin from the endothelium.[33,34] While

Table 4–4

Example of Risk Factors for the Development of Venous Thromboembolism

Nonmodifiable Risk Factors	Modifiable Risk Factors
Factor V Leiden or hematological disorders	Immobility
Age > 40 years	Medications
Familial history of thrombosis	Obesity
Oncological disorders	Transfusion related
Male sex	Surgery or trauma

SCDs certainly have numerous benefits, they should not be the sole therapy for prevention of VTE in critically ill patients unless chemical prophylaxis is contraindicated, such as patients who are actively hemorrhaging.

Prevention of VTE in critically ill patients poses a unique challenge in that clinicians must weigh the risk of thromboprophylaxis with bleeding risk. Clinicians should evaluate the factors associated with the patient's risk of thrombosis with risk of bleeding while continually monitoring laboratory values and clinical criteria to hold or administer thromboprophylaxis. For example, patients with traumatic brain injury are at high risk for the development of VTE, but anticoagulation could cause hematoma expansion within the brain. A clinician must understand when the risk outweighs the benefit and if those risk and benefits change throughout a patient's illness.

BOWEL PROPHYLAXIS

KEY CONCEPT Critically ill patients experience numerous disruptions in normal homeostatic functions, including abnormalities within their GI tract. Irregularities in bowel motility can occur in critically ill patients secondary to acute illness, bed rest, medications, and dietary variances.[35] Constipation, during critical illness, has been reported to occur in up to 83% of patients, which may affect important clinical outcomes such as mechanical ventilation, ICU length of stay, or even mortality by contributing to increased intra-abdominal pressures, ileus, or prevented ventilator weaning.[36] While diarrhea can occur in critically ill patients, it is not as prevalent and often linked with an infectious etiology or the result of an adverse drug event.

Definitions of constipation vary but can be thought of as the lack of defecation over a specific time period (typically less than three stools per week). Constipation has been associated with increased abdominal distension, pain, diet intolerance, vomiting leading to aspiration, and obstructions.[37] Common agents used to treat constipation include laxatives (eg, polyethylene glycol, bisacodyl, or senna) and, in certain cases, prokinetic agents like metoclopramide. These agents would ideally be administered prior to constipation symptoms occurring as prophylaxis. Opioids are commonly utilized within critically ill patient populations and can be associated with a phenotypically different type of constipation than a patient who has a bowel obstruction. Initially management of constipation in critical illness will consist of bulk forming or osmotic laxatives, such as, psyllium or polyethylene glycol, with the addition of a stool softener, such as docusate. If response is not achieved after the addition of these agents, stimulants, such as senna are reasonable options.

In addition to selecting the appropriate agents as a bowel prophylaxis, proper regimens to ensure euglycemia, electrolyte and fluid management, and adequate enteral feeding can be used to mitigate ICU-associated constipation. Lastly, early mobility exercises improve clinical outcomes including those associated with GI motility.[38]

NEUROMUSCULAR BLOCKADE

Neuromuscular blockade, or pharmacologic paralysis, can be used for a variety of reasons within the ICU aside from RSI, including acute respiratory distress syndrome (ARDS) and therapeutic hypothermia, also known as code chill, following cardiac arrest. Currently, use of neuromuscular blockade is not recommended for status asthmaticus while no recommendations are made for its use for elevated intracranial or intraabdominal pressure.[39] Neuromuscular blockers are initiated only after a deep level of sedation is documented. Neuromuscular blockers can be divided into two types: depolarizing and nondepolarizing. Because of the adverse event profiles in combination with issues surrounding organ dysfunction within the critically ill patients, cisatracurium (nondepolarizing) is usually selected first line in this population as it is not hepatically metabolized or renally excreted (Hoffman elimination). Because of its slower onset of effect, cisatracurium is not used in emergent scenarios such as RSI.[40] Neuromuscular blockade is titratable based on disease-specific parameters or depth of paralysis. Depth of paralysis can be monitored using a peripheral nerve stimulator. This device delivers four electrical impulses at a time to the ulnar or facial nerves and assesses response. No twitches in response to stimulation would mean complete paralyzation while four twitches in response would be no, or minimal, paralyzation. The neuromuscular blocker dose is titrated based on twitch response.

Complications of neuromuscular blockade include prolonged weakness, corneal abrasions, and thrombosis. For this reason, patients require monitoring and use of prophylactic regimens such as eye lubrication and VTE prophylaxis.

Patient Encounter Part 2

A 62-year-old man presents to the neurological ICU after experiencing a massive ischemic stroke to his middle cerebral artery. In the emergency department, the patient received intravenous thrombolytic therapy as well as endovascular thrombectomy of the clot. While unable to speak due to his stroke, his previous admissions showed his wife was his surrogate and did not have advanced directives in place. He is intubated for airway protection; additionally, the attending begins to discuss goals of care given the patient's debilitating stroke and options in terms of recovery.

What therapies should we consider for this patient now that they are intubated?

If the patient requires paralysis during mechanical ventilation, what supportive care must be considered?

FEEDING AND NUTRITION

Nutrition can be administered either via an enteral (via a feeding tube into the stomach) or parenteral (IV) route, with the latter reserved for situations where enteral nutrition is not feasible or possible. Nutrition supplementation is started early in poorly nourished patients but can be delayed up to 7 days following admission in patients at low nutritional risk. Enteral nutrition (EN) (see Chapter 101), if it is possible, should be initiated within 24 to 48 hours of ICU admission.[41] Delaying can worsen risk of gastromucosal changes, bacterial translocations, and ileus. The contraindications to EN are bowel obstruction, perforation, mesenteric ischemia, or major GI bleeding. Typically, EN can be started at roughly 25% to 50% of the caloric goal, increasing to target over 72 hours, up to 1 week. While a variety of formulations exist for EN, there is no evidence to support the utilization of one over another. Patients who have trouble tolerating EN can be supported with placement of their feeding tube after the pylorus or with prokinetic agents to increase gut motility. Patients should roughly be given 25 kcal/kg/day (105 kJ/kg/day) of EN with 1 to 2 g/kg of protein accounting for a significant portion of caloric intake.

There are considerations to make for special populations. Patients with renal failure complicated by electrolyte abnormalities may warrant renal-specific formulations, while immune-modulating formulas may be helpful in the trauma-surgical population. Patients who have diarrhea should be started on tube feeds with fiber or small peptides, and fluid-restricted formulations can be considered in those patients with volume overload. In obese patients, a lower caloric need is necessary, roughly 11 to 14 kcal/kg/day (46–59 kJ/kg/day) or 22 to 25 kcal/kg/day (92–105 kJ/kg/day) of ideal body weight, once a body mass index exceeds 50. In the obese, protein should be administered at 2 to 2.5 kcal/kg/day (8–10.5 kJ/kg/day). Refer to Chapters 100 and 101 for further information on nutritional support.

END-OF-LIFE CARE/COMFORT CARE

There are times that the interventions performed by the ICU team are ultimately unsuccessful or would be futile to pursue. Comfort care therapy is a compassionate part of the end-of-life process that aims to prevent or relieve discomfort, suffering, or pain to improve the quality of life for a patient. The decision to pursue comfort care or end-of-life management involves a physician and the patient, if able, or caregivers who know the advanced directives of the patient.[42] After all curative therapies have been exhausted or have been deemed ineffective, the attending physician will typically begin discussing goals of care with the patient, caregivers, and team. Should the patient be incapable of making decisions on goals of care, and no caregivers are available, the discussion will include other providers involved in the patients care. In some discussions, the ethics team may be involved.

Comfort care management can be vital to ensure the patient does not have protracted pain or discomfort during the dying process. Sedatives, such as lorazepam, opiates, such as morphine, and steroids, such as dexamethasone, are often utilized to relieve anxiety, pain, or inflammation-related discomfort. Atropine or glycopyrrolate can be administered orally or intraocular to minimize secretions. In addition to pharmacologic therapies, nonpharmacologic therapies have a role at managing anxiety, pain, and depression. Aromatherapy, music therapy, and pet therapy are just a few of the different strategies that have shown success

Patient Encounter Part 3

A 62-year-old man presents to the neurological ICU after experiencing a massive ischemic stroke to his middle cerebral artery. In the emergency department, the patient received intravenous thrombolytic therapy as well as endovascular thrombectomy of the clot. While unable to speak due to his stroke, his previous admissions showed his wife was his surrogate and did not have advanced directives in place. He is intubated for airway protection; additionally, the attending begins to discuss goals of care given the patient's debilitating stroke and options in terms of recovery. Family decides to continue full care; however, after intubation, the patient becomes hemodynamically unstable requiring vasopressors.

What considerations need to be made for the pharmacotherapy regimen given the acute change?

What type of questions would you consider in determining goals of care for this patient?

Patient Care Process

Collect Information:

- Collect past medical history as well as home medication reconciliation.
- Gather pertinent laboratory values, particularly regarding organ function and perfusion.
- Evaluate IV fluids, current medication list, and nutrition prescriptions. Identify current lines and devices and pertinent parameters, such as dialysis or mechanical ventilation.
- Evaluate vital signs, such as fluid balance, blood pressure, oxygenation, and daily weights.

Assess the Information:

- Ensure that all medications are dosed for organ dysfunction, such as liver failure or renal dysfunction.
- Assess whether IV lines are appropriate based on current medication list.
- Evaluate need for additional regimens, such as stress ulcer prophylaxis or DVT prophylaxis.
- Assess whether patient infusions and medications are targeting appropriate goals and whether such is being achieved.
- Evaluate current goals of care, ranging from primary problem to end-of-life care.

Develop a Care Plan:

- Discuss plan of care with team and patient-specific considerations.
- When possible, discuss options with patient and patient's family.
- Determine appropriate plan based on current laboratory results, vital signs, and other patient-specific parameters.
- Implement prophylaxis in patients at risk of complications.
- Determine appropriate monitoring parameters for current goals of care.

Implement the Care Plan:

- Deliver recommendations to the interdisciplinary team.
- Assess orders for changes necessary to medication dosing or to end target goals (ie, target mean arterial pressure or blood glucose).
- Relay information to next shift to ensure continuity of care.

Follow-up: Monitor and Evaluate:

- Continue to evaluate pertinent laboratory values, particularly regarding organ function and perfusion.
- Evaluate medication profile and consider discontinuation of medications not clinically necessary.
- Monitor changes in intake and output, vital signs, such as blood pressure, oxygenation, and daily weights.
- Evaluate trajectory of clinical support needed, such as dialysis, mechanical ventilation, and other devices.

in the end-of-life process in conjunction with pharmacologic therapies.[43] While the pharmacologic and nonpharmacologic therapies listed above are not all encompassing, they do represent a cornerstone of the end-of-life comfort care management.

The end-of-life process, like critical care, should incorporate those with specialized training in the management of dying patients in the form of palliative care physicians, nurses, physician assistants, chaplains, pharmacists, and social workers. Effective communication and expectation management are a crucial aspect of the end-of-life process, which can require having in-depth conversations with patients who may not have acknowledged their own mortality. Open dialogue about the end-of-life process can reduce fear, anxiety, and even depression associated with it. Standard institutional protocols can create a systematic approach to the care of end-of-life patients; however, targeted goals of therapy, as it relates to the end-of-life process, should be assessed daily from the team, patient, or caregivers. Lastly, screening may occur during the comfort care process for organ procurement in select patients. Further information about this care can be found in Chapter 3.

The end-of-life or comfort care process is vital to ensuring patients are relieved from suffering during the dying process. Communication, training, and team-based guidance on goals of care can ensure optimal comfort treatment in the patient's most vulnerable state.

Abbreviations Introduced in This Chapter

AUC	Area under the curve
AKI	Acute kidney injury
ARDS	Acute respiratory distress syndrome
CIB	Clinically important bleeding
DOAC	Direct oral anticoagulation
DVT	Deep vein thrombosis
EN	Interal nutrition
ETT	Endotracheal tube
ICU	Intensive care unit
IV	Intravenous
LMWH	Low-molecular-weight heparin
MIC	Minimum inhibitory concentration
PADIS	Pain, agitation, delirium, immobility, and sleep
PICS	Post-intensive care syndrome
PICC	Peripherally inserted central catheter
PE	Pulmonary embolism
PPI	Proton pump inhibitor
RSI	Rapid sequence intubation
SCCM	Society of Critical Care Medicine
SCD	Sequential compression device
UFH	Unfractionated heparin
VAD	Venous access devices
VTE	Venous thromboembolism

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5

Global Health and Travel Medicine

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Discern the difference between equality and equity.
2. Explain the social determinants of health and their contribution to health outcomes.
3. Identify the main contributors to the global burden of disease.
4. Contrast benefits and possible harms of cross-cultural health work.
5. Discuss neglected tropical diseases and the different treatment approaches used to manage them.
6. Discuss the different components of medication access to optimize health outcomes.
7. Describe the key components of a pretravel consultation.
8. Summarize the advantages and disadvantages of four antimalarial prophylactic regimens.
9. Explain the difference between prophylactic and self-directed therapy for traveler's diarrhea.
10. Identify two reasons for urgent evaluation of returned travelers with illness.

INTRODUCTION

Global health is an effort to reduce health inequities for people all over the world. Prior to the 1800s, average life expectancy was 30 to 40 years globally. Since then, advancements in agriculture, economics, public health, medicine, and society have led to dramatic improvements in health, including increased life expectancy and decreased under-five mortality (Figure 5–1). However, significant variations persist across different world regions, underlined by health inequities.[1,2]

The field of global health rose in part from a recognition of these inequities, aiming to alleviate them. Numerous international development organizations, philanthropic foundations, academic medical centers, and development consulting firms have consistently devoted economic and/or human resources to global health practice. This includes, but is not limited to, the United States Agency for International Development (USAID), United Kingdom Agency for International Development (UKAID), Swedish International Development Cooperation Agency (SIDA), German Agency for International Cooperation (GiZ), Japan International Cooperation Agency (JICA), United Arab Emirates International Development Cooperation, the Gates and Rockefeller foundations, and Family Health International 360 and Management Sciences for Health. Government-based organizations have typically provided the most aid with the United States providing the most funding in terms of absolute amount of overseas development assistance and Sweden providing the highest percentage of gross national income as seen in Figure 5–2.[3]

KEY CONCEPT Of note, global health does not necessarily refer to high-income countries supporting lower-income ones, as this is problematic for several reasons. It creates a false perception that high-income countries are at the center of the world and everything outside of those borders is considered "global," a misnomer that presents a challenge for defining who a global health practitioner is. For example, should a South Africa-born pharmacist who practices in South Africa consider themself to be a global health pharmacist? Furthermore, it is clear that health disparities also exist within high-income countries. For example, while overall life expectancy for a baby born in 2016 in the United States is 78.6 years and higher than the worldwide average,[1] some counties within the United States have a much lower life expectancy of only 56.3 years,[4] worse than the average life expectancy in low-income countries of 63.8 years.[5]

It is for these reasons that the term health equity will be used throughout this chapter to refer to the borderless pursuit of improving health for populations around the world. This moniker more accurately describes the disparities than a term defined by country borders that diseases do not respect. Unsurprisingly, regions with lower life expectancies tend to also have subpar economic stability, educational opportunities, food insecurity, relatively less-safe neighborhoods, and suboptimal healthcare access. Furthermore, the drivers of these health inequities are similar across the world. This chapter will provide a better understanding of these broader determinants. This chapter will also provide representative examples of how these disparities are manifested around the world, with illustrative descriptions of efforts to address them in a culturally contextualized fashion. This approach will facilitate discussion of novel approaches to address determinants of health alongside more traditional healthcare system approaches that can be applied regardless of the practice setting or discipline.

EQUITY VERSUS EQUALITY

KEY CONCEPT When trying to understand the concept of global health equity, it is important to differentiate equity from equality. Equality focuses on treating all people the same regardless of other factors, while equity considers the circumstances of each individual

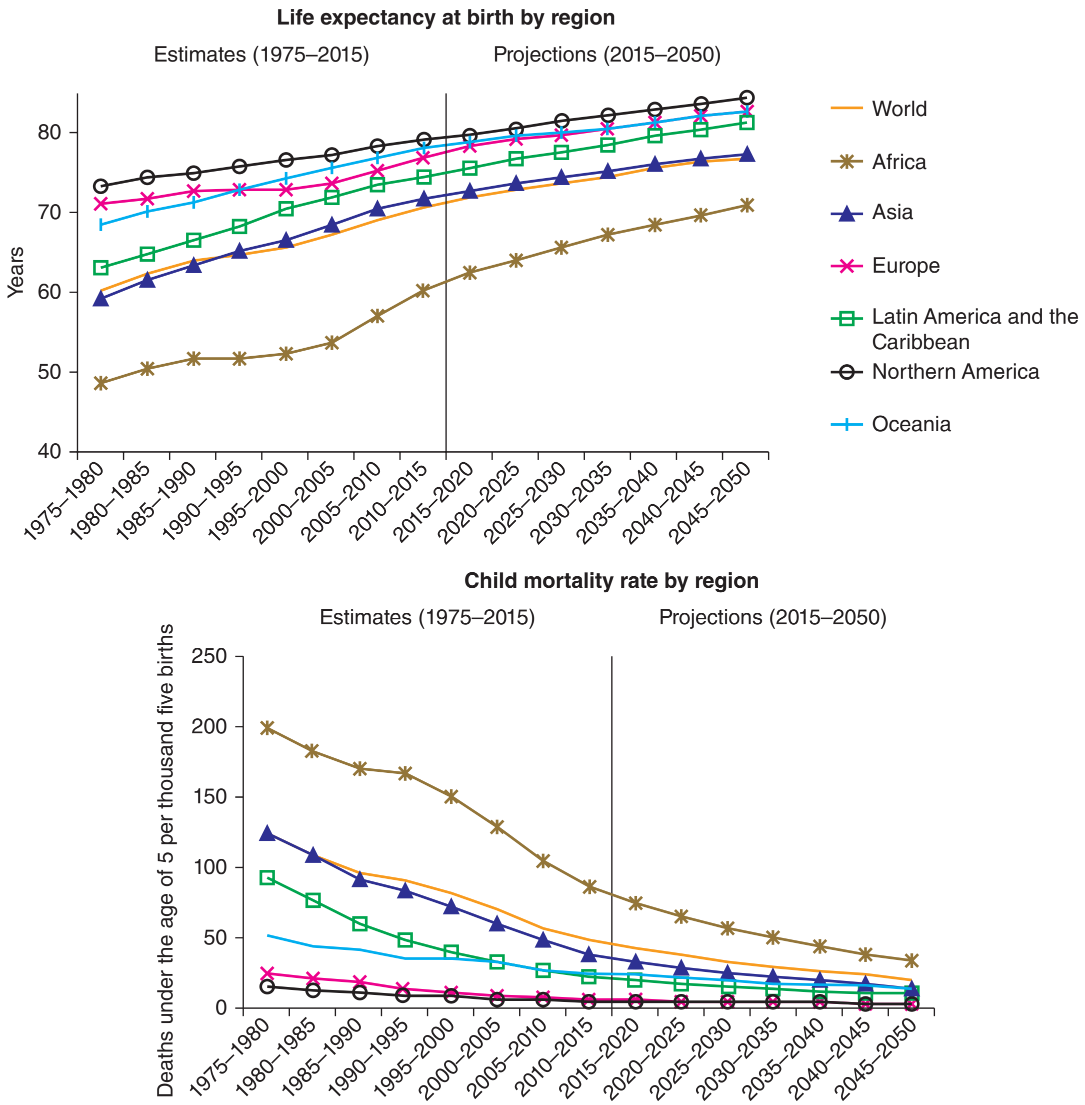


FIGURE 5–1. Estimated and projected life expectancy at birth and child mortality rate by region between 1975 and 2050. Reproduced with permission from World Population Prospects 2017 - Data Booklet United Nations, Department of Economic and Social Affairs, Population Division; 2017. Report No.: Contract No.: (ST/ESA/SER.A/401).

and attempts to allocate resources and solutions based on each individual's particular context. The difference in an approach focused on equality and equity is illustrated in Figure 5–3.

The top image shows how each individual receives a chair to have a seat at the table. While this reflects equal treatment of the three individuals, it does not consider their needs or circumstances. In this scenario, only one individual has a functional seat at the table while the infant and individual in a wheelchair do not. The bottom image exemplifies an approach focused on equity where the three individuals are provided with different seating options that fit their context. The normally abled adult still receives a chair; however, the infant receives a high chair to prevent them from falling, and the individual in the wheelchair receives no chair and instead has space for their wheelchair so they can sit at the table.

HEALTHCARE SYSTEM: A CASE EXAMPLE FROM THE UNITED STATES

The US healthcare system provides a representative example of health inequities across the globe. Large segments of the population, especially those with lower financial means, are priced out of accessing various aspects of care. As illustrated in Figure 5–4, equality in the US healthcare system is promoted by having all populations rely on the same system for their healthcare needs. Despite accessing the same system, low-income populations have limited access to primary care services and disproportionately rely on emergency room-based care.[6] This dynamic ultimately leads to increased costs within the healthcare system. More expensive emergency room visits are used to manage needs, which could be more effectively managed through outpatient visits.[7] In contrast, high- and middle-income populations with employer-based health insurance in the United States have better geographical and financial access to primary care and preventive services. These limit their reliance on the costlier emergency room-based care.[6] In addition to the challenges low-income populations face with accessing healthcare services, they also face a disproportionate burden of other health-related challenges. These include, but are not limited to, economic instability, insecure housing, poor educational choices, and limited nutritional options.

To counter this, US federal and state agencies have introduced a variety of initiatives to strive for more equitable access

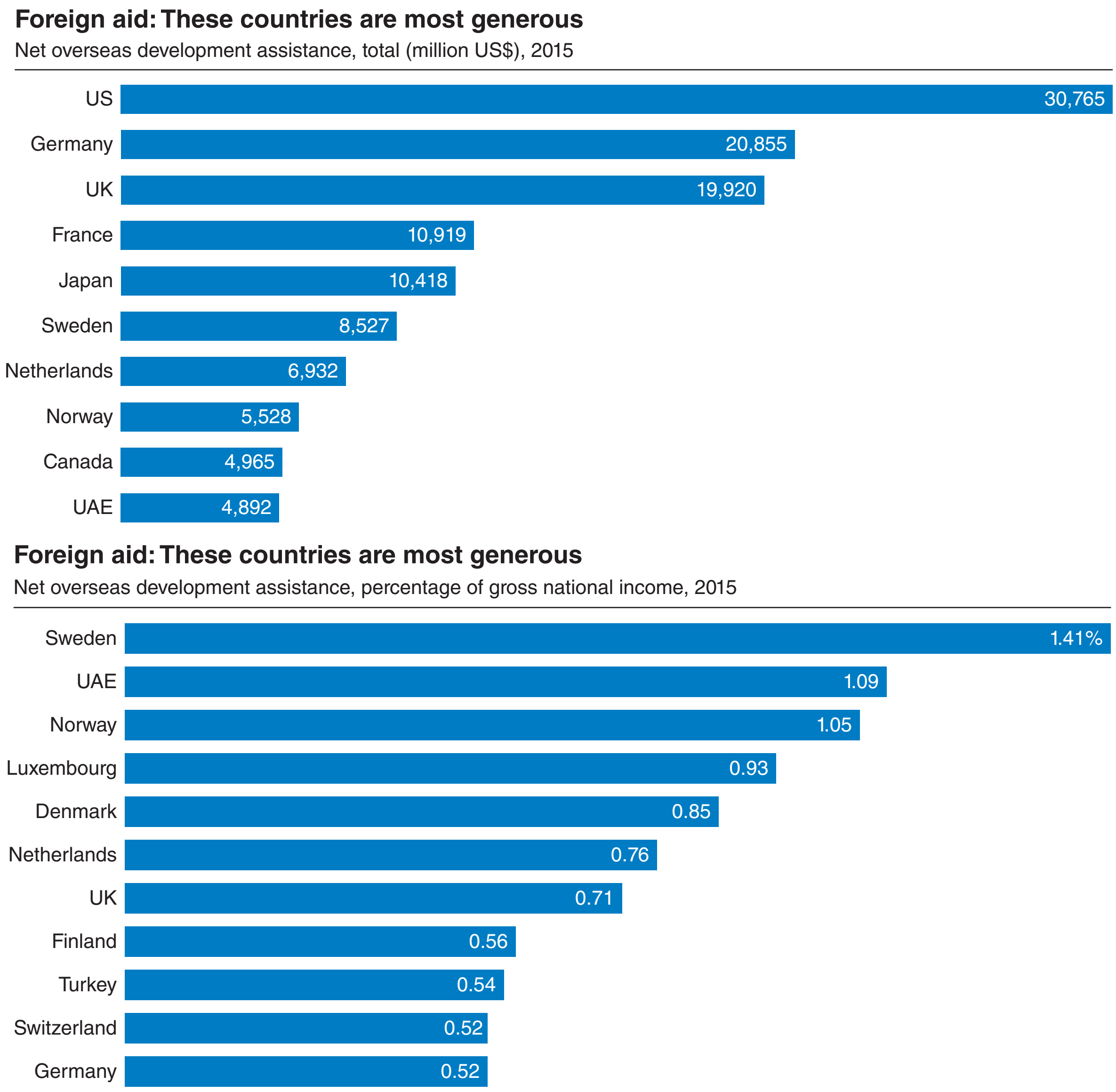


FIGURE 5–2. Foreign aid by high-income countries in terms of absolute financial support (in $) and percentage of gross national income (%). Reproduced with permission from Myers J. Foreign aid: These countries are the most generous 2016 [cited 2020 Aug 15].

to health across the different economic strata of the population as illustrated in Figure 5–5. Programs such as the Affordable Care Act and the associated Medicaid expansion to cover additional low-income populations have addressed these inequities by increasing access to health insurance for low-income populations. While these programs have helped provide low-cost insurance to millions of Americans, many of these programs include high deductible, lean plans, which insure against high-cost healthcare expenses. However, many of these non-Medicaid insurance plans still require significant copays for outpatient visits which leads to relatively lower uptake of primary care services. Increases in the uptake of primary care services have been seen, however, they still lag behind higher-income populations with more comprehensive insurance plans as seen in Figure 5–5.[8,9]

There are also efforts to address other aspects of health beyond direct clinical care to assist low-income populations. This includes, but is not limited to, programs like Temporary Assistance for Needy Families (TANF) (frequently referred to as welfare), Supplemental Nutrition Assistance Program (formerly known as food stamps), and Affirmative Action to promote good faith efforts to advance enrollment in higher education and job opportunities for historically underrepresented segments of the population. While many fail to recognize the government assistance services provided to high- and middle-income populations, these populations also benefit from government aid in the form of home mortgage interest deductions, preferential tax cuts, and school voucher programs that facilitate school choice.

Despite these efforts to promote equity, dramatic differences still exist in health outcomes across different socioeconomic strata. While there has been progress in improving access to clinical care, recent estimates suggest that direct clinical care is responsible for only 20% of the health outcomes of the US population, with other social determinants of health being responsible for the majority of health outcomes as seen in Figure 5–6.[10]

The Social Determinants of Health

KEY CONCEPT The social determinants of health include both the healthcare system and "the conditions in which people are born, grow, live, work, and age" as defined by the World Health Organization (WHO). The WHO definition further explains that "these circumstances are shaped by the distribution of money, power, and resources at global, national, and local levels. The social determinants of health are mostly responsible for health inequities—the unfair and avoidable differences in health status seen within and between countries."[11] The social determinants of health are characterized by the Centers for Disease Control and Prevention (CDC) as relating to economic stability, education, neighborhood and built environments, school and community contexts, and the healthcare system. Some organizations, such as the Kaiser Family Foundation, specifically draw attention to the importance of food and describe many of the contributors of the social determinants of health as seen in Figure 5–6.[12]

The impacts of these social determinants of health have been consistently illustrated in numerous studies that show the correlations between these factors and health outcomes.[11–15] Several illustrative examples come from research done in the United States.

As seen in the combination of illustrations and graphs in Figure 5–7a–d, different social determinants of health play an outsized role in determining health outcomes of the population. The impact of neighborhood, physical environment, community, and social context is illustrated through an analysis of the life expectancy within the city of New Orleans in Louisiana, United States.[16] As seen in Figure 5–7a, there is a 25-year disparity

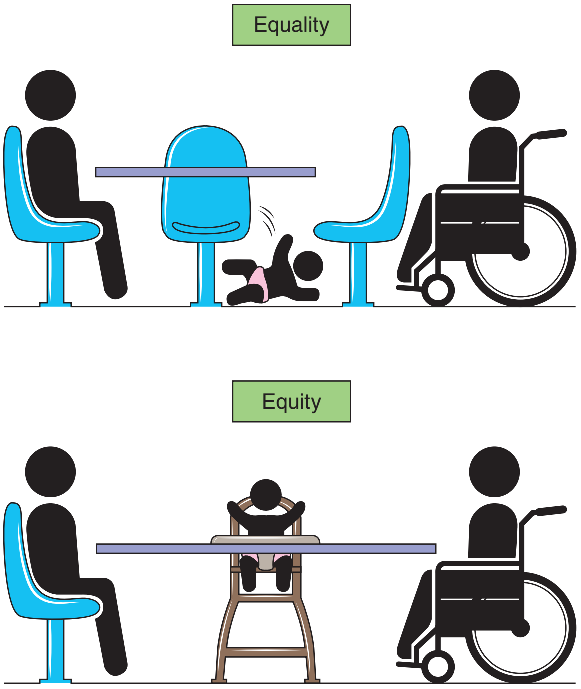

Equality
Equity

FIGURE 5–3. Visual illustration of equality versus equity.

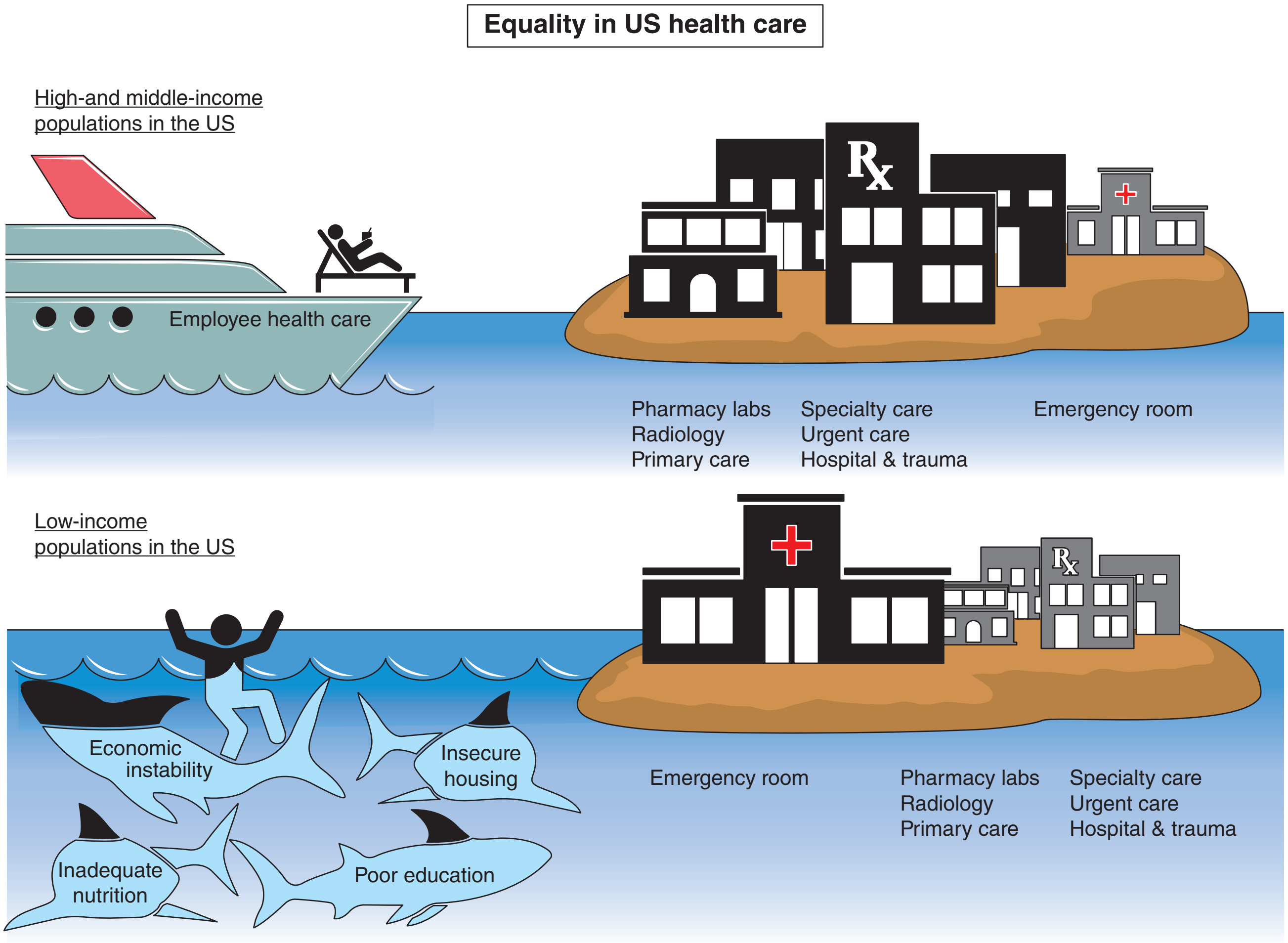

Equality in US health care
High-and middle-income populations in the US
Employee health care
Pharmacy labs
Radiology
Primary care
Specialty care
Urgent care
Hospital & trauma
Emergency room
Low-income populations in the US
Economic instability
Insecure housing
Inadequate nutrition
Poor education
Emergency room
Pharmacy labs
Radiology
Primary care
Specialty care
Urgent care
Hospital & trauma

FIGURE 5–4. Visual representation of equality in health care for high-, middle-, and low-income populations in the United States.

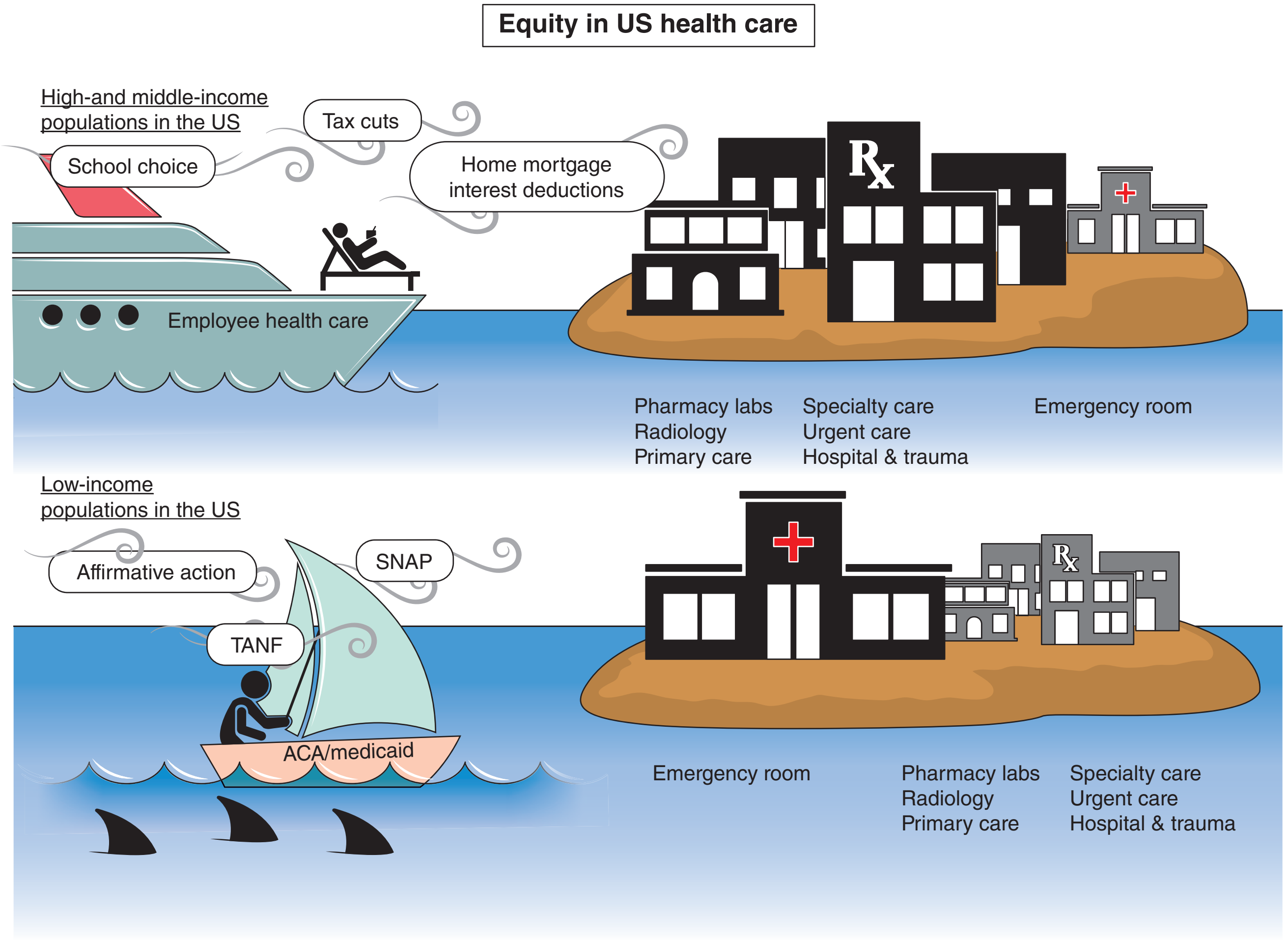

Equity in US health care
High-and middle-income populations in the US
School choice
Tax cuts
Home mortgage interest deductions
Employee health care
Pharmacy labs
Radiology
Primary care
Specialty care
Urgent care
Hospital & trauma
Emergency room
Low-income populations in the US
Affirmative action
SNAP
TANF
ACA/medicaid
Emergency room
Pharmacy labs
Radiology
Primary care
Specialty care
Urgent care
Hospital & trauma

FIGURE 5–5. Visual representation of approaches to achieve equity for high-, middle-, and low-income populations in the United States.

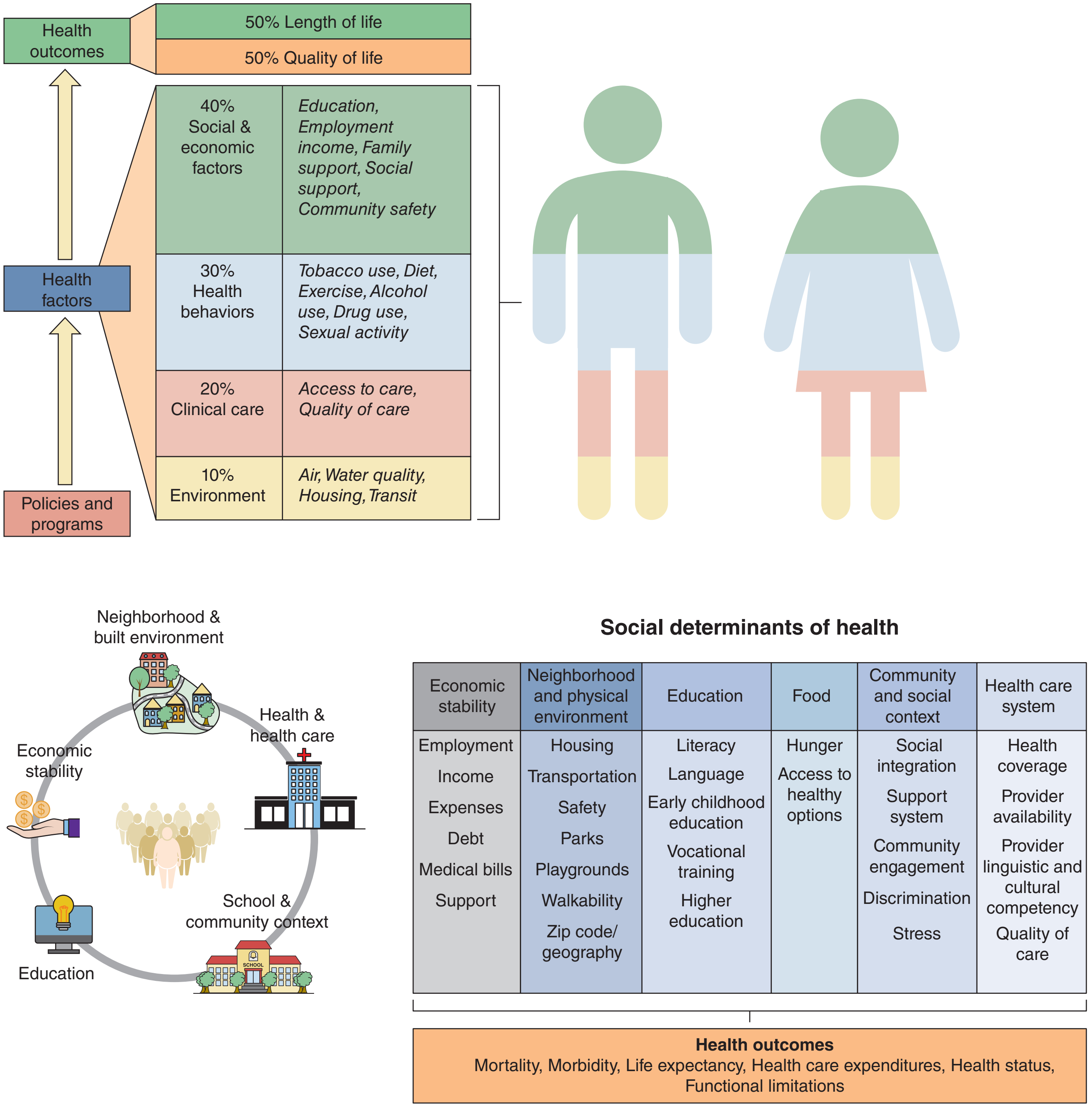
in life expectancy based simply on which part of New Orleans you were born in.[16] National data from the United States highlight the impact of the financial situation of parents on the health of their children as families with the highest levels of poverty have the greatest proportion of children with "less than very good health" and highest proportion of children who are overweight or obese, as seen in Figure 5–7b.[16] In Figure 5–7c, the impact of ethnicity and family income on health is illustrated as non-Hispanic black individuals in the United States tend to have a higher proportion of people in poor/fair health at all levels of income. Lastly, Figure 5–7d illustrates the impact of educational attainment on health, as the proportion of adults who have poor/fair health for each ethnicity goes up as the level of educational attainment they have achieved goes down.[16,17]

The WHO established a commission to drive greater progress in addressing social determinants of health. While the need for this focused effort is especially pronounced in low- and middle-income countries (LMICs), which tend to have relatively less progress on social determinants of health, high-income countries have also realized the importance of addressing these factors and have completed numerous population level studies. KEY CONCEPT Studies from the United States assessing determinants of health have found that socioeconomic factors, physical environment, and health behaviors are responsible for 40%, 10%, and 30% of health outcomes respectively, with clinical care being responsible for only 20%.[10] Similarly, in the United Kingdom and Canada, clinical care was only responsible for 10% and 25%, respectively, of healthcare outcomes while socioeconomic factors, genetics, environment, and health behaviors were responsible for the rest.[15,18] Because of the growing awareness of the importance of social determinants of health on outcomes, it is important that consideration for social determinants of health be incorporated into all aspects of the healthcare system including pharmacy.[19] Table 5–1 provides representative examples of the incorporation of social determinants of health into pharmacy services from programs around the world.

For additional descriptions of how social determinants of health impact the health of populations around the world, the WHO commission on Social Determinants of Health has prepared case studies on over 30 countries (https://www.who.int/sdhconference/resources/case_studies/en/).

Global Burden of Disease

An understanding of the importance of the aforementioned social determinants of health is crucial to appreciate the burden of disease for different regions around the world. While it is difficult to sufficiently describe the situation in every country, there are several examples that help illustrate the key trends when assessing the global burden of disease. As seen in Figure 5–1, LMICs, especially those in Africa, continue to have the lowest life expectancy at birth. Fortunately, however, this region is in the midst of a promising upward trajectory. Life expectancy has improved from 50.4 in the year 2000 to 61.3 in 2018 as this region transitions from facing excess preventable mortality from infectious diseases



50% Length of life	
50% Quality of life	
40% Social & economic factors	*Education, Employment income, Family support, Social support, Community safety*
30% Health behaviors	*Tobacco use, Diet, Exercise, Alcohol use, Drug use, Sexual activity*
20% Clinical care	*Access to care, Quality of care*
10% Environment	*Air, Water quality, Housing, Transit*

Social determinants of health

Economic stability	Neighborhood and physical environment	Education	Food	Community and social context	Health care system
Employment Income Expenses Debt Medical bills Support	Housing Transportation Safety Parks Playgrounds Walkability Zip code/ geography	Literacy Language Early childhood education Vocational training Higher education	Hunger Access to healthy options	Social integration Support system Community engagement Discrimination Stress	Health coverage Provider availability Provider linguistic and cultural competency Quality of care

Health outcomes
Mortality, Morbidity, Life expectancy, Health care expenditures, Health status, Functional limitations

FIGURE 5–6. Illustration of the different social determinants of health, their contribution to health outcomes, and representative examples.

to now facing a growing burden of noncommunicable diseases much like the rest of the world.[5,20]

Figure 5–8 illustrates these transitions in burden between noncommunicable diseases and neonatal, maternal, and communicable diseases. **KEY CONCEPT** Noncommunicable diseases such as ischemic heart disease have risen in their contribution to disability-adjusted life years (DALYs—the sum of healthy years of life lost due to illness or its consequences in the form of disability or premature death[20]), while communicable infectious diseases like HIV and tuberculosis were a much bigger negative contributor to DALYs in 2007 than they are in 2017. This transition, along with the dramatic increase in life expectancy in Africa over the past two decades, is due, in small part, to the collaborations which have been established in response to these diseases.

The most notable of these international collaborations is the remarkable response to the HIV epidemic through the President's Emergency Plan for AIDS Relief (PEPFAR). In 2003, President George W. Bush authorized an unprecedented $15 billion investment in global health over 5 years with support from both major US political parties (ie, Republicans and Democrats) and the American public. At the time, this program instantaneously became the largest financial contribution from any government to address a health crisis in another region. The initial authorization of the PEPFAR program required funding recipients to collaborate with

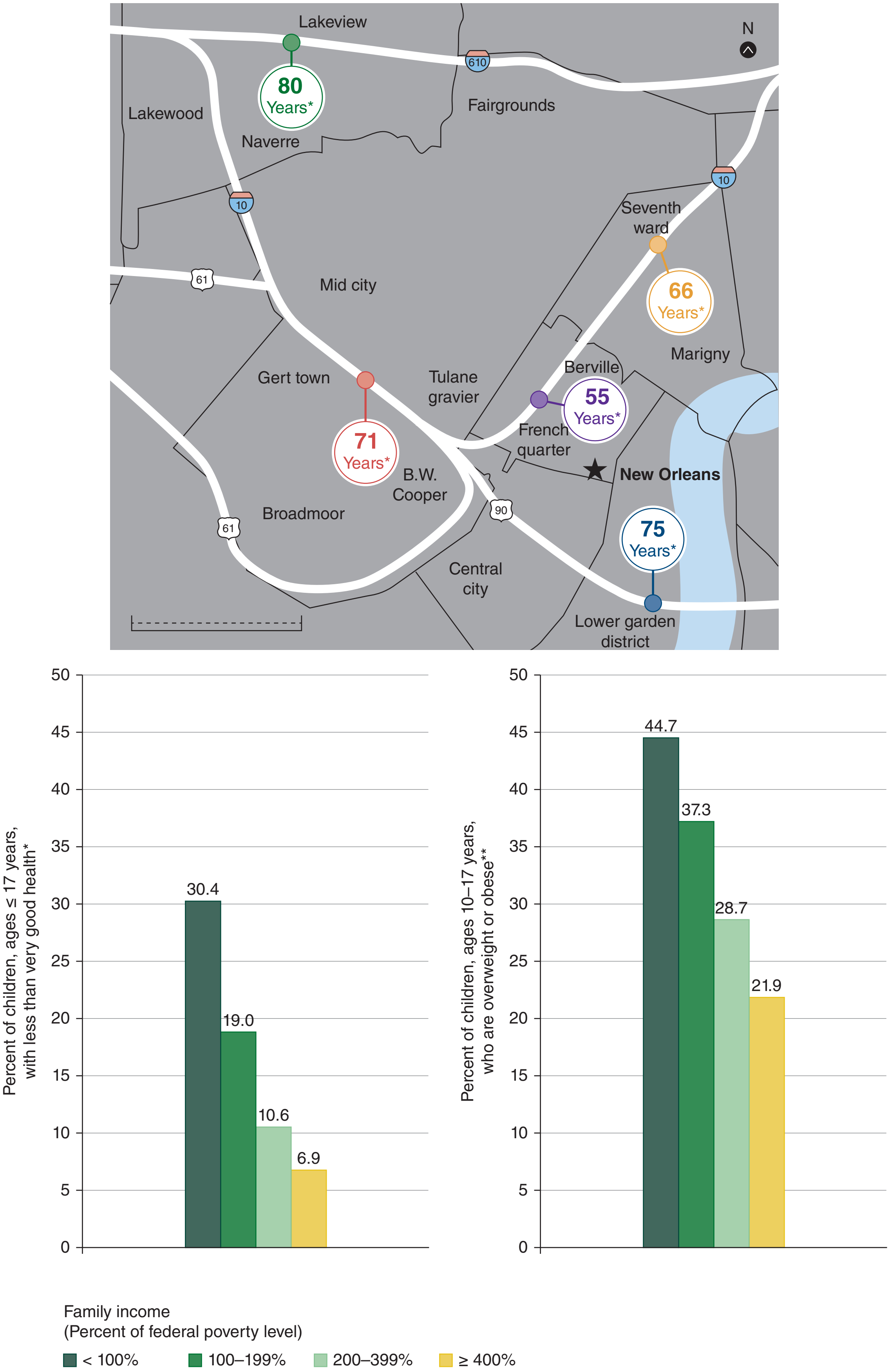


FIGURE 5–7. A: Disparities in life expectancy based on location of birth in New Orleans, Louisiana, United States. B: Impact of parental incomes on the health of children. C: Impact of ethnicity and family income on health. D: Impact of educational attainment by ethnicity on health.

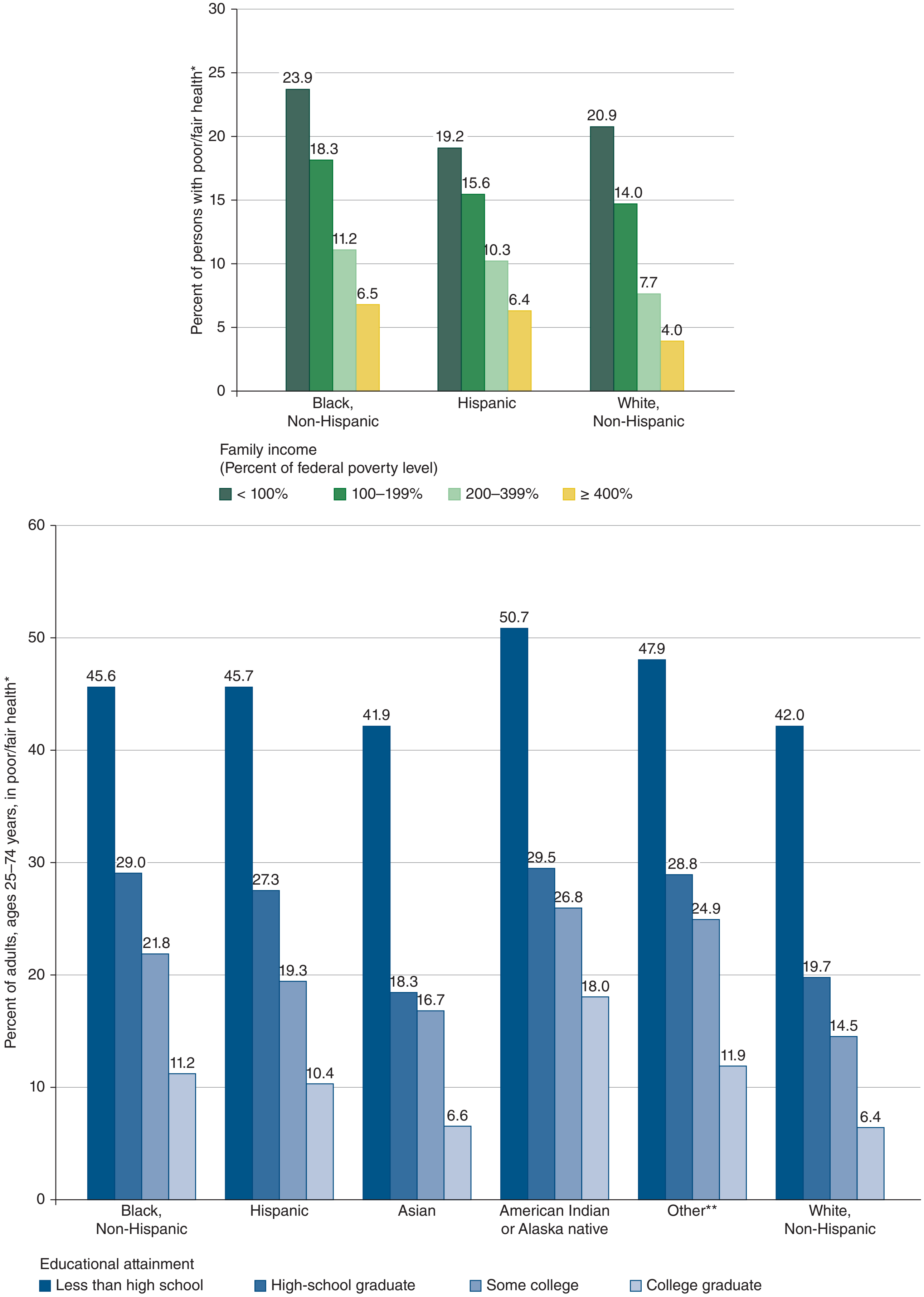
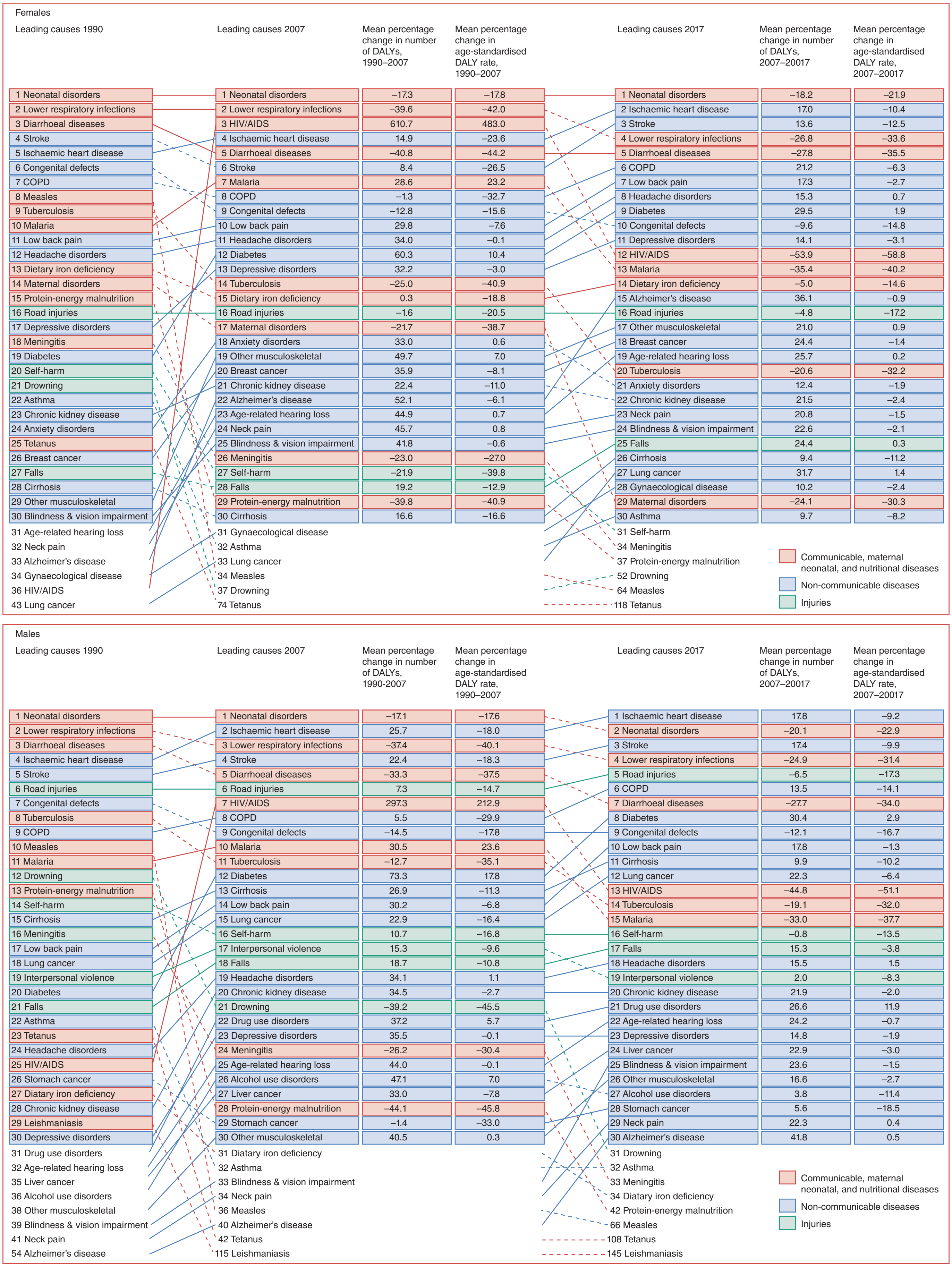


FIGURE 5–7 (Continued)

Table 5–1

Representative Examples of Pharmacotherapy Integration with Other Social Determinants of Health

	Location of Study	Brief Description of Initiative	Social Determinants of Health Addressed	Key Outcomes Observed
Victor RG et al.[93]	United States	Black male patrons of black-owned barbershops were randomized participants to a hypertension control program where pharmacists adjusted medications at the barbershop and trained barbers to provide education. Participants in the control group only received education from their barbers.	Community context	Patients in the pharmacist care group experienced statistically significant reductions in blood pressure (27 mm Hg vs 9.3 mm Hg).
Pastakia et al.[94]	Kenya	Bridging Income Generation through Group Integrated Care (BIGPIC)—community events were held for rural Kenyan communities where attendees received information on microfinance, agribusiness, and healthcare services. Interested participants then formed community groups where they could participate in microfinance activities, agriculture cooperatives, and receive portable care services (consultation, laboratories, and medications) from an interdisciplinary team of local practitioners working with the ministry of health.	Economic stability, neighborhood and physical environment, education, food, community and social context	Statistically significant improvements in participation in care were seen along with statistically significant reductions in blood pressure control with patients demonstrating a 21 mm Hg reduction in systolic blood pressure.
Palazuelos D et al.[95]	Haiti, Kazakhstan, Lesotho, Liberia, Malawi, Mexico, Peru, Rwanda, Sierra Leone	Partners in Health (www.pih.org) revamps healthcare systems around the world. Central to their model is the integration of community health workers (accompagnateurs) who assist with a wide range of activities (education, supply chain support, medication deliveries, adherence support, counseling, screening, home visits) across different disease states.	Community context	Haiti—100% clinical cure rate for tuberculosis patients Mexico—doubling of the odds of sustaining clinical control for diabetes and hypertension beyond 2 years Malawi—83% 12-month survival after chemotherapy for patients with Kaposi sarcoma and HIV Lesotho—no maternal deaths in first 2 years Rwanda—92.3% retention with 97.5% with a viral load less than 500 copies/mL among people living with HIV
Jackson C et al.[96]	India	In order to address the growing burden of tuberculosis and multidrug-resistant tuberculosis, Operation Asha (OpAsha) has developed a community health worker-based model to track directly observed therapy by using digital fingerprints to document the receipt and consumption of tuberculosis medications.	Community and social context	OpAsha was able to achieve treatment success rates (84.9%) comparable to the national average for India despite working exclusively with disadvantaged populations predominantly residing in urban slums.
Ali GK. (Sudan)[97] Murakami et al. (Lao)[98] Manji et al. (Kenya)[99] Uzochukwu et al. (Nigeria)[100]	Sudan, Lao, Kenya, Nigeria	Revolving Drug Fund (RDF) pharmacies have been established in multiple countries to serve as a parallel or backup to the ministry of health supply chain to minimize stockouts for patients seeking care in the public sector.	Community context, affordability of healthcare services	Sudan—achieved 97% availability of essential medicines through the RDF Lao—87% of outpatients could fill their prescriptions Kenya—availability of essential medicines was increased from < 50% in three facilities to > 90% in the first three RDF pharmacies Nigeria—centers with RDF pharmacies had greater average availability of essential medicines (35.4 vs 15.3, $p < 0.05$)



Females

Leading causes 1990	Leading causes 2007	Mean percentage change in number of DALYs, 1990–2007	Mean percentage change in age-standardised DALY rate, 1990–2007	Leading causes 2017	Mean percentage change in number of DALYs, 2007–20017	Mean percentage change in age-standardised DALY rate, 2007–20017
1 Neonatal disorders	1 Neonatal disorders	–17.3	–17.8	1 Neonatal disorders	–18.2	–21.9
2 Lower respiratory infections	2 Lower respiratory infections	–39.6	–42.0	2 Ischaemic heart disease	17.0	–10.4
3 Diarrhoeal diseases	3 HIV/AIDS	610.7	483.0	3 Stroke	13.6	–12.5
4 Stroke	4 Ischaemic heart disease	14.9	–23.6	4 Lower respiratory infections	–26.8	–33.6
5 Ischaemic heart disease	5 Diarrhoeal diseases	–40.8	–44.2	5 Diarrhoeal diseases	–27.8	–35.5
6 Congenital defects	6 Stroke	8.4	–26.5	6 COPD	21.2	–6.3
7 COPD	7 Malaria	28.6	23.2	7 Low back pain	17.3	–2.7
8 Measles	8 COPD	–1.3	–32.7	8 Headache disorders	15.3	0.7
9 Tuberculosis	9 Congenital defects	–12.8	–15.6	9 Diabetes	29.5	1.9
10 Malaria	10 Low back pain	29.8	–7.6	10 Congenital defects	–9.6	–14.8
11 Low back pain	11 Headache disorders	34.0	–0.1	11 Depressive disorders	14.1	–3.1
12 Headache disorders	12 Diabetes	60.3	10.4	12 HIV/AIDS	–53.9	–58.8
13 Dietary iron deficiency	13 Depressive disorders	32.2	–3.0	13 Malaria	–35.4	–40.2
14 Maternal disorders	14 Tuberculosis	–25.0	–40.9	14 Dietary iron deficiency	–5.0	–14.6
15 Protein-energy malnutrition	15 Dietary iron deficiency	0.3	–18.8	15 Alzheimer's disease	36.1	–0.9
16 Road injuries	16 Road injuries	–1.6	–20.5	16 Road injuries	–4.8	–17.2
17 Depressive disorders	17 Maternal disorders	–21.7	–38.7	17 Other musculoskeletal	21.0	0.9
18 Meningitis	18 Anxiety disorders	33.0	0.6	18 Breast cancer	24.4	–1.4
19 Diabetes	19 Other musculoskeletal	49.7	7.0	19 Age-related hearing loss	25.7	0.2
20 Self-harm	20 Breast cancer	35.9	–8.1	20 Tuberculosis	–20.6	–32.2
21 Drowning	21 Chronic kidney disease	22.4	–11.0	21 Anxiety disorders	12.4	–1.9
22 Asthma	22 Alzheimer's disease	52.1	–6.1	22 Chronic kidney disease	21.5	–2.4
23 Chronic kidney disease	23 Age-related hearing loss	44.9	0.7	23 Neck pain	20.8	–1.5
24 Anxiety disorders	24 Neck pain	45.7	0.8	24 Blindness & vision impairment	22.6	–2.1
25 Tetanus	25 Blindness & vision impairment	41.8	–0.6	25 Falls	24.4	0.3
26 Breast cancer	26 Meningitis	–23.0	–27.0	26 Cirrhosis	9.4	–11.2
27 Falls	27 Self-harm	–21.9	–39.8	27 Lung cancer	31.7	1.4
28 Cirrhosis	28 Falls	19.2	–12.9	28 Gynaecological disease	10.2	–2.4
29 Other musculoskeletal	29 Protein-energy malnutrition	–39.8	–40.9	29 Maternal disorders	–24.1	–30.3
30 Blindness & vision impairment	30 Cirrhosis	16.6	–16.6	30 Asthma	9.7	–8.2
31 Age-related hearing loss	31 Gynaecological disease			31 Self-harm		
32 Neck pain	32 Asthma			34 Meningitis		
33 Alzheimer's disease	33 Lung cancer			37 Protein-energy malnutrition		
34 Gynaecological disease	34 Measles			52 Drowning		
36 HIV/AIDS	37 Drowning			64 Measles		
43 Lung cancer	74 Tetanus			118 Tetanus		

🟥 Communicable, maternal neonatal, and nutritional diseases

🟦 Non-communicable diseases

🟩 Injuries

Males

Leading causes 1990	Leading causes 2007	Mean percentage change in number of DALYs, 1990-2007	Mean percentage change in age-standardised DALY rate, 1990–2007	Leading causes 2017	Mean percentage change in number of DALYs, 2007–20017	Mean percentage change in age-standardised DALY rate, 2007–20017
1 Neonatal disorders	1 Neonatal disorders	–17.1	–17.6	1 Ischaemic heart disease	17.8	–9.2
2 Lower respiratory infections	2 Ischaemic heart disease	25.7	–18.0	2 Neonatal disorders	–20.1	–22.9
3 Diarrhoeal diseases	3 Lower respiratory infections	–37.4	–40.1	3 Stroke	17.4	–9.9
4 Ischaemic heart disease	4 Stroke	22.4	–18.3	4 Lower respiratory infections	–24.9	–31.4
5 Stroke	5 Diarrhoeal diseases	–33.3	–37.5	5 Road injuries	–6.5	–17.3
6 Road injuries	6 Road injuries	7.3	–14.7	6 COPD	13.5	–14.1
7 Congenital defects	7 HIV/AIDS	297.3	212.9	7 Diarrhoeal diseases	–27.7	–34.0
8 Tuberculosis	8 COPD	5.5	–29.9	8 Diabetes	30.4	2.9
9 COPD	9 Congenital defects	–14.5	–17.8	9 Congenital defects	–12.1	–16.7
10 Measles	10 Malaria	30.5	23.6	10 Low back pain	17.8	–1.3
11 Malaria	11 Tuberculosis	–12.7	–35.1	11 Cirrhosis	9.9	–10.2
12 Drowning	12 Diabetes	73.3	17.8	12 Lung cancer	22.3	–6.4
13 Protein-energy malnutrition	13 Cirrhosis	26.9	–11.3	13 HIV/AIDS	–44.8	–51.1
14 Self-harm	14 Low back pain	30.2	–6.8	14 Tuberculosis	–19.1	–32.0
15 Cirrhosis	15 Lung cancer	22.9	–16.4	15 Malaria	–33.0	–37.7
16 Meningitis	16 Self-harm	10.7	–16.8	16 Self-harm	–0.8	–13.5
17 Low back pain	17 Interpersonal violence	15.3	–9.6	17 Falls	15.3	–3.8
18 Lung cancer	18 Falls	18.7	–10.8	18 Headache disorders	15.5	1.5
19 Interpersonal violence	19 Headache disorders	34.1	1.1	19 Interpersonal violence	2.0	–8.3
20 Diabetes	20 Chronic kidney disease	34.5	–2.7	20 Chronic kidney disease	21.9	–2.0
21 Falls	21 Drowning	–39.2	–45.5	21 Drug use disorders	26.6	11.9
22 Asthma	22 Drug use disorders	37.2	5.7	22 Age-related hearing loss	24.2	–0.7
23 Tetanus	23 Depressive disorders	35.5	–0.1	23 Depressive disorders	14.8	–1.9
24 Headache disorders	24 Meningitis	–26.2	–30.4	24 Liver cancer	22.9	–3.0
25 HIV/AIDS	25 Age-related hearing loss	44.0	–0.1	25 Blindness & vision impairment	23.6	–1.5
26 Stomach cancer	26 Alcohol use disorders	47.1	7.0	26 Other musculoskeletal	16.6	–2.7
27 Diatary iron deficiency	27 Liver cancer	33.0	–7.8	27 Alcohol use disorders	3.8	–11.4
28 Chronic kidney disease	28 Protein-energy malnutrition	–44.1	–45.8	28 Stomach cancer	5.6	–18.5
29 Leishmaniasis	29 Stomach cancer	–1.4	–33.0	29 Neck pain	22.3	0.4
30 Depressive disorders	30 Other musculoskeletal	40.5	0.3	30 Alzheimer's disease	41.8	0.5
31 Drug use disorders	31 Diatary iron deficiency			31 Drowning		
32 Age-related hearing loss	32 Asthma			32 Asthma		
35 Liver cancer	33 Blindness & vision impairment			33 Meningitis		
36 Alcohol use disorders	34 Neck pain			34 Diatary iron deficiency		
38 Other musculoskeletal	36 Measles			42 Protein-energy malnutrition		
39 Blindness & vision impairment	40 Alzheimer's disease			66 Measles		
41 Neck pain	42 Tetanus			108 Tetanus		
54 Alzheimer's disease	115 Leishmaniasis			145 Leishmaniasis		

🟥 Communicable, maternal neonatal, and nutritional diseases

🟦 Non-communicable diseases

🟩 Injuries

FIGURE 5–8. Top 30 leading causes of disability-adjusted life years around the world. Reproduced with permission from Kyu HH, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018;392(10159):1859–922.

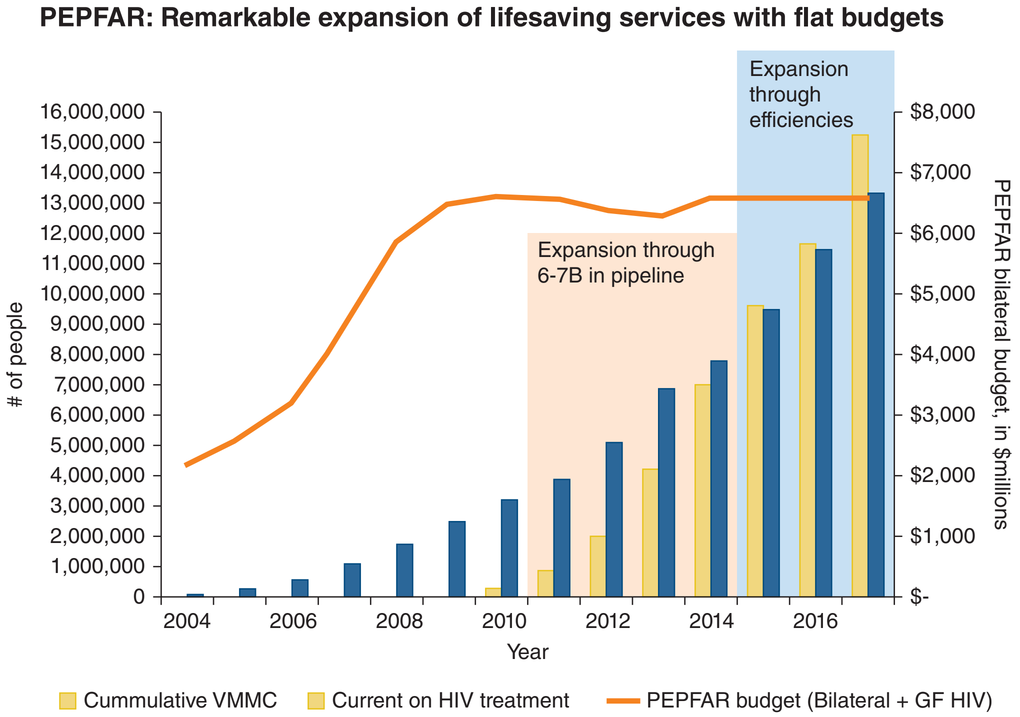


FIGURE 5–9. PEPFAR funding commitments and reach by year. (VMMC, voluntary medical male circumcision; GF, global fund.) From PEPFAR 2018 Annual Report to Congress. U.S. Department of State Office of the U.S. Global AIDS Coordinator and Health Diplomacy, April 2018. https://www.state.gov/wp-content/uploads/2019/08/PEPFAR-2018-Annual-Report-to-Congress.pdf.

North American organizations including academic institutions. This investment has helped seed many of the academic collaborations, which have now grown to expand beyond HIV.

While US funding for the PEPFAR is now declining as seen in Figure 5–9, many efficiencies in program activities have helped sustain and expand the impact of this investment. As seen in the 2019 PEPFAR annual report in Figure 5–10, 79.6 million people have received HIV screening, and 15.7 million people are on lifesaving antiretroviral treatment across PEPFAR-supported countries. This success has supported the realistic hope that PEPFAR-supported countries can end the HIV epidemic by 2030 by consistently meeting the 90-90-90 targets (ie, 90% of the people living with HIV knowing their HIV status, 90% of the people living with HIV on antiretroviral therapy, 90% of the people receiving antiretroviral therapy achieving virological suppression). PEPFAR has reinforced the importance of these targets in hastening the end of the HIV epidemic by advocating that countries attempt to reach 95% for each of the three domains. This will continue to reduce the number of new infections below 200,000 per year and limit the future burden of HIV.

Other notable examples of international funding collaborations focused on infectious diseases include, but are not limited to, the Global Alliance for Vaccines and Immunizations (www.gavi.org) (GAVI), the President's (US) Malaria Initiative (www.pmi.gov), and The Global Fund to Fight AIDS, Tuberculosis, and Malaria (www.theglobalfund.org). Throughout human history, there have been numerous other viral epidemics besides HIV, as seen in Table 5–2. These epidemics have had devastating effects on the morbidity and mortality faced by populations around the world with entire populations being decimated as viruses have rapidly spread throughout certain regions. While these partnerships have helped us envision an end to the HIV epidemic, many of these same strategies could help us combat other viral illnesses and prevent the high mortality seen in past epidemics.[21] As we continue to manage the challenges with the recent COVID-19 pandemic, it is important that we adopt

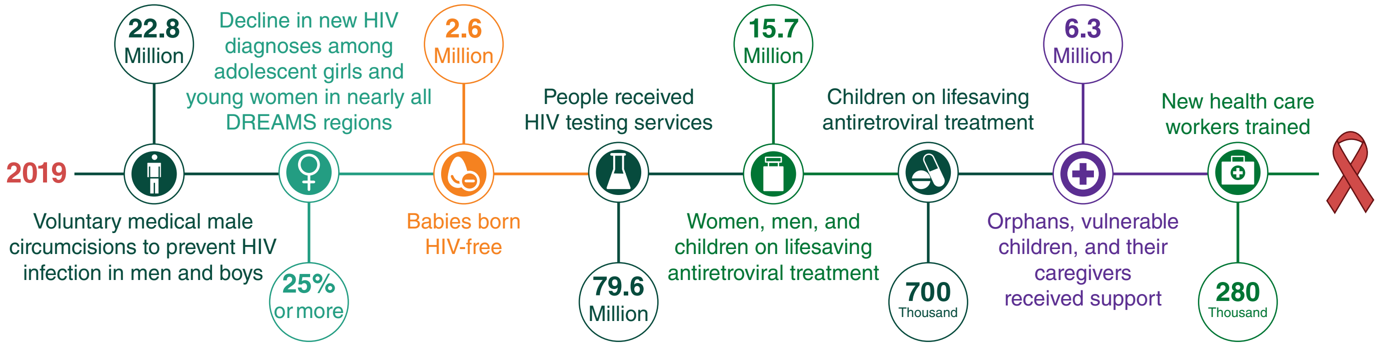

2019
22.8 Million
Voluntary medical male circumcisions to prevent HIV infection in men and boys
Decline in new HIV diagnoses among adolescent girls and young women in nearly all DREAMS regions
25% or more
2.6 Million
Babies born HIV-free
People received HIV testing services
79.6 Million
15.7 Million
Women, men, and children on lifesaving antiretroviral treatment
Children on lifesaving antiretroviral treatment
700 Thousand
6.3 Million
Orphans, vulnerable children, and their caregivers received support
New health care workers trained
280 Thousand

FIGURE 5–10. PEPFAR impact metrics as of 2019. From The United States President's Emergency Plan for AIDS Relief Latest Results United States Department of State 2020 [updated June 16, 2020; cited 2020 June 16]. Available from: https://www.pepfar.gov/funding/results/index.htm.

Table 5–2

Notable Epidemics and Pandemics since the Middle Ages[101]

Starting Year	Event	Geographic Extent	Estimated Direct Morbidity or Mortality	Estimated Economic, Social, or Political Impact
1347	Bubonic plague (Black Death) pandemic	Eurasia	30%–50% mortality of the European population	Likely hastened end of the feudal system in Europe
Early 1500s	Introduction of smallpox	Americas	More than 50% mortality in some communities	Destroyed native societies, facilitating the hegemony of European countries
1881	Fifth cholera pandemic	Global	More than 1.5 million deaths (9.7 per 10,000 persons)	Sparked attacks on Russian tsarist government and medical officials
1918	Spanish flu influenza pandemic	Global	20–100 million deaths (111–555 deaths per 10,000 persons)	GDP loss of 3% in Australia, 15% in Canada, 17% in the United Kingdom, 11% in the United States
1957	Asian flu influenza pandemic	Global	0.7–1.5 million deaths (2.4–5.1 deaths per 10,000 persons)	GDP loss of 3% in Canada, Japan, the United Kingdom, and the United States)
1968	Hong Kong flu influenza pandemic	Global	1 million deaths (2.8 deaths per 10,000 persons)	US$23–US$26 billion direct and indirect costs in the United States
1981	HIV/AIDS pandemic	Global	More than 70 million infections, 36.7 million deaths (WHO Global Health Observatory data)	2%–4% annual loss of GDP growth in Africa[a]
2003	SARS pandemic	4 continents, 37 countries	8098 possible cases, 744 deaths	GDP loss of US$4 billion in Hong Kong SAR, China; US$3–US$6 billion in Canada; and US$5 billion in Singapore
2009	Swine flu influenza pandemic	Global	151,700–575,500 deaths (0.2–0.8 per 10,000 persons)	GDP loss of US$1 billion in the Republic of Korea
2012	MERS epidemic	22 countries	1879 symptomatic cases, 659 deaths	US$2 billion loss in the Republic of Korea, triggering US$14 billion in government stimulus spending
2013[b]	West Africa Ebola virus disease epidemic	10 countries	28,646 cases, 11,323 deaths	US$2 billion loss in Guinea, Liberia, and Sierra Leone
2015	Zika virus pandemic	76 countries	2656 reported cases of microcephaly or central nervous system malformation	US$7–US$18 billion loss in Latin America and the Caribbean

[a] Studies of the effects of HIV/AIDS on per capita gross national product have found smaller effects.

[b] The West Africa Ebola virus outbreak occurred from 2013 to 2016, but the peak and international response efforts began in 2014.

GDP, gross domestic product; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

Note: List of events is illustrative rather than exhaustive. All US dollar amounts are rounded to nearest billion. From Jamison DT, Gelband H, Horton S, et al., editors. 2017. Disease Control Priorities: Improving Health and Reducing Poverty. third edition, volume 9. Washington, DC. The International Bank for Reconstruction and Development/The World Bank. doi: 10.1596/978-1-4648-0527-1. License: Creative Commons Attribution CC BY 3.0 IGO.

successful historic strategies while avoiding the mistakes, which have led to excess morbidity/mortality and preventable economic losses.

Noncommunicable Diseases

Since the early 2000s, an epidemiological transition that has accompanied urbanization has occurred. This has led to a rise in noncommunicable diseases (NCDs) and a reduction in the burden on communicable diseases. As seen in Figure 5–8, NCDs are the leading causes of death and disability, responsible for 73% of deaths and 61% of DALYs globally, and disproportionately so in LMICs.[22,23] Eighty percent of global NCDs are among LMIC individuals, and 80% of premature deaths (ie, deaths occurring before age 70) from NCDs occur in LMICs. The net effect of rising NCDs in LMICs is a dual burden of disease that puts significant strain on the health system. For example, in Africa, while 29% of DALYs in 2017 were attributable to NCDs, these were still second to communicable, maternal, neonatal, and nutritional disorders. In addition, incident cases of HIV/AIDS remain highest in Africa.[24] Further, recent infectious pandemics such as Ebola and COVID-19 are notable for exposing existing deficiencies on LMIC health systems.[25]

Inequities in access to quality health care contribute to the disproportionate burden: morbidity and mortality of NCDs in LMICs.[26] Equitable access incorporates four key domains. First, health services should be made available to a population in need. Consideration in this domain should factor in the availability of health workers and health facilities, geographical considerations, and the associated direct and indirect costs of physically accessing the services. Second, available services must be usable by the population, that is, they must be both affordable and acceptable. Third, health services should be available in a timely fashion to enable prevention, management, and treatment of disease in order to prevent unnecessary death and disability. Fourth, and overarching the three domains above, that access is equitable—enabling all those in need to receive health services.[27] Limited access to health care pervades LMICs, with emerging diseases like hypertension and diabetes having lower control rates than high-income countries. Access to standard drugs such as statins for primary and secondary prevention of cardiovascular disease is also low. Capacity for screening, diagnosis, and treatment of common cancers (eg, cervical) is limited in LMICs. Key causes for the above include lack of access to necessary evidence-based interventions such as essential medicines. This is particularly problematic given that NCDs require lifelong treatment and surveillance for disease complications. Catastrophic healthcare spending—that is, healthcare spending that risks a household's ability to meet their basic needs relative to their income—occurs in 60% to 92% of LMIC households in which an NCD diagnosis has been made.[28,29]

The connection between ill health and socioeconomic disparity, its causes, and consequences on overall health is an important consideration in clinical practice. It informs prevention, diagnosis, and treatment decisions in the various contexts. Standard evidence-based treatments and interventions recommended for specific clinical indications may be inaccessible in a specific setting (see Patient Encounter 1) necessitating use of less ideal, yet suitable alternatives. If a key goal of global health practice is to improve population health, greater understanding of these drivers and results will increase effectiveness of practice by aligning service delivery to contextual needs and available resources. While less ideal alternatives may sometimes have to be utilized due to these constraints, healthcare practitioners and the healthcare system at large must ensure that continuous efforts are made to optimize access to the preferred treatment for each individual patient.

Patient Encounter 1

EK is a 28-year-old woman, weight 61 kg, admitted for management of new-onset atrial fibrillation at a cardiac care unit in a referral hospital in Western Kenya. She has underlying rheumatic heart disease, one of the leading causes of cardiovascular disease (CVD)-related DALYs among young patients in LMICs, with severe mitral regurgitation and heart failure with preserved ejection fraction and is on regular follow-up at the outpatient cardiac clinic.[20] At her last visit 4 days ago, she was noted to have an irregular heart rate at 145 beats/min. Her home medications before this admission were oral furosemide 40 mg once daily and once monthly benzathine penicillin 1.2 million unit injection for secondary prophylaxis of rheumatic fever. She is a single mother of two children who are both in primary school. She runs a small shop that provides the family income, just enough for her family's subsistence, children's education, her medicines, and her inpatient health insurance plan. Her health insurance does not cater for outpatient treatment or home medications. On day 4 of her hospital stay, EK is eager to be discharged, as her shop has had to remain closed while she has been in the hospital as she has no one to run it. The medical team believes she is stable enough for discharge but would like to put in place an anticoagulation plan because of her new-onset atrial fibrillation and mitral valve disease. She is currently on oral furosemide 40 mg once daily, oral metoprolol succinate 25 mg once daily, and subcutaneous enoxaparin 60 mg twice daily. While reviewing the current guidelines for management of atrial fibrillation, you note that either a direct oral anticoagulant (DOAC) such as rivaroxaban or a vitamin K antagonist such as warfarin may be appropriate for her atrial fibrillation and mitral regurgitation. The referral hospital has a busy anticoagulation monitoring service, but EK lives approximately 3 hours away by public transport. Rivaroxaban is also available but costly. At the hospital, a month's prescription is priced at about a third of her current monthly income, and if available, is likely to be two times higher in private pharmacies closer to her home.

What additional considerations would you need to make in discussing EK's options with her and the clinical care team?

What are the trade-offs this patient is being forced to consider?

What is the best way forward for EK's anticoagulation discharge plan?

MATERNAL AND CHILD HEALTH

KEY CONCEPT While infectious diseases have been the main funding priority for international donors over the last three decades, development funding focused on addressing the maternal and child health needs of populations has consistently been shown to be one of the most impactful investments in improving the long-term productivity and economic performance of LMICs.[30,31] These broader improvements are tied to improvements in several key metrics which include, but are not limited to, (1) maternal mortality ratio, (2) fertility rate, and (3) unmet needs for family planning.

The maternal mortality ratio is the main measure used to judge progress in health care for pregnancy-related needs. This ratio is calculated by taking the number of maternal deaths in a calendar year and dividing it by the number of live births for the same period multiplied by 100,000. As seen in Figure 5–11, maternal mortality remains highest in the low-income classification countries in Africa while high-income countries tend to have the lowest maternal mortality ratios.

A closer examination of trends for high-income countries in Figure 5–12 illustrates the higher maternal mortality ratio experienced by pregnant mothers in the United States compared to their high-income country peers.

Efforts to improve the maternal mortality ratio, especially in LMICs, often focus on the three delays model that suggests maternal mortality is related to delays in (1) deciding to seek care, (2) reaching the healthcare facility, and (3) receiving care.[32]

The total fertility rate is an important metric which has considerable ramifications for the economic growth of countries. Between 2010 and 2015, the average global fertility rate was 2.5 live births per woman. If the fertility growth is too low (< 2.1 live births per woman), the current population is unable to replace the parents' generation (ie, below replacement fertility). However, if the fertility rate goes too high without concomitant economic growth and increased employment opportunities, the growth in population frequently worsens the economic outlook for the country and especially for women as they take on more child rearing responsibilities and become more dependent on income from spousal partners trying to find economic opportunities in a more competitive job market.[33]

Because of the growing understanding of the impact of fertility rate on economic growth, the proportion of women with unmet family planning needs has become an important target to promote development in Africa and other LMICs with elevated fertility rates (see Figure 5–13). Studies have consistently demonstrated the cost-effectiveness of this investment, and increasing access to family planning remains a time-tested and proven intervention in improving health and economic outcomes.[34]

Furthermore, increased access to family planning reduces the need for provider-assisted and unsafe abortions.[35]

Access to family planning has also been estimated to reduce maternal deaths by 44% or 272,040 each year. If the unmet needs for contraception were addressed, an additional 29% or 104,000 maternal deaths could be prevented each year.[36]

ALGRAWANY

Breast and Cervical Cancer—Diseases of Disparities

These two prominent cancers in women highlight the many disparities in health described throughout this chapter. Globally, the majority of women who die from breast and cervical cancer live in low- and middle-income countries with many of these deaths being preventable. In contrast, most women living in high-income countries who develop these cancers will survive. This contrast is especially stark for cervical cancer where numerous preventative strategies have demonstrated effectiveness and are readily available in high-income countries. As seen in **Figure 5–14**, Africa faces a disproportionate burden in terms of the incidence of new cases and an exceptionally high mortality rate compared to all other regions of the world. This is due to a combination of socioeconomic factors which have limited the widespread scale up of (1) vaccination against harmful strains of human papillomavirus (HPV), (2) routine screening through Pap smear testing or visual inspection with acetic acid, and (3) access to effective chemotherapy and/or radiotherapy where appropriate.

In contrast, Figure 5–14 illustrates the higher incidence of breast cancer in high-income countries where women tend to live longer, which increases their likelihood of developing breast cancer over their lifetime. However, women in low- and middle-income countries, especially those in Africa, experience a higher mortality rate than women with breast cancer in high-income countries. This disparity is largely due to earlier diagnosis combined with greater access to effective chemotherapy and radiotherapy in high-income countries. Urgent action is needed to protect the health of women from these cancers as they currently take the lives of three times as many women each year than complications from pregnancy and childbirth.[37]

Fortunately, recent efforts from organizations like GAVI to increase access to HPV vaccine in LMICs are gaining traction, and countries are now making demonstrable headway in increasing vaccine uptake and averting preventable cervical cancer–related morbidity and mortality.

GLOBAL PROGRAMS

Medication Access

The right to health, including access to essential medicines, is a fundamental human right; however, an estimated 2 billion people have no access to essential medicines.[38] KEY CONCEPT Three major barriers to medication access—availability, accountability, and adherence—are summarized in **Figure 5–15**.[39] To help tackle the first barrier of *availability*, WHO released the initial version of their Essential Medicines List (EML) in 1977 with subsequent revisions published every 2 years. This EML includes medications that are considered safe, effective, and cost-effective and satisfy the priority healthcare needs of the population. It is intended to serve as a model list for countries to use when developing national EMLs, akin to a suggested national formulary. In response to rising global antibiotic consumption, WHO more recently added the Access, Watch, Reserve (AWaRe) classification of antibiotics to the EML framework to help promote antimicrobial stewardship and combat development of resistance. While the EML has increased

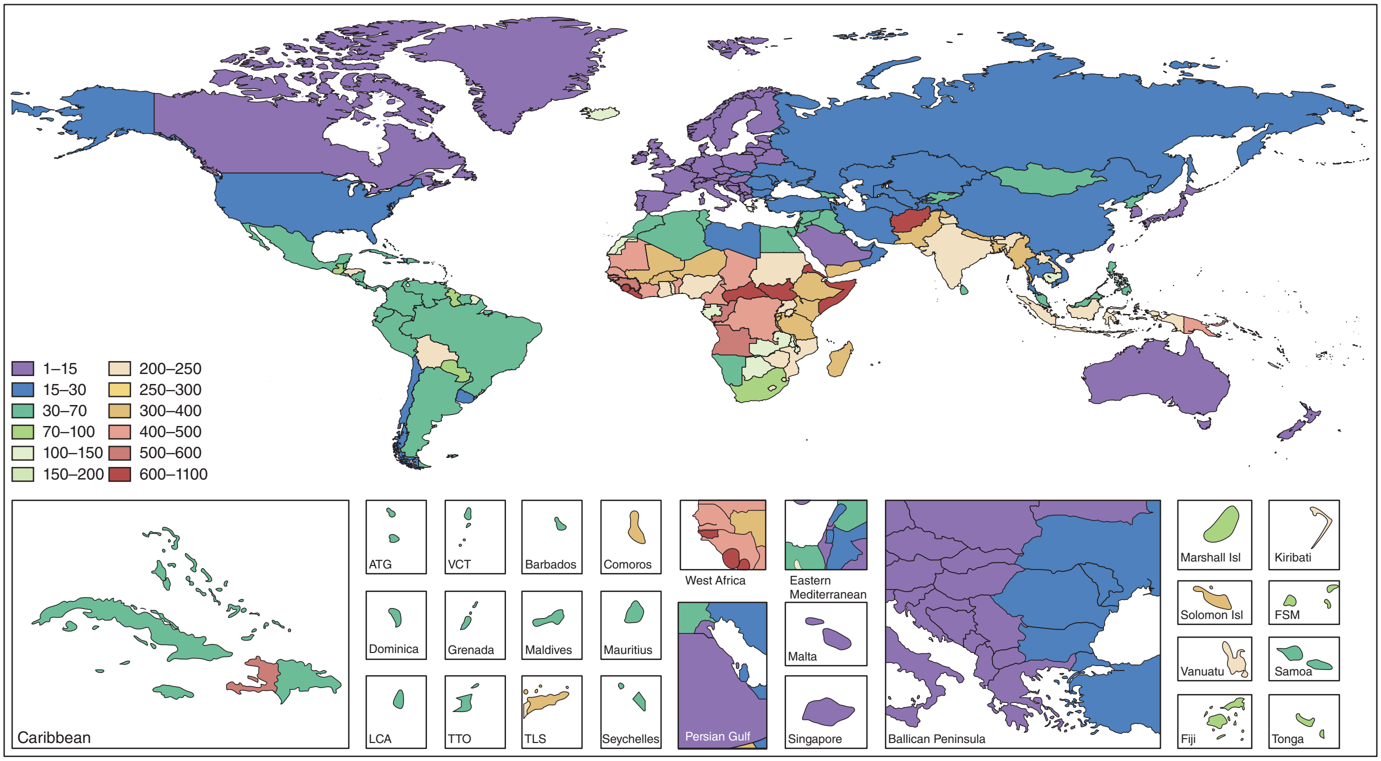


FIGURE 5–11. Maternal mortality ratio for countries and territories, 2015. From GBD 2015 Maternal Mortality Collaborators. Global, regional, and national levels of maternal mortality, 1990–2015; a systematic analysis for the Global Burden of Disease Study 2015. The Lancet. 2016;388(10053):1775–1812.

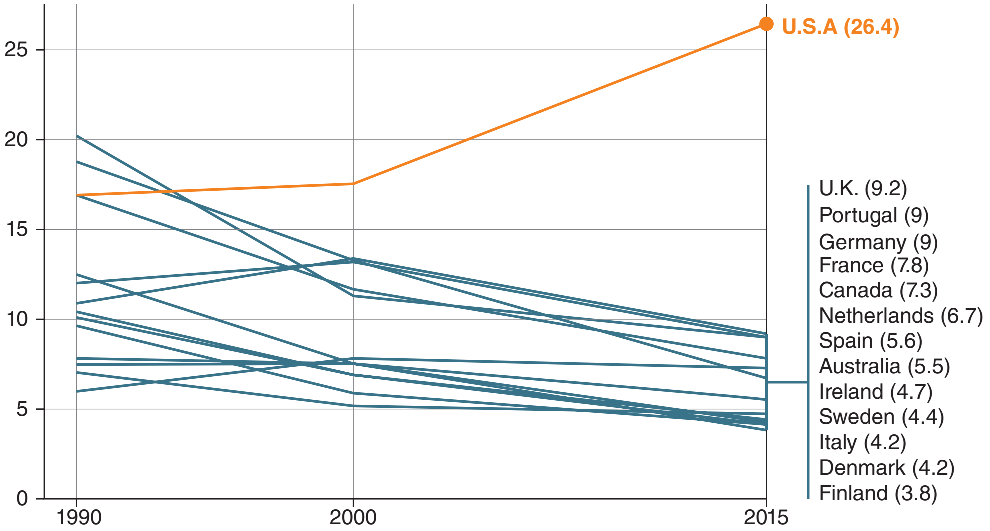


FIGURE 5–12. Maternal mortality ratio trends within high-income countries. From Martin N, Montagne R. US Has The Worst Rate Of Maternal Deaths In The Developed World: National Public Radio; 2017 [cited 2020 Aug 1]. Available from: https://www.npr.org/2017/05/12/528098789/u-s-has-the-worst-rate-of-maternal-deaths-in-the-developed-world.

access in some countries, numerous gaps in medication availability remain in many regions, as a lack of infrastructure has hindered the practical implementation of this guidance.[40,41] Underresourced multitier supply chains and poor operations management within a pharmacy or hospital also limit availability. Facilities often lack reliable inventory systems to track and forecast medication use and inconsistent financial means, making it difficult to identify the optimal time to order before the available supply is depleted.[39] These systems frequently lack real-time documentation and reporting, which contributes to delayed or inconsistent procurement.

A lack of *accountability* for upholding standards of quality assurance perpetuates limited access to medications. This is exacerbated by complicated supply chains with multiple tiers between initial drug acquisition and end user, as each tier places blame on another step in the chain when something goes awry.[39,42] In order to cut costs and maximize profit, wholesalers and distributors are often compelled to purchase the cheapest available medicine

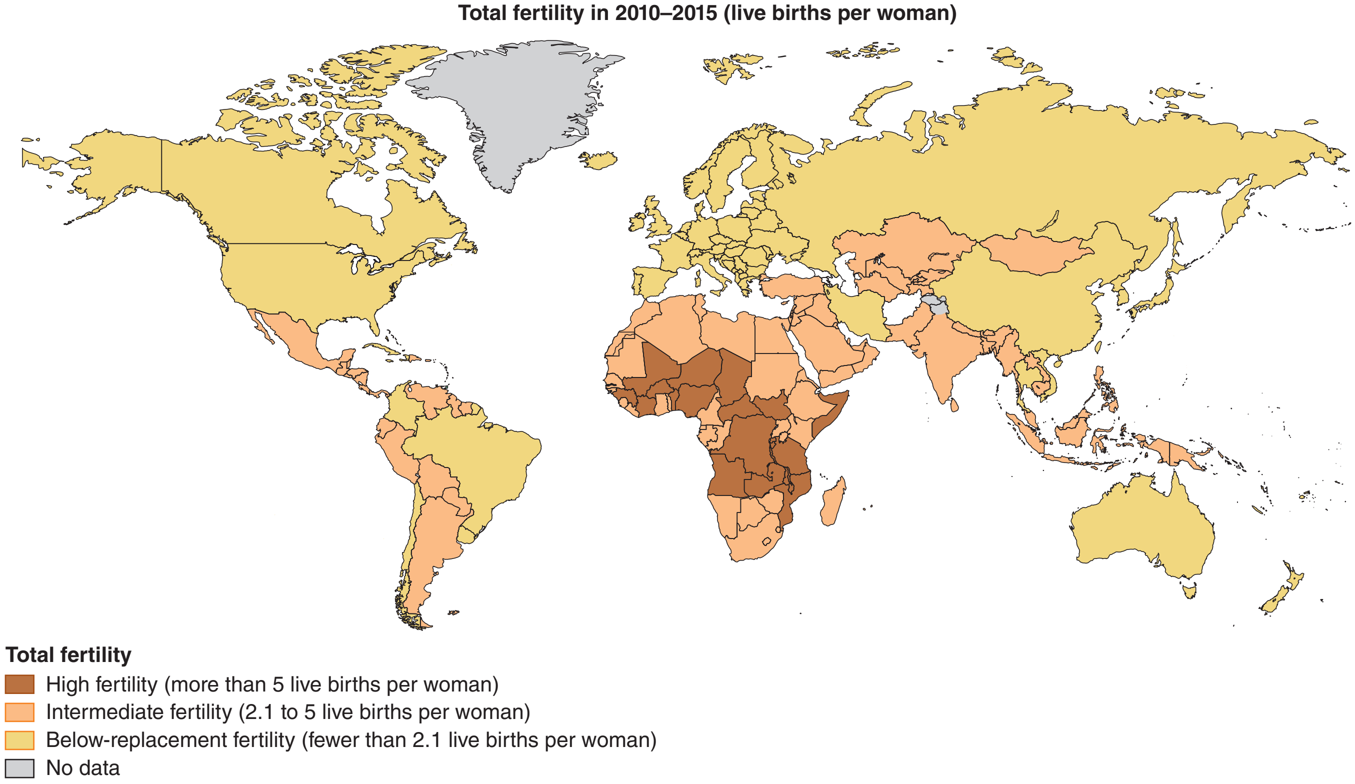

Total fertility in 2010–2015 (live births per woman)
Total fertility
High fertility (more than 5 live births per woman)
Intermediate fertility (2.1 to 5 live births per woman)
Below-replacement fertility (fewer than 2.1 live births per woman)
No data

FIGURE 5–13. Total fertility rate from 2010 to 2015 for countries and territories. From United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Prospects: The 2017 Revision, Data Booklet. ST/ESA/SER.A/401. https://population.un.org/wpp/Publications/Files/WPP2017_DataBooklet.pdf.

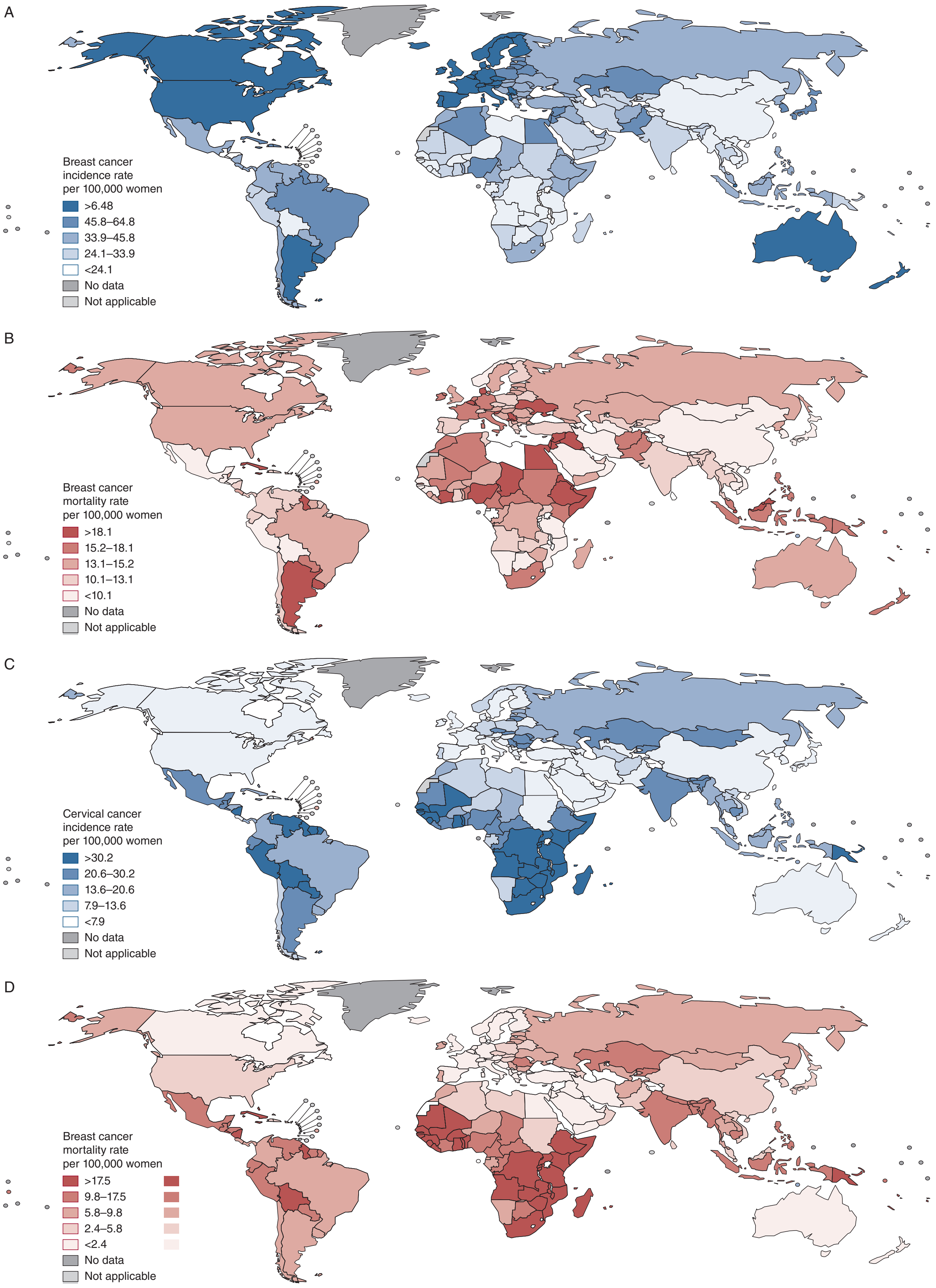

A
Breast cancer incidence rate per 100,000 women
>6.48
45.8–64.8
33.9–45.8
24.1–33.9
<24.1
No data
Not applicable
B
Breast cancer mortality rate per 100,000 women
>18.1
15.2–18.1
13.1–15.2
10.1–13.1
<10.1
No data
Not applicable
C
Cervical cancer incidence rate per 100,000 women
>30.2
20.6–30.2
13.6–20.6
7.9–13.6
<7.9
No data
Not applicable
D
Breast cancer mortality rate per 100,000 women
>17.5
9.8–17.5
5.8–9.8
2.4–5.8
<2.4
No data
Not applicable

FIGURE 5–14. Breast and cervical cancer incidence and mortality rate for countries and territories. From Ginsburg O, Bray F, Coleman MP, et al. The global burden of women's cancers: a grand challenge in global health. The Lancet. 2016;389(10071):847–860.

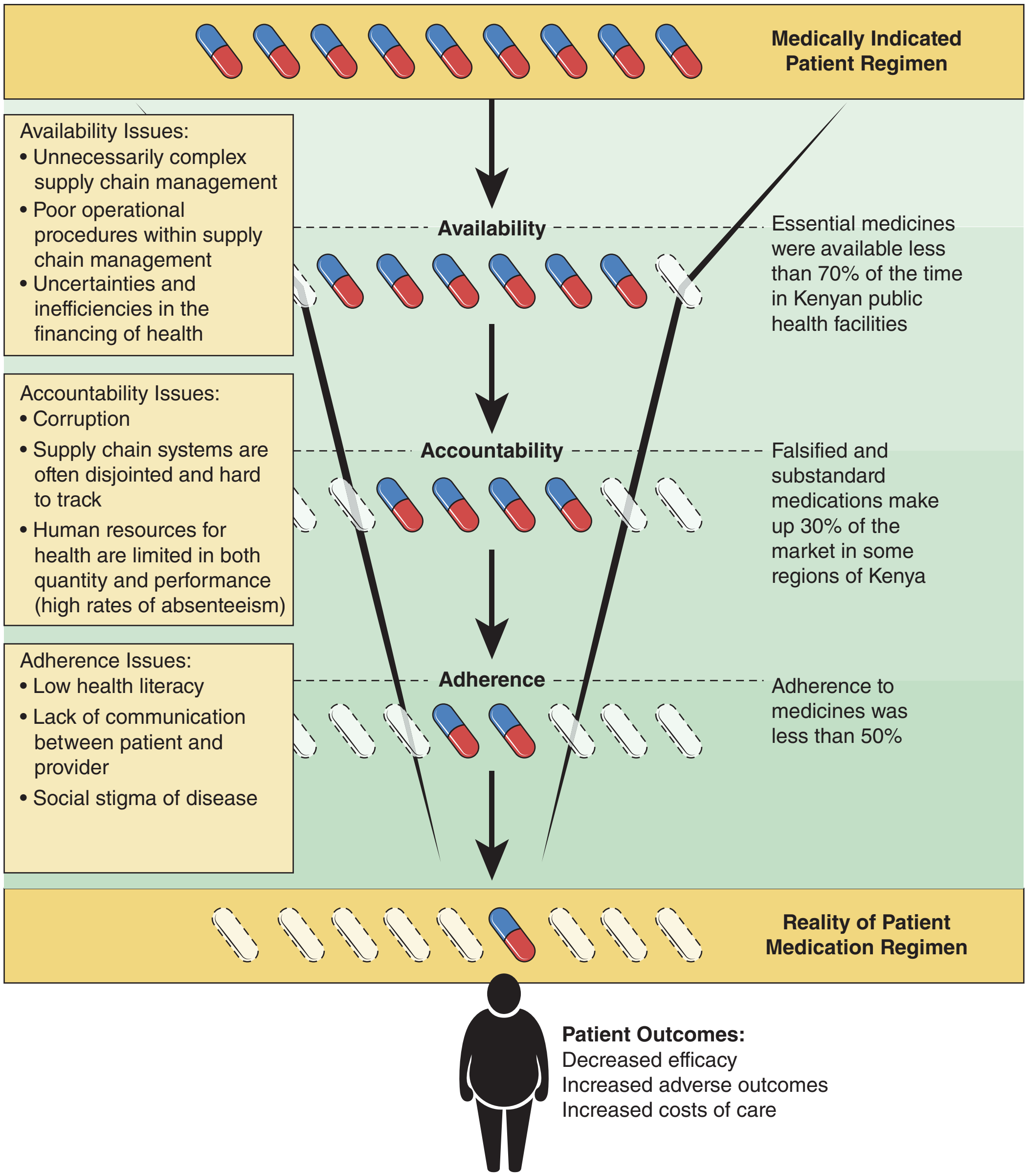

Medically Indicated Patient Regimen
Availability Issues:
• Unnecessarily complex supply chain management
• Poor operational procedures within supply chain management
• Uncertainties and inefficiencies in the financing of health
Availability
Essential medicines were available less than 70% of the time in Kenyan public health facilities
Accountability Issues:
• Corruption
• Supply chain systems are often disjointed and hard to track
• Human resources for health are limited in both quantity and performance (high rates of absenteeism)
Accountability
Falsified and substandard medications make up 30% of the market in some regions of Kenya
Adherence Issues:
• Low health literacy
• Lack of communication between patient and provider
• Social stigma of disease
Adherence
Adherence to medicines was less than 50%
Reality of Patient Medication Regimen
Patient Outcomes:
Decreased efficacy
Increased adverse outcomes
Increased costs of care

FIGURE 5–15. Factors contributing to medication-related outcomes. Reproduced with permission from Karwa R, Tran DN, Maina M, et al. Addressing the 3A's (Availability, Accountability, Adherence) of Supply Chain Systems in Western Kenya. Mobilizing Chemistry Expertise To Solve Humanitarian Problems Volume 1. ACS Symposium Series, Vol. 1267. 2017. Copyright © 2017 American Chemical Society.

including from sources with unproven validity who may not have completed the appropriate registration and manufacturer processes.[39] Due to poor infrastructure and a lack of regulatory bodies to enforce good manufacturing practices, many LMICs are unable to hold the culprits responsible or stop counterfeit medications from infiltrating the supply chain.[43] Countries with poor pharmacovigilance systems have the greatest risk of impact from substandard or falsified (SF) medications.[44] Not only do SF medications contribute to worse clinical outcomes due to not providing the intended drug/dose to achieve the desired therapeutic outcome, but they undermine people's trust in the legitimacy of the health system.[44] A review and meta-analysis of 265 studies estimated the overall prevalence of counterfeit medications to be 13.6% across LMICs, ranging from 13.7% in Asia to 18.7% in Africa.[44] Antimicrobials are the most commonly SF medication class, leading to concerns not only for a lack of appropriate therapy but also for potential development of resistance with subtherapeutic doses (for more information on the importance of providing an optimal antimicrobial regimen, see Chapter 72). A study assessing the quality of amoxicillin and amoxicillin/clavulanate across retail and private hospital pharmacies in Nairobi, Kenya found that almost 40% of analyzed drugs did not comply with quality standards.[45] In particular, SF antimalarials lead to significant morbidity and mortality in LMICs. The estimated prevalence of SF antimalarials in select African countries ranged from 10.3% in Zambia to 22% in Uganda, and a 10% reduction in poor-quality antimalarials would avoid an estimated $578 million in Nigeria.[46]

Medication access does not stop once the drug reaches the patient—patient *adherence* is another key component. It is estimated that 50% of patients are nonadherent to prescribed medication regimens.[38] One of the most prominent factors associated with medication nonadherence is financial burden, including cost of medication, provider visit, and transportation to clinic and

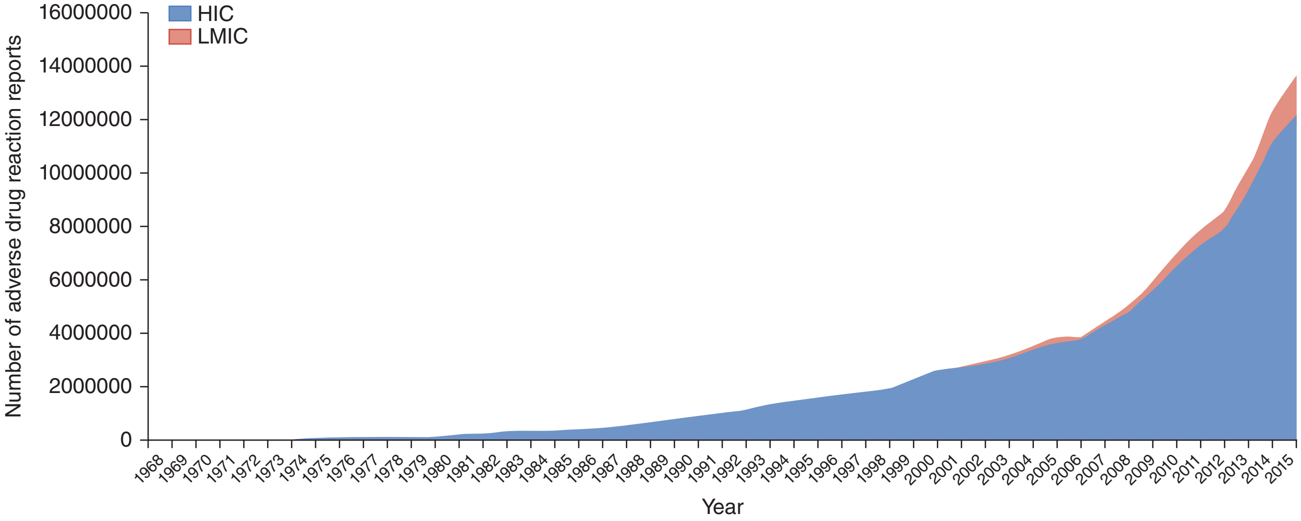


FIGURE 5–16. Number of adverse drug reaction reports in high- versus low- and middle-income countries. Reproduced with permission from Wirtz VJ, Hogerzeil HV, Gray AL, et al. Essential medicines for universal health coverage. The Lancet. 2017;389(10067):403–476.

pharmacy.[39] When medications are not covered by insurance or a national health system, and patients have to pay out of pocket, they may be unable to afford the prescribed therapy or may resort to obtaining a medication from an unlicensed supplier such as in a street market.[47] Factors associated with the regimen itself also play a role. Complex medication regimens with a significant pill burden or those requiring numerous doses per day have been shown to reduce patient adherence.[39,48] Studies have shown once-daily antiretroviral therapy regimens have improved adherence compared to twice-daily regimens.[49,50] Medication-related adverse effects are also a barrier to adherence and have been associated with a twofold increased risk of nonadherence.[39] The challenge of adverse effects in LMIC settings is further complicated by the limited availability of data describing the incidence of side effects in their populations as most of the data come from high-income countries as seen in Figure 5–16.[51] Of more than 10 million individual safety reports submitted to a global pharmacovigilance database as of 2015, less than 10% were from LMICs.

Overall, there are numerous barriers contributing to the lack of medication access for disadvantaged populations. While there are initiatives in place intended to reduce these disparities, additional work is needed to maximize health outcomes from appropriate pharmacotherapy. In particular, treatments for neglected tropical diseases (NTDs) deserve greater focus to lower disease burden and increase quality of life. While this section focused on increasing the availability, accountability, and adherence to medications for common diseases, there are many neglected tropical diseases that occur more commonly in LMICs and lack therapeutic options.

Neglected Tropical Diseases

NTDs are a group of 20 communicable diseases that are estimated to affect over 1.5 billion people per year, particularly those with low socioeconomic status (Table 5–3).[52] While they primarily affect impoverished communities in developing countries, the developed world is not immune to NTDs: a study in rural Alabama found that 35% of participants had stool samples positive for hookworm.[53,54] The morbidity burden of NTDs far outweighs that of mortality, leading to reduced quality of life manifesting in a variety of ways.[52] Physical impairment or disfigurement may lead to stigmatization and social discrimination and ultimately higher rates of mental health conditions such as depression.[55] Physical impairment may also reduce ability to work or for children to attend school, leading to loss of productivity. Healthcare costs often worsen the financial hardship of people living with NTDs. In Malawi, people with lymphatic filariasis have been shown to earn more than 50% less per week than those without the disease.[56] Billions of dollars are lost annually due to reduced productivity, perpetuating the cycle of poverty for nations plagued with endemic NTDs.[52] The projected economic gain from increased productivity with the end of five NTDs, that is, onchocerciasis, lymphatic filariasis, schistosomiasis, trachoma,

Table 5–3

List of Neglected Tropical Diseases[101]

Category	Neglected Tropical Disease
Bacterial infections	Buruli ulcer Leprosy Trachoma Yaws
Viral infections	Dengue and chikungunya Rabies
Fungal infections	Mycetoma, chromoblastomycosis, deep mycosis
Protozoan infections	Chagas disease Human African trypanosomiasis Leishmaniasis
Helminth infections	Taeniasis, neurocysticercosis Dracunculiasis Echinococcus Foodborne trematodiases Lymphatic filariasis Onchocerciasis Schistosomiasis Soil-transmitted helminths (ascariasis, hookworm, trichuriasis, strongyloidiasis)
Ectoparasitic infections	Scabies, myiasis
Venom	Snakebite envenomation

Data from Addisu A, Adriaensen W, Balew A, et al. Neglected tropical diseases and the sustainable development goals: an urgent call for action from the front lines. BMJ Global Health. 2019;4(1):e001334.

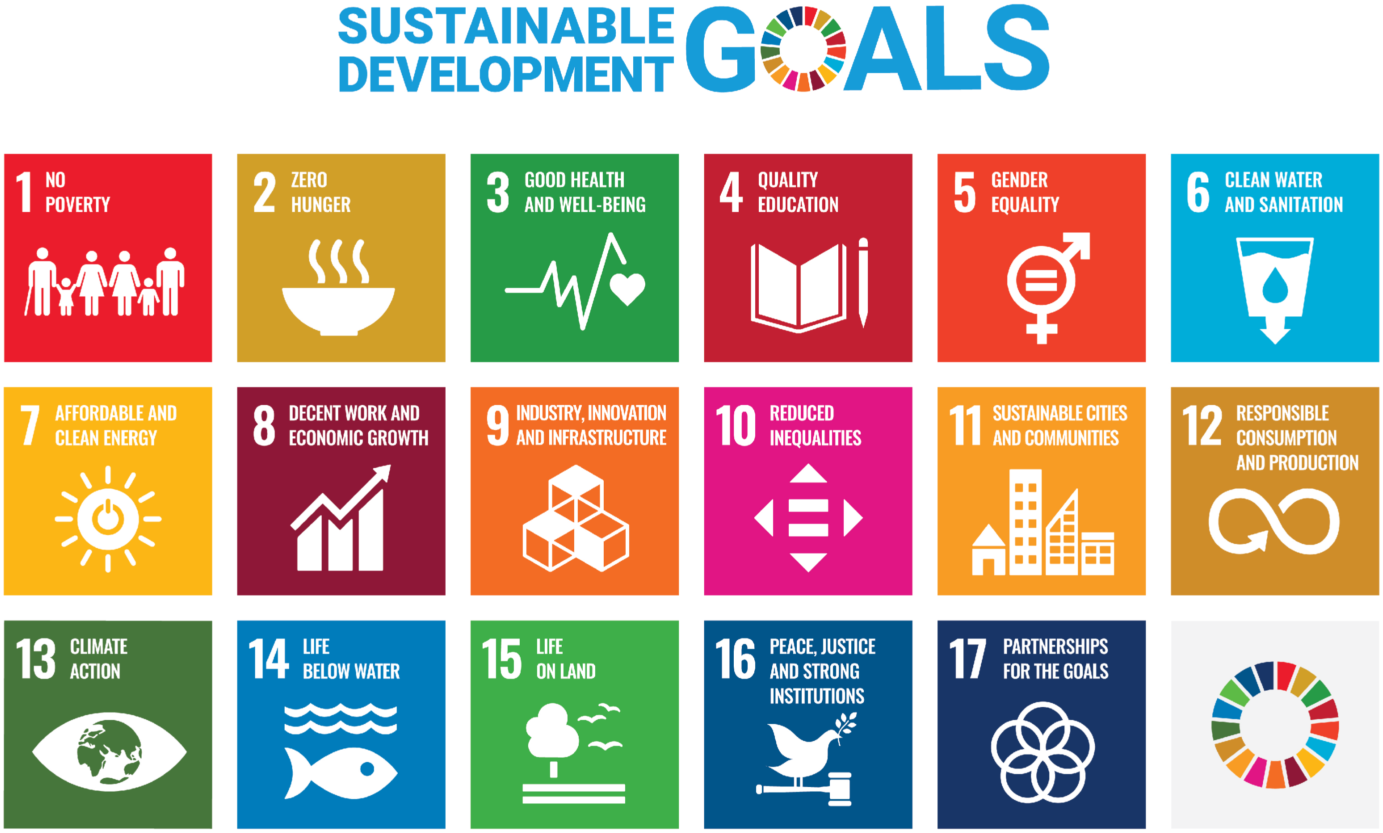

SUSTAINABLE DEVELOPMENT GOALS
1 NO POVERTY
2 ZERO HUNGER
3 GOOD HEALTH AND WELL-BEING
4 QUALITY EDUCATION
5 GENDER EQUALITY
6 CLEAN WATER AND SANITATION
7 AFFORDABLE AND CLEAN ENERGY
8 DECENT WORK AND ECONOMIC GROWTH
9 INDUSTRY, INNOVATION AND INFRASTRUCTURE
10 REDUCED INEQUALITIES
11 SUSTAINABLE CITIES AND COMMUNITIES
12 RESPONSIBLE CONSUMPTION AND PRODUCTION
13 CLIMATE ACTION
14 LIFE BELOW WATER
15 LIFE ON LAND
16 PEACE, JUSTICE AND STRONG INSTITUTIONS
17 PARTNERSHIPS FOR THE GOALS

FIGURE 5–17. Sustainable development goals.[61] (Reproduced with permission from United Nations Sustainable Development Goals, United Nations, New York, NY (www.un.org/sustainabledevelopment). The content of this publication has not been approved by the United Nations and does not reflect the views of the United Nations or its officials or Member States.)

and soil-transmitted helminths, is $127 billion between 2021 and 2030, equating to a net benefit of $42.8 for every dollar invested during the same time period.[57]

NTDs have historically received little global attention. They were not explicitly described in the 2000 Millennium Development Goals (MDGs). Although they were intended to fall under "other diseases" within MDG 6, this goal was largely focused on HIV/AIDS, malaria, and tuberculosis.[58] Since 2010, WHO has released numerous reports outlining comprehensive plans for eliminating NTDs.[59] The most recent report summarizes considerable progress in the past decade, such as near eradication of dracunculiasis and the elimination of at least one NTD in 40 countries or regions, before providing revised recommendations for further impact.[60] NTDs are also now specifically mentioned within the Sustainable Development Goals (SDG 3.3 aims to end epidemics of NTDs).[61] The sustainable development goals (SDGs) (shown in Figure 5–17) consist of 17 interconnected goals to achieve by 2030. They are intended to expand upon the progress made by the MDGs and are applicable to all nations rather than only developing countries. Compared to the MDGs, the SDGs are more comprehensive and place a greater emphasis on an integrated approach for attainment.

▸ *Mass Drug Administration*

Preventive chemotherapy for diseases that can be treated pharmacologically is one of the more successful NTD interventions. Preventive chemotherapy is typically accomplished by treating entire populations via mass drug administration (MDA) or to specific at-risk groups via targeted treatment.[62,63] The goals of these programs are to treat those with infection, prevent development of additional morbidity, and interrupt disease transmission.[52,63] Treatment is typically provided by community drug distributors and may be offered anywhere from every few months to years, depending on the disease endemicity of the region as described in Table 5–4.[62] Five NTDs most amenable to control via MDA are onchocerciasis, lymphatic filariasis, trachoma, schistosomiasis, and soil-transmitted helminths. Largely due to robust donation programs by pharmaceutical companies, MDA initiatives combatting NTDs are incredibly economical with an estimated cost of less than $ 0.50 per person per year.[53] To date, MDA has primarily been provided via vertical programs targeting a single disease state. More recently there has been an effort to move away from siloed, disease-specific programs in favor of integrated delivery of health services to sustain ongoing success.[60] Vertical programs often perform parallel functions of one another, providing duplicative therapies across common populations.[64] Alternatively, integration of multiple NTD targets within a single campaign improves efficiency, increases the impact of health interventions, alleviates the burden on health systems and communities, and reduces costs compared to vertical programs.[53,64,65] Other non-MDA strategies that help combat NTDs which may be incorporated into MDA campaigns include education around water, sanitation, and hygiene (WASH), vector control, zoonosis, and integrated disease management.[66]

▸ *Priority Review Voucher Programs*

One of the primary concerns regarding MDA programs involves the potential for antimicrobial resistance when only one drug is used for a given disease, as evidenced by the emergence of chloroquine resistance during malaria eradication efforts in the 1960s. Research and development (R&D) of novel agents to treat NTDs

Table 5–4

Neglected tropical diseases amenable to mass drug administration[62,102]

Disease	Causative Organism(s)	Transmission	Common Symptoms	Therapy	Frequency of MDA	Prevention
Onchocerciasis (river blindness)	*Onchocerca volvulus*	Blackflies	Ocular changes (punctate or sclerosing keratitis, optic atrophy, etc.), subcutaneous nodules, pruritus	**Ivermectin** 150 mcg/kg × 1 dose Moxidectin 8 mg × 1 dose	Every 6–12 months	Vector management
Lymphatic filariasis	*Wuchereria bancrofti, Brugia malayi, Brugia timori*	Mosquitoes	Often asymptomatic; lymphangitis, localized pain and swelling, lymphedema, hydrocele	*Regions with coendemic onchocerciasis:* **Ivermectin** 150 mcg/kg × 1 dose PLUS **albendazole** 400 mg × 1 dose *Regions without coendemic onchocerciasis:* **Diethylcarbamazine** (DEC) 6 mg/kg × 1 dose PLUS **albendazole** 400 mg × 1 dose	Every 12 months	Vector management
Schistosomiasis (bilharzia)	*Schistosoma* spp.	Contaminated freshwater	*Acute*: Pruritus, fever, myalgia, headache, abdominal pain, cough *Chronic*: Urogenital symptoms (hematuria, urinary frequency and burning, bladder cancer) and intestinal symptoms (abdominal pain, diarrhea, rectal bleeding, hepatomegaly)	**Praziquantel** 40–60 mg/kg divided in 2–3 doses × 1 day	Depends on local prevalence	Environmental improvements (water, sanitation, hygiene)
Trachoma	*Chlamydia trachomatis* serotypes A, B, Ba and C	Body fluids, flies	Conjunctivitis (redness, irritation, discharge), conjunctival scarring, trichiasis, blindness	**Azithromycin** 20 mg/kg (max 1 g) × 1 dose Tetracycline 1% ointment twice daily × 6 weeks Surgery if trichiasis present	Every 12 months	Facial cleanliness, environmental improvements (water, sanitation, hygiene)
Soil-transmitted helminths (particularly ascariasis, trichuriasis, and hookworms)	*Ascaris lumbricoides, Trichuris trichiura, Necator americanus*, and *Ancylostoma duodenale*, among others	Fecal–oral route, penetration through skin (typically bare feet)	Often asymptomatic; diarrhea or constipation, weight loss, abdominal pain, small bowel obstruction, rectal prolapse, anemia, protein deficiency, cough	**Albendazole** 400 mg or **mebendazole** 500 mg × 1 dose Ivermectin 150–200 mcg/kg × 1 dose Surgery in severe cases	Every 6–12 months based on prevalence	Environmental improvements (water, sanitation, hygiene), use of footwear

Data from Montresor A, Gabrielli AF, Chitsulo L, et al. Preventive chemotherapy and the fight against neglected tropical diseases. Expert Rev Anti Infect Ther. 2012;10(2):237–242 and Addisu A, Adriaensen W, Balew A, et al. Neglected tropical diseases and the sustainable development goals: an urgent call for action from the front line. BMJ Glob Health. 2019;4(1):e001334.

is greatly needed; however, there is little motivation for pharmaceutical companies to devote funding to diseases that are likely to have minimal return on investment. For this reason, the priority review voucher program was created to provide financial incentives for sponsors of NTD therapies.[67] If a company brings a new drug to market that fills a gap in therapy related to NTDs, they are awarded a voucher, which may either be used for expedited review of any subsequent new drug application or may be sold to another company, often for millions of dollars.[67,68] While the program is not without criticism, six new NTD therapies have come to market due to the priority review voucher program.[68] Moxidectin, which was shown to be superior to ivermectin for onchocerciasis in clinical trials, received FDA approval in 2018 and is the first new onchocerciasis drug to come to market in over 20 years.[69] Furthermore, all revenue from moxidectin sales will be used to support further access to the drug and R&D on other novel NTD therapies.[69] Additional incentives for R&D are urgently needed to drive control and elimination of NTDs.

INTERNATIONAL PARTNERSHIP PRINCIPLES

Context Matters

Global health practice occurs in various and varied contexts—in terms of geography, setting, culture, organizational structures, resources, and capabilities.[70] While it is common to extrapolate global health experiences in one setting to another, it is important to recognize that even between settings within the same country, contexts can be significantly different. International partners practicing **cross-culturally** need adequate preparation on what the context holds, in addition to being willing and open to learn more while at practice and collaboration.[71]

KEY CONCEPT Culture, resources, and capabilities are key contextual considerations to keep in mind and applicable at both the micro- (individual, organizational) and macro level (health system, population level). Cultural competence is the ability to understand, communicate with, and effectively interact with people and systems across cultures; in global health practice, this includes respecting diverse values, beliefs, and feelings from patients and their families, as well as those of local health practitioners. Resources refer to the preventive, diagnostic, and treatment options available, while capabilities refer to how and to what extent individuals can utilize these resources, and in the context of global health, to achieve health and well-being. Taken together, resources and capabilities play particular prominence to access issues; that is, to what extent health resources are equitably available, usable (affordable and acceptable), and can be leveraged in a timely fashion to avert death and disability.[27]

Understanding the context in global health promises more effective partnership in several ways. Firstly, collaboration may be smoother as cultural faux pas and gaffes, which may create friction between partners, are less likely to be made. Secondly, problems and their root causes may be more clearly comprehended. One is less likely to project their own point of view toward a health problem—be it at the individual level or health system level—and solutions are more likely to be appropriate and acceptable. For example, in resource-limited settings, cost of medicines is often highlighted as a barrier to medication adherence, with potential solutions such as providing access to free medicines proposed. Unfortunately, such programs have at times failed to improve adherence. Root causes, however, include patient deprioritization of the need for medicines, particularly in asymptomatic patients such as in uncomplicated hypertension.[72] In such an instance, given competing priorities for personal resource use, the **opportunity cost** of adherence may be perceived to be higher by a patient and its benefits negligible. Therefore, a more effective intervention would target improving the patient's understanding of the need for adherence.

True Collaboration in Problem Solving Through Bilateral Learning

A prevailing mindset in global health has been the need to deliver solutions developed and demonstrated to work in high-income settings to target foreign LMIC settings. This knowledge and skills transfer may be what is needed in some instances; for example, training on use of a new health technology, which may be novel in the LMIC setting but the visiting global health practitioner has wide experience with its use in their high-income home country. However, it is inappropriate to assume that one-way knowledge and skills transfer is required in all situations. Given the context considerations described above, differences in care delivery between home and target settings should not be assumed to be a result of knowledge or skills deficits that practitioners from high-income settings are there to address. Instead, it is the case that local practitioners have spent years refining their skills around the infrastructure in their setting and have a contextualized understanding of delivering healthcare services and optimizing health outcomes for their population. Consequently, visiting practitioners should strive to learn and understand this, prior to trying to guide others in implementing strategies from their home country, which may be inappropriate in a different context.

An additional effect of the antiquated mindset of global health practice is the predisposition to create inappropriate power dynamics between global health collaborators, whereby the visiting practitioner is viewed as the expert, and the host practitioner is viewed as the learner. For example, a visiting student may perceive themselves to be more knowledgeable on treatment than a local clinician with more contextualized training and experience on managing the diseases in their setting. This mindset, and the subsequent inappropriate power dynamic, impedes true collaboration as it creates a one-way learning channel—north to south. However, given the importance of context discussed above, similar problems may have drastically different root causes and varying solutions.

KEY CONCEPT Making the mindset shift from expert to learner involves striving first to understand, before trying to be understood, much as one would do when undertaking any clinical rotation in different practice sites in your country of origin. It compels prioritization of local needs and local knowledge, setting up the conditions for true **bilateral learning** and collaborative development of solutions to global health challenges.[72]

Focus on Sustainable Solutions

Sustainability in the global health context refers to continuity of care beyond the engagement period. Solutions—both for individual patient care and at the health system level—should be able to outline an individual's or program's period of engagement. This is necessary so that health gains made are not eroded immediately when engagement ends.[73] An example of this is a hypertension care program that includes free supply of medicines where, without donor support for the program, patients will be expected to pay for their own medicines. Instead, at the outset, the program should align itself with what the payer system is like in the setting in which it is being implemented. If cost is a significant barrier to adherence, a sustainable solution for this needs to be included and planned for, for example, increasing insurance uptake.

Professional Ethics and Ethical Dilemmas

Professional ethics refers to the principles that govern right and wrong behavior in a given profession. Ethics should be distinguished from rules and regulations of practice, which may differ from setting to setting. Professional ethics for clinicians, however, are universal. Patient confidentiality, accountability, trustworthiness, respect for others, etc. should be upheld regardless of the context. Common examples of breaches include not protecting patient confidentiality through taking and sharing of clinical pictures without patient consent and inappropriate power dynamics in interprofessional work.

Ethical dilemmas arise when decisions have to be made where the only available options are not wholly appropriate from an ethical perspective. For example, a commonly reported ethical dilemma in global health is when professional ethics clash with cultural values and norms, such as when balancing patient autonomy and transparency with cultural expectations on how much to share with a patient or their family regarding a potentially poor prognosis.[74] In some settings, for example, informing the patient and/or family of a poor prognosis may be misconstrued as not doing all that is possible to help the patient, or as an attempt to control an outcome which is not up to you as a provider. In general, professional ethics should always be upheld when the alternative is unambiguous such as in the example of taking and sharing clinical pictures without patient consent. Other ethical dilemmas require individualized and contextualized solutions that should almost always be deferred to local practitioners.

Lastly, practitioners traveling to provide healthcare services in foreign settings must also make sure their own health is protected. With the growing frequency of communicable infectious diseases outbreaks, such as the Ebola virus and COVID-19, it is important that the healthcare workforce is adequately protected to ensure they can continue to treat those in need rather than exacerbating the well-described limitations in the supply of the healthcare workforce in LMICs.[75,76]

TRAVEL MEDICINE

People travel for many reasons, including tourism, study, business, visiting family, or altruistic work. The practice of travel medicine focuses on preventing illnesses and managing the health needs of international travelers. International travel has expanded substantially over the last few years. In the roughly 50 years between 1970 and 2020, the world population increased from approximately 2.5 billion to approximately 7.5 billion people, a threefold increase.[77] Concurrently, air travel increased during the same time from 310 million to 4.2 billion passengers—a 13-fold increase, and passenger-kilometer traveled increased 16-fold from 500 billion to 8 trillion.

The practice of travel medicine expanded to care for the increasing number of people traveling internationally and over greater distances than ever before. These travelers may also have preexisting medical illnesses that can be exacerbated by travel. Clinicians caring for travelers can provide valuable service to reduce their risks, and also fill a valuable public health need of reducing the risk of importing disease across borders. Many resources are available to assist clinicians to make appropriate decisions for international travelers, both prior to an international trip or following their return.

Pretravel Assessment

The medical risks of travel have a significant range. Depending on the itinerary, the risk of traveler's diarrhea is often around 50%, while the risk of acquiring Japanese encephalitis can have an incidence rate of 0.0001% per month.[78] Appropriate counseling and interventions can reduce these risks. A structured approach to the pretravel consultation, such as using the HUMID mnemonic described below, can help a clinician cover the most important topics.[79]

Patient Encounter 2, Part 1

The Ndubisi family is planning a trip to Nigeria. Mr. Ndubisi is a 32-year-old graduate student in psychology. He was born in Nigeria but attended high school in the United States. Mrs. Ndubisi is a 28-year-old pharmacy student. She was born in America and has traveled previously to Europe but has never traveled to Africa. They have two children, ages 1 and 4, and they plan to visit his extended family both in Lagos, Nigeria and the more rural areas for 6 weeks this coming summer after graduation.

What are some of the travel-related illnesses this family should consider as they prepare for their trip?

Does the fact that Mr. Ndubisi has family in Nigeria increase or decrease their risk of illness?

What medical history should be obtained before making recommendations prior to travel?

Human (individual risk assessment)

- List of chronic medical conditions and allergies
- List of medications and doses, with an adequate supply available for duration of travel
- Review drug interactions with new prescriptions
- Name and contact information of primary physician

Unique locations and hazards

- Review travel itinerary and potential threats
- Evaluate extreme environmental threats (heat, cold, altitude)
- Consider unique pathogens such as parasites, arthropods, and marine life
- Consider inaccessible or remote location without medical care
- Review safe sex, sunscreens, hygiene, etc.

Malaria prophylaxis

- Review appropriate prophylaxis for location and patients
- Issue prescriptions (may require weeks to obtain in some areas)
- Reinforce continuation of prescription after return and immediate evaluation for unexplained fevers for 1 year after travel

Immunizations

- Review current immunization status and update as needed
- Review immunization requirements for destination
- Give immunizations (yellow fever might require advance planning)

Diarrhea

- Review food safety, water safety, and hygiene
- Issue prescriptions for empiric treatment based on location of travel, age, and health status of patient
- Instruct to seek medical care if diarrhea does not resolve after treatment

▶ *Human*

KEY CONCEPT Providing a pretravel evaluation requires understanding the traveler's plans and reviewing their health needs. Patients may have chronic health conditions that will affect their travel plans.[80] Patients need to be certain they have an adequate supply of medications for their entire trip—and preferably enough additional doses to last in case their trip is unexpectedly delayed or prolonged. Medications should be brought in their original bottles with their name and prescriber's name printed on them to reduce problems going through customs.

Chronic health conditions can be affected by travel. Patients with diabetes may find that eating local cuisine while traveling can have a significant impact on their blood glucose levels, and their activity level as tourists may be different than their usual activities at home. Patients with asthma may be exposed to a different set of allergens; those who are sensitive to tobacco smoke may find variations in local laws and practices change their exposure to second-hand smoke.

Also, it is reasonable to anticipate some potential emergency situations that could be managed with self-directed care.[81] Navigating a health emergency in a foreign country and a different healthcare system with potential language barriers can be difficult. Self-directed care may be preferable to attempting to access a foreign health system for conditions that can be anticipated. Conditions like a chronic obstructive pulmonary disease exacerbation or dysuria with typical urinary tract infection symptoms could potentially be managed empirically in certain situations. Coronary artery disease is the leading cause of deaths globally, including among travelers.[82] Patients with known cardiac disease should bring a copy of their electrocardiography (ECG) or any implanted cardiac device cards in case problems develop while abroad. Allergies are also a common problem, which can be exacerbated by a language barrier.[83] People with food allergies, such as peanuts, may wish to bring a photograph of allergenic foods to better communicate to others which ingredients they must avoid. These patients should also anticipate possible emergencies and bring doses of emergency epinephrine, diphenhydramine, and potentially corticosteroids.

Even with the best preparations, travel emergencies can happen. Travelers from the United States can access the Department of State website for information on local hospitals and physicians from local embassies.[84] The International Association of Medical Assistance to Travelers is a nonprofit organization that maintains a list of clinicians in many countries that will evaluate English-speaking travelers.[85] Serious problems that require medical evacuation can be very expensive as well as frightening and are often not covered by a traveler's usual health financing plan. Evacuation insurance can fill this gap. For US travelers, the CDC provides some guidance on features to consider.[86]

▶ *Unique Risks*

Each traveler has an expected itinerary of where they will be going and some anticipated plans of what they will be doing. Evaluating this itinerary starts with which countries they will be visiting, but one should also consider some of the details. Risks will be different if they will be staying in largely urban or rural areas, if their time will be spent in forests or jungle, if they will be swimming at salt-water beaches or fresh-water lakes, or if they will be traveling to areas with significant elevation. While it is nearly impossible to have a comprehensive knowledge about every risk in every corner of the globe, there are many continually updated resources available to learn about geographically specific risks that are either free or require a subscription.

English-language resources for geographic health considerations:

Free:

CDC Travel Health Website: http://wwwnc.cdc.gov/travel

CDC's Yellow Book: http://wwwnc.cdc.gov/travel/page/yellowbook-home-2014

WHO Travel Advice: https://www.who.int/travel-advice

Global TravEpiNet: http://gten.travel/prep/prep

Canada: https://travel.gc.ca/travelling/health-safety/vaccines

Great Britain: https://travelhealthpro.org.uk/countries

Subscription required

Travax: www.travax.com

Tropimed: www.tropimed.com

One interesting group that deserves special attention is patients who are visiting friends or relatives, or "VFRs." [86] Typically, they are patients who have ethnic origins from a low-income country, but now live in a high-income country. When such patients plan to visit their family or friends in the low-income country of origin, they often perceive their personal risk of illness to be quite low. They may assume they are immune to endemic diseases such as malaria and typhoid, but their actual risk of acquiring these illnesses is approximately eight times that of an expatriate tourist. VFR patients often have longer visits, stay in local homes, eat more authentic food, and have a higher risk of acquiring sexually transmitted diseases.[86]

Travelers planning to spend time at significant altitude may consider prophylaxis against altitude sickness. This can be a spectrum of diseases ranging from mild dyspnea, to headaches and nausea, to more severe forms of cerebral or pulmonary edema. Roughly 25% of people will be affected at 2500 m, although the severe manifestations are uncommon below 3500 m. The best prevention is to take a slow ascent over several days. For travelers going by car or airplane, acetazolamide at a dose of 125 mg twice daily can help prevent some of the symptoms.[88]

▶ *Malaria*

Malaria is the most common life-threatening travel-related illness, with roughly 2000 cases per year in US travelers. In a pretravel consultation, there are several issues of importance to discuss for malaria prevention, including prevention of mosquito bites, need for evaluation and treatment if symptoms develop, and prophylactic medications.

Malaria risk in travelers depends on the countries on the itinerary but can also vary significantly depending on regions within the country, lodging arrangements, and planned activities. While some countries have malaria endemic throughout their borders, some have the disease restricted to certain areas. Good resources are available and updated regularly by groups like the World Health Organization and Centers for Disease Control and Prevention.[89]

Preventing mosquito bites is the first step against preventing all mosquito-borne diseases, including malaria. Other insect-borne diseases like **Zika and West Nile encephalitis** are carried by mosquitoes and do not have vaccines available currently. People who are sleeping in rooms should ensure that they are air conditioned and have screens over the windows. If not, they should sleep under a bed net. A room fan at the end of the bed can also keep mosquitoes from flying.

The most common insect repellent in the United States is N,N-diethyl-meta-toluamide, also called DEET. Lotions and sprays are available in strengths from 10% to 100% DEET. Little additional benefit is provided in strengths beyond 50%, which will last approximately 6 hours. CDC and AAP recommend DEET may be used in infants as young as 2 months. Picaridin is a newer preventive lotion that is available in 15% to 30% strengths and has a similar spectrum of activity. Some patients may prefer to treat their clothes with permethrin—this strategy will typically last about 6 weeks through several washes. Other agents like citronella provide some activity, although only for about 20 minutes. Soybean oil can provide some protection for about 90 minutes. Other information can be found at the National Pesticide Information Center.[90]

In addition to precautions to avoid mosquito bites, travelers should use a recommended antimalarial prophylactic medication to areas where malaria is endemic, as described in Tables 5–5 and 5–6. Four agents are most commonly used.[86] Chloroquine is a highly effective preventive medication that is dosed once weekly. However, widespread resistance limits its use to few areas of the globe, including the Caribbean, Central America west of the Panama Canal, and parts of the Middle East. Mefloquine is also dosed once weekly and overcomes this resistance in nearly every part of the world except for parts of Southeast Asia. However, it comes with a significantly greater risk of toxicity. Doxycycline is taken daily when used for malaria prevention. It is effective, although its relatively short half-life means that missed doses pose a significant risk to the effectiveness of the regimen. Atovaquone/proguanil is one of the newer agents available for prophylaxis. It also is taken daily and has little known resistance. It has become the most widely prescribed antimalarial drug in the United States.[88] Less frequently used as prophylaxis are the agents primaquine and tafenoquine. These medications are especially effective against *Plasmodium vivax* but are contraindicated in patients with glucose-6-phosphatase dehydrogenase (G6PD) deficiency. Any patient wishing to take these medications must be tested for G6PD before starting them.

▸ *Immunizations*

A pretravel consultation is an opportunity to review the patient's immunization status and ensure they are up to date on routinely recommended vaccinations based on their age and risk factors as described in Table 5–7.[91] Additional vaccines that are unique to travel can then be considered based on local epidemiology and risks. Since these risks vary significantly from location to location and change over time, consulting one of the continually updated resources can help a clinician make appropriate decisions.

▸ *Diarrhea*

Traveler's diarrhea is the most common medical complaint of travelers—reaching nearly 50% for some itineraries. This clinical syndrome typically consists of 3 to 5 days of watery diarrhea, often with nausea and cramping. Fever is a red flag that would suggest a more invasive disease. Bacterial agents are considered as the cause the majority of the time, with the most common infectious agent being enterotoxigenic *Escherichia coli*, although *Campylobacter* species are also common in Southeast Asia. Traveler efforts to prevent this by simple dietary avoidance of raw fruits and vegetables, and contaminated water sources are often imperfect, and even conscientious travelers can still develop symptoms (Table 5–8).[92]

Bismuth subsalicylate can be taken as a prophylactic agent and can reduce the risk of traveler's diarrhea by about 50% in short-term exposures. Longer-term use has not been studied and is limited by the need to take a large number of tablets. Certain antibiotics such as fluoroquinolones, rifaximin, and azithromycin can also prevent traveler's diarrhea, but concern about antimicrobial resistance from widespread use limits these recommendations. Patients with significant comorbidities or immunosuppression may find the benefits of prophylaxis can outweigh the risks.

Self-directed therapy is another option that may be more appropriate for a wider range of travelers. Every patient with diarrhea should maintain an adequate fluid intake to replenish losses. Loperamide is also effective at reducing symptoms temporarily and is generally considered safe when diarrhea is not associated with fever or blood in the stool. Antibiotics can also be used for self-directed treatment for moderate to severe symptoms, and generally reduce symptoms to 24 hours or less (Table 5–9).[86]

Evaluation of the Returned Traveler

Travelers who develop illness while traveling internationally or shortly after returning have some unique challenges. Their additional activities and itineraries often add a wider range of diagnostic possibilities to their clinical symptoms. These additional possibilities may include conditions that are unfamiliar to the evaluating clinicians, some of which may be mild while some are life threatening. Ill returned travelers therefore should be promptly evaluated by clinicians who are able to manage these possibilities.

Gastrointestinal complaints are the most common problem seen after travel as seen in Table 5–10. While traveler's diarrhea is most commonly due to gram-negative enteric bacteria, this condition usually has an onset within 1 to 3 days after ingesting the infectious agent, and symptoms generally abate after 3 to 7 days. Patients with gastrointestinal symptoms who have a longer incubation period or have symptoms persisting beyond this period are more likely to have more specific travel-related illnesses such as *Giardia* or strongyloidiasis.

Patient Encounter 2, Part 2

After further discussion, the Ndubisi family indicates that Mr. Ndubisi has previously had an episode of clinical depression but has been taking sertraline with remission of symptoms for the last 2 years. Mrs. Ndubisi received routine prenatal care for her two pregnancies, and just finished breast-feeding her youngest child. She is now using combined estrogen/progesterone pills for contraception. The two children make all of their routine pediatric well visits and are currently on age-appropriate immunizations as recommended by the US Center for Disease Control and Prevention.

What human aspects of the Ndubisi family merit additional attention?

What unique aspects of their travel itinerary would pose a risk of travel-related illness?

What antimalarial precautions would be recommended? Would you recommend a prescription medication? If so, which one?

What immunizations would be recommended prior to the family's trip to Nigeria?

Would prophylactic treatment for traveler's diarrhea be recommended? What about prescribing antibiotics for self-directed therapy?

Table 5–5

Considerations When Choosing a Drug for Malaria Prophylaxis[86]

Drug	Reasons to Consider Use of This Drug	Reasons to Consider Avoiding Use of This Drug
Atovaquone-proguanil	• Good for last-minute travelers because the drug is started 1–2 days before travel • Some people prefer to take a daily medicine • Good choice for shorter trips because the traveler takes the medicine for only 7 days after traveling rather than 4 weeks • Well tolerated—side effects uncommon • Pediatric tablets are available and may be more convenient	• Cannot be used by women who are pregnant or breast-feeding a child that weighs < 5 kg • Cannot be taken by people with severe renal impairment • Tends to be more expensive than some of the other options (especially for long trips) • Some people (including children) would rather not take a medicine every day
Chloroquine	• Some people would rather take medicine weekly • Good choice for long trips because it is taken only weekly • Some people are already taking hydroxychloroquine chronically for rheumatologic conditions; in those instances, they may not have to take an additional medicine • Can be used in all trimesters of pregnancy	• Cannot be used in areas with chloroquine or mefloquine resistance • May exacerbate psoriasis • Some people would rather not take a weekly medication • For short trips, some people would rather not take medication for 4 weeks after travel • Not a good choice for last-minute travelers, because drug needs to be started 1–2 weeks before travel
Doxycycline	• Some people prefer to take a daily medicine • Good for last-minute travelers because the drug is started 1–2 days before travel • Tends to be the least expensive antimalarial • People who are already taking doxycycline chronically to prevent acne do not have to take an additional medicine • Doxycycline can also prevent some additional infections (eg, rickettsial infections, leptospirosis), so it may be preferred by people planning to hike, camp, and swim in fresh water	• Cannot be used by pregnant women and children aged < 8 years • Some people would rather not take a medicine every day • For short trips, some people would rather not take medication for 4 weeks after travel • Women prone to getting vaginal yeast infections when taking antibiotics may prefer taking a different medicine • People may want to avoid the increased risk of sun sensitivity • Some people are concerned about the potential of getting an upset stomach from doxycycline
Mefloquine	• Some people would rather take medicine weekly • Good choice for long trips because it is taken only weekly • Can be used in all trimesters of pregnancy	• Cannot be used in areas with mefloquine resistance • Cannot be used in patients with certain psychiatric conditions • Cannot be used in patients with seizure disorders • Not recommended for people with cardiac conduction abnormalities • Not a good choice for last-minute travelers because drug needs to be started ≥ 2 weeks before travel • Some people would rather not take a weekly medication • For short trips, some people would rather not take medication for 4 weeks after travel
Primaquine	• It is the most effective medicine for preventing *P. vivax*, so it is a good choice for travel to places with > 90% ***P. vivax*** • Good choice for shorter trips because the traveler takes the medicine for only 7 days after traveling rather than 4 weeks • Good for last-minute travelers because the drug is started 1–2 days before travel • Some people prefer to take a daily medicine	• Cannot be used in patients with G6PD deficiency • Cannot be used in patients who have not been tested for G6PD deficiency • There are costs and delays associated with getting a G6PD test; however, it only has to be done once. Once a normal G6PD level is verified and documented, the test does not have to be repeated the next time primaquine is considered • Cannot be used by pregnant women • Cannot be used by women who are breast-feeding, unless the infant has also been tested for G6PD deficiency • Some people would rather not take a medicine every day • Some people are concerned about the potential of getting an upset stomach from primaquine
Tafenoquine	• One of the most effective drugs for prevention of *P. vivax* malaria, though also prevents *P. falciparum* • Good choice for shorter trips because the traveler takes the medicine once, 1 week after traveling rather than 4 weeks • Good for last-minute travelers because the drug is started 3 days before travel	• Cannot be used in people with G6PD deficiency • Cannot be used in patients who have not been tested for G6PD deficiency • There are costs and delays associated with getting a G6PD test; however, it only has to be done once. Once a normal G6PD level is verified and documented, the test does not have to be repeated the next time tafenoquine or primaquine is considered • Cannot be used by children • Cannot be used by pregnant women • Cannot be used by women who are breast-feeding • Not recommended in those with psychotic disorders

G6PD, glucose-6-phosphatase dehydrogenase. From CDC Yellow Book 2020: Health Information for International Travel. 2020.

Table 5–6

Drugs Used in the Prophylaxis of Malaria[86]

Drug	Usage	Adult Dose	Pediatric Dose	Comments
Atovaquone-proguanil	Prophylaxis in all areas	Adult tablets contain 250 mg atovaquone and 100 mg proguanil hydrochloride 1 adult tablet daily	Pediatric tablets contain 62.5 mg atovaquone and 25 mg proguanil hydrochloride 5–8 kg: 1/2 pediatric tablet daily > 8–10 kg: 3/4 pediatric tablet daily > 10–20 kg: 1 pediatric tablet daily > 20–30 kg: 2 pediatric tablets daily > 30–40 kg: 3 pediatric tablets daily > 40 kg: 1 adult tablet daily	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas. Contraindicated in people with severe renal impairment (creatinine clearance < 30 mL/min). Atovaquone-proguanil should be taken with food or a milky drink. Not recommended for prophylaxis for children weighing < 5 kg, pregnant women, and women breast-feeding infants weighing < 5 kg. Partial tablet doses may need to be prepared by a pharmacist and dispensed in individual capsules, as described in the text.
Chloroquine	Prophylaxis only in areas with chloroquine-sensitive malaria	300 mg base (500 mg salt) orally, once/week	5 mg/kg base (8.3 mg/kg salt) orally, once/week, up to maximum adult dose of 300 mg base	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 weeks after leaving such areas. May exacerbate psoriasis.
Doxycycline	Prophylaxis in all areas	100 mg orally, daily	≥ 8 years of age: 2.2 mg/kg up to adult dose of 100 mg/day	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 4 weeks after leaving such areas. Contraindicated in children < 8 years of age and pregnant women.
Hydroxychloroquine	An alternative to chloroquine for prophylaxis only in areas with chloroquine-sensitive malaria	310 mg base (400 mg salt) orally, once/week	5 mg/kg base (6.5 mg/kg salt) orally, once/week, up to a maximum adult dose of 310 mg base	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 weeks after leaving such areas.
Mefloquine	Prophylaxis in areas with mefloquine-sensitive malaria	228 mg base (250 mg salt) orally, once/week	≤ 9 kg: 4.6 mg/kg base (5 mg/kg salt) orally, once/week > 9–19 kg: 1/4 tablet once/week > 19–30 kg: 1/2 tablet once/week > 30–45 kg: 3/4 tablet once/week > 45 kg: 1 tablet once/week	Begin ≥ 2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 weeks after leaving such areas. Contraindicated in people allergic to mefloquine or related compounds (quinine, quinidine) and in people with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in people with psychiatric disturbances or a previous history of depression. Not recommended for people with cardiac conduction abnormalities.
Primaquine	Prophylaxis for short-duration travel to areas with principally *P. vivax*	30 mg base (52.6 mg salt) orally, daily	0.5 mg/kg base (0.8 mg/kg salt) up to adult dose orally, daily	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas.
	Presumptive antirelapse therapy (PART or terminal prophylaxis) to decrease the risk for relapses of *P. vivax* and *P. ovale*	30 mg base (52.6 mg salt) orally, daily	0.5 mg/kg base (0.8 mg/kg salt) up to adult dose orally, daily	PART indicated for people with prolonged exposure to *P. vivax*, *P. ovale*, or both: daily for 14 days after departure from the malarious area. Contraindicated in people with G6PD deficiency. Also contraindicated during pregnancy and lactation, unless the infant being breast-fed has a documented normal G6PD level.
Tafenoquine	Prophylaxis in all areas	200 mg orally	Not indicated in children < 16 years old	Begin taking daily for 3 days prior to travel to malarious areas. Then, take weekly while at the malarious area, and for 1 week after leaving the malarious area.
	Presumptive antirelapse therapy (PART or terminal prophylaxis) to decrease the risk for relapses of *P. vivax* and *P. ovale*	300 mg orally	300 mg orally	PART indicated for people who had prolonged exposure to *P. vivax, P. ovale*, or both: administered as a single dose. Contraindicated in people with G6PD deficiency. Also contraindicated during pregnancy and lactation unless the infant being breast-fed has a documented normal G6PD level.

G6PD, glucose-6-phosphatase dehydrogenase. From CDC Yellow Book 2020: Health Information for International Travel. 2020.

Table 5–7

Vaccines Which Should Be Available During Pretravel Consultation[88]

Disease and Vaccine Type	Adult Dose	Route of Administration	Standard Schedule	Accelerated Schedule for Series	Estimated Duration of Protection	References
Available in the United States						
Cholera: live attenuated bacteria	1 sachet	Oral	Single dose	NA	3-6 mo	Jackson and Chen[19]
Hepatitis A: inactivated virus	1 mL	Intramuscular	2 doses: day 0 and at 6-12 mo[†]	Available in combined hepatitis A and B formulation: days 0, 7, and 21 and at 12 mo[‡]	>20 yr (seropositivity); >40 yr (antibody modeling)	ACIP,[20] Theeten et al.[21]
Hepatitis B: recombinant hepatitis B surface antigen	1 mL	Intramuscular	3 doses: day 0 and at 1 mo and 6 mo	Available in combined hepatitis A and B formulation: days 0, 7, and 21 and at 12 mo[‡]	30 yr	Mast et al.,[22] FitzSimons et al.[23]
Combined hepatitis A and B: inactivated virus and recombinant viral antigen	1 mL	Intramuscular	3 doses: day 0 and at 1 mo and 6 mo	4 doses: days 0, 7, and 21 and at 12 mo[‡]	>15 yr (data on monovalent vaccines support long-term protection from anamnestic response)	Van Damme et al.[24]
Influenza						Grohskopf et al.[25]
Inactivated virus or recombinant, trivalent or quadrivalent	0.5 mL (0.1 mL for intradermal administration)	Intramuscular (intradermal formulation for age 18-64 yr)	1 dose	NA	1 yr	
Live attenuated virus, quadrivalent	0.1 mL in each nostril	Intranasal spray	1 dose	NA	1 yr	
Japanese encephalitis: inactivated virus, derived from cell culture	0.5 mL	Intramuscular	2 doses: days 0 and 28	2 doses: days 0 and 7	1-2 yr after initial dose; >6 yr if boosted at 1-2 yr	Fischer et al.,[26] CDC,[27] Jelinek et al.,[28] EMA,[29] Paulke-Korinek et al.,[30] Rabe et al.[31]
Measles-mumps-rubella: live attenuated virus	0.5 mL	Subcutaneous	2 doses: day 0 and at 4 wk		Lifelong, after 2 doses total at any time in life	McLean et al.[32]
Meningococcal disease — quadrivalent ACYW-135: bacterial polysaccharide, conjugated[§]	0.5 mL	Intramuscular	1 dose (off-label for those >55 yr old)	NA	3-5 yr	Cohn et al.,[33] Baxter et al.[34]
Poliomyelitis: inactivated virus	0.5 mL	Subcutaneous	Single dose in those who received primary childhood series	NA	Lifelong, after primary series plus a booster in adulthood (age ≥18 yr)	Wallace et al.[35]
Rabies: inactivated virus, derived from cell culture	1 mL	Intramuscular (0.1 mL intradermally may be considered for use off-label)	3 doses before exposure: days 0,7, and 21-28	NA	Patient should be informed that 2 additional doses are required on days 0 and 3 after each possible rabies exposure; no boosters are otherwise indicated	Manning et al,[36] Wieten et al,[37]

(Continued)

Table 5–7

Vaccines Which Should Be Available During Pretravel Consultation[88] (*Continued*)

Disease and Vaccine Type	Adult Dose	Route of Administration	Standard Schedule	Accelerated Schedule for Series	Estimated Duration of Protection	References
Tetanus-diphtheria-acellular pertussis (Tdap) or tetanus-diphtheria (Td): toxoid, protein antigen	0.5 mL	Intramuscular	1 dose in those who received primary childhood series	NA	10 yr; 5 yr for travelers at high risk for wounds (eg, adventure travelers, those engaging in activities that may result in injuries, and travelers to places where medical care is substandard)	CDC[38]
Typhoid						Jackson et al.[39]
Bacterial cell-wall polysaccharide	0.5 mL	Intramuscular	1 dose	NA	2-3 yr	
Live attenuated bacteria	4 capsules	Oral	4-capsule series, one every other day		5 yr	
Yellow fever: live attenuated virus	0.5 mL	Subcutaneous	1 dose	NA	10 yr for high-risk patients (in some countries, protection is considered to be long-term)	Gershman and Staples,[40] WHO,[41] Staples et al.[42]
Not currently available in the United States						
Cholera: inactivated whole-cell bacteria combined with recombinant B subunit of cholera toxin	1 sachet	Oral	2 doses, 1 wk apart	NA	2 yr	WHO[43]
Tickborne encephalitis: inactivated virus derived from cell culture	0.5 mL	Intramuscular	3 doses: day 0, at 1-3 mo, and at 5-12 mo	3 doses: days 0, 7, and 21 (protective 7 days after dose 3)	3 yr	WHO[44]

*Consideration may be given to stocking human papillomavirus and herpes zoster vaccines, as well as other vaccines (eg, pneurnococcal vaccines) for travelers with chronic illnesses, since the travel consultation is an excellent opportunity to update routine immunizations. CDC denotes Centers for Disease Control and Prevention, EMA, European Medicines Agency, FDA, Food and Drug Administration, NA not applicable, and WHO World Health Organization.

†The Advisory Committee on Immunization Practices (ACIP) recommends that the first dose of hepatitis A vaccine and IgG be administered in travelers older than 40 years of age who are departing in less than 14 days for a destination where hepatitis A is endemic; however, this is rarely done in practice and is not included in any non-U.S. national guideline.

‡The initial accelerated schedule, with doses on days 0, 7, and 21, provides protection for up to 1 year; the additional dose at 12 months provides long-term protection similar to that with the standard schedule.

§The ACIP recommends use of the conjugate vaccine in persons 55 years of age or older who need repeated meningococcal vaccination, including travelers who may need another dose in 5 years or more. From Freedman DO, Chen LH, Kozarsky PE. Medical Considerations before International Travel. N Engl J Med. 2016 Jul 21;375(3):247–60.

Table 5–8

Traveler's Diarrhea Treatment Recommendations[86]

Therapy of mild travelers' diarrhea
- Antibiotic treatment is not recommended in patients with mild travelers' diarrhea.
- Loperarnide or BSS may be considered in the treatment of mild travelers' diarrhea.

Therapy of moderate travelers' diarrhea
- Antibiotics may be used to treat cases of moderate travelers' diarrhea.
- Fluoroquinolones may be used to treat moderate travelers' diarrhea.
- Azithromycin may be used to treat moderate travelers' diarrhea.
- Rifaximin may be used to treat moderate, noninvasive travelers' diarrhea.
- Loperarnide may be used as adjunctive therapy for moderate to severe travelers' diarrhea. Antimotility agents alone are not recommended for patients with bloody diarrhea or those who have diarrhea and fever.
- Loperarnide may be considered for use as monotherapy in moderate travelers' diarrhea.

Therapy of severe travelers' diarrhea
- Antibiotics should be used to treat severe travelers' diarrhea.
- Azithromycin is preferred to treat severe travelers' diarrhea.
- Fluoroquinolones may be used to treat severe, nondysenteric travelers' diarrhea.
- Rifaximin may be used to treat severe, nondysenteric travelers' diarrhea.[1]
- Single-dose antibiotic regimens may be used to treat travelers' diarrhea.

[1] These treatment recommendations were developed prior to the approval of rifamycin SV in the United States. Because it is in the same category of antimicrobial drug as rifaximin and because they have the same mechanism of action, rifamycin SV can he considered as an alternative to rifaximin. From CDC Yellow Book 2020: Health Information for International Travel. 2020.

A traveler returning from a tropical country with a new onset of a fever should be evaluated urgently, if not emergently. Malaria due to *Plasmodium falciparum* can be a life-threatening condition, especially in travelers who have never developed any immunity from prior or ongoing exposures. Fever in a traveler returning from a malaria-endemic region therefore must prompt a through and expedited evaluation. Other febrile diseases such as dengue or chikungunya also should be evaluated quickly and appropriately treated. Some diseases like viral hemorrhagic fevers are rarely seen but are of such substantial public health concern that they must be ruled out (Figure 5–18).

Table 5–9

Acute Diarrhea Antibiotic Treatment Recommendations[86]

Antibiotic[1]	Dose	Duration
Azithromycin[2,3]	1,000 mg	Single or divided dose[4]
	500 mg daily	3 days
Levofloxacin	500 mg daily	1-3 days[4]
Ciprofloxacin	750 mg	Single dose[4]
	500 mg bid	3 days
Ofloxacin	400 mg bid	1-3 days[4]
Rifamycin SV[5]	388 mg bid	3 days
Rifaximin[5]	200 mg tid	3 days

[1] Antibiotic regimens may be combined with loperamide 4 mg initially followed by 2 mg after each loose stool, not to exceed 16 mg in a 24-hour period.

[2] Use empirically as first-line in Southeast Asia or other areas if fluoroquinolone-resistant bacteria are suspected.

[3] Preferred regimen for dysentery or febrile diarrhea.

[4] If symptoms are nor resolved after 24 hours, continue daily dosing for up to 3 days.

[5] Do not use if clinical suspicion for *Compylobacter, Salmonella, Shigella,* or other causes of invasive diarrhea. Use may he reserved for patients unable to receive fluoroquinolones or azithromycin. From CDC Yellow Book 2020: Health Information for International Travel. 2020.

SUMMARY

This chapter provides an overview of the key considerations for promoting health equity around the world. It considers ways of protecting travelers while also protecting the involved healthcare workforce. Conscientious international partnerships can be formed to tackle the global burden of disease. The role of social determinants of health in driving health outcomes must be considered when establishing such collaborations. Furthermore, it is essential that responses to these social determinants of health be integrated into the more traditional role of the healthcare system, which focuses on direct clinical care.[19] Future generations of practitioners should strive to build upon the early progress made in developing more comprehensive, ethical, socially accountable, and population-centered initiatives.

Table 5–10

Chief Complaints in Returned Travelers Presenting to Travel Clinics[87]

Complaint	Percentage (n: 42,178)
Gastrointestinal	34%
Febrile illness	23%
Dermatologic	19%
Respiratory/pharyngeal	11%
Neurologic	1.7%
GU/STI	2.9%

GU, genitourinary; STI, sexually transmitted infection. Data from Leder K, Tong S, Weld L, Kain KC, Wilder-Smith A, von Sonnenburg F, et al. Illness in travelers visiting friends and relatives: a review of the GeoSentinel Surveillance Network. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2006;43(9):1185–93.

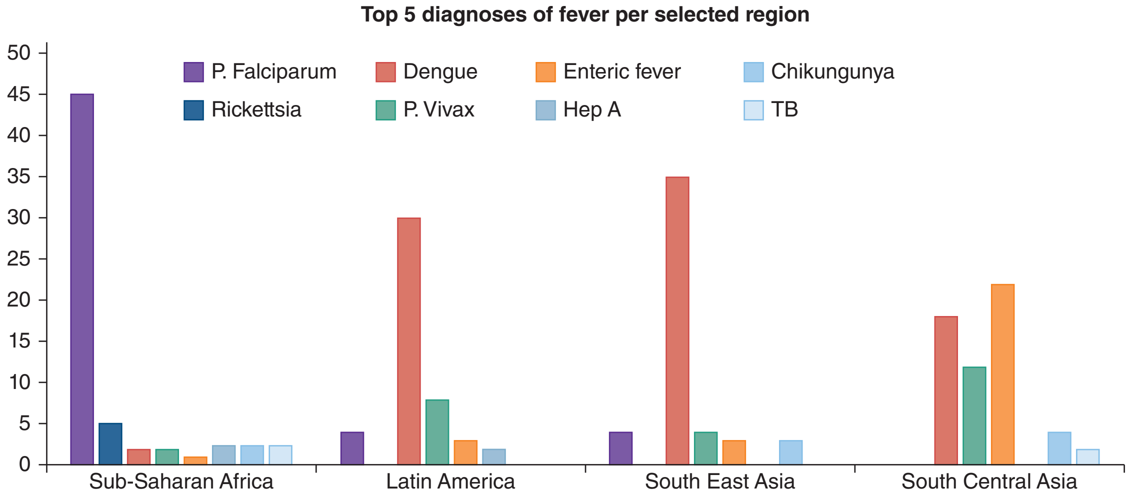


FIGURE 5–18. Top five diagnoses made in febrile patients returning from the selected region and presenting to specialty travel clinics. Reproduced with permission from From Leder K, Torresi J, Libman MD, et al. GeoSentinel Surveillance of Illness in Returned Travelers, 2007–2011. Ann Intern Med. 2013;158:456–468.

Patient Care Process

Collect Information:

- Obtain a thorough medical and medication history.
- Review prior immunization history, including both routine and prior travel immunizations.
- Obtain a detailed travel itinerary including locations and planned activities.

Assess the Information:

- Use an updated resource to determine risk of malaria and other geographically specific risks.
- Assess risks of other vaccine-preventable diseases based on travel, medical, and immunization history.
- Identify any noninfectious risks based on travel, medical, and immunization histories.
- Determine the risks and benefits of self-directed treatment for traveler's diarrhea.

Develop a Care Plan:

- Select an appropriate antimalarial medication for prophylaxis. Consider drug interactions, duration of travel, and potential toxicities.
- Develop an immunization regimen appropriate for the proposed itinerary.
- Counsel on food and water precautions and develop a strategy for treating the potential of traveler's diarrhea.

Implement the Care Plan:

- Review drugs, duration, dose, frequency, and side effects of selected medications.
- Educate the patient about the importance of compliance with the regimen and the risks of noncompliance.
- Ensure appropriate documentation of immunization administration for medical and legal purposes.

Follow up: Monitor and Evaluate: Glucose-6-Phosphatase Dehydrogenase Deficiency

- Follow up on subsequent immunizations for those that require multiple doses at precise intervals.
- Educate that patients who develop fever after returning from travel should be promptly evaluated with itinerary-specific diseases such as malaria considered among possible diagnoses.

Abbreviations Introduced in This Chapter

AIDS	Acquired immunodeficiency syndrome
COVID-19	Coronavirus disease-2019
DOAC	Direct oral anticoagulant
PEPFAR	President's Emergency Plan for AIDS Relief
WHO	World Health Organization
HALE	Healthy life expectancy
DALY	Disability-adjusted life year
EML	Essential medicines list
LMIC	Low- and middle-income country
MDA	Mass drug administration
MDG	Millennium Development Goal
NCD	Noncommunicable disease
NTD	Neglected tropical disease
R&D	Research and development
SDG	Sustainable Development Goal
SF	Substandard or falsified
STH	Soil-transmitted helminth
UNFPA	United Nations Fund for Population Activities
IHD	Ischemic heart disease
MMR	Maternal mortality ratio
TFR	Total fertility rate

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Part II

Disorders of Organ Systems

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6 Hypertension

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Shannon W. Finks

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Identify guideline-based treatment goals for patients with hypertension.
2. Recognize underlying causes and contributing factors in the development of hypertension.
3. Describe the appropriate measurement of blood pressure (BP).
4. Classify BP levels after measurement.
5. Recommend lifestyle modifications.
6. Determine patient-centered pharmacotherapy for individuals with hypertension.
7. Identify specific conditions and populations requiring special consideration when designing a treatment plan for hypertension.
8. Construct an appropriate monitoring plan to assess hypertension treatment.

INTRODUCTION

It is well established that reducing elevated blood pressure (BP) in patients at sufficient cardiovascular event risk provides significant benefit. However, despite efforts to promote awareness and widespread use of antihypertensive medications, BP control remains suboptimal.[1]

Various algorithms recommend nonpharmacologic and pharmacologic management, with the underlying premise that lowering elevated BP reduces target organ damage leading to reductions in stroke, myocardial infarction (MI), end-stage renal disease, and heart failure (HF).[2,3] BP-related definitions, targets, and treatment recommendations for a particular patient may vary based on different guidelines and/or position statements, depending on their interpretation of the clinical evidence available at the time of development and the translatability of clinical data to their local practice. This chapter primarily focuses on the most recent comprehensive, evidence-based 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, put forth by the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Clinical Practice Guidelines and hereafter referred to as the 2017 ACC/AHA guidelines.[2] This is not to minimize or discount other guidelines but to improve consistency for the learner.

KEY CONCEPT The 2017 ACC/AHA guidelines classify BP and provide guidance on accurate assessment of BP as well as the nonpharmacologic and pharmacologic approaches to managing hypertension. Various guidelines recognize that the lowest risk of adverse cardiovascular or renal outcomes is at a BP around 115/75 mm Hg, with risk rising as BP increases. For each increase of 20 mm Hg in systolic BP (SBP), or approximately 10 mm Hg increase in diastolic BP (DBP), the risk of death from ischemic heart disease, stroke, and other vascular diseases increases by twofold in individuals aged 40 to 69 years. The risk is even greater in older individuals.

KEY CONCEPT The 2017 ACC/AHA guidelines classify elevations in BP beyond specific thresholds as elevated BP, stage 1 hypertension, and stage 2 hypertension (Table 6–1) to imply different levels of risk and the need for varying intensities of intervention with drug therapy.[2] Specific BP thresholds for treatment and BP goals of therapy are established based on cardiovascular risk assessment or the presence of specific comorbid conditions (Figure 6–1 and Table 6–2).[2] Recommendations for BP-lowering medications typically begin with one or two (in the case of stage 2 hypertension and average BP of 20/10 mm Hg above the BP target) antihypertensive drugs. In addition, recommendations for specific medications are provided by race and/or the presence of compelling indications (Table 6–3) for which explicit evidence in the literature exists to document the utility of a particular agent or class of agents.[2] Selection of subsequent drug therapy involves an iterative process of adding antihypertensive drugs with different mechanisms of action as needed to achieve target BP. Although calls for greater personalization in selecting drug therapy have been advocated, including plasma renin activity (PRA) testing or noninvasive hemodynamic monitoring, these approaches are

Table 6–1

Classification of Hypertension in Adults[a,2]

BP Classification	Systolic BP (mm Hg)		Diastolic BP (mm Hg)
< Normal	< 120	AND	< 80
Elevated	120–129	AND	< 80
Stage 1 hypertension	130–139	OR	80–89
Stage 2 hypertension	≥ 140	OR	≥ 90

[a]Adults with systolic BP and diastolic BP in two categories should be assigned to the higher BP classification.

BP, blood pressure.

Table 6–2

Blood Pressure Thresholds and Goals of Pharmacologic Therapy in Patients With Hypertension According to Clinical Conditions[2]

Clinical Condition(s)	BP Threshold for Antihypertensive Therapy Initiation (mm Hg)	BP Goal (mm Hg)
General		
Clinical CVD or 10-year ASCVD risk ≥ 10%	≥ 130/80	< 130/80
No clinical CVD and 10-year ASCVD risk < 10%	≥ 140/90	< 130/80
Older persons (≥ 65 years of age; noninstitutionalized ambulatory, community-living adults)	≥ 130 (SBP)	< 130 (SBP)
Specific Conditions		
Diabetes mellitus	≥ 130/80	< 130/80
Chronic kidney disease	≥ 130/80	< 130/80
Chronic kidney disease postrenal transplantation	≥ 130/80	< 130/80
Heart failure	≥ 130/80	< 130/80
Stable ischemic heart disease	≥ 130/80	< 130/80
Secondary stroke prevention	≥ 140/90	< 130/80
Secondary stroke prevention (lacunar)	≥ 130/80	< 130/80
Peripheral arterial disease	≥ 130/80	< 130/80

ASCVD, atherosclerotic cardiovascular disease (calculator available online at http://tools.acc.org/ascvd-risk-estimator/); BP, blood pressure; CVD, cardiovascular disease; SBP, systolic blood pressure.

Adapted from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Hypertension. 2017, with permission.

not widely used.[4,5] In contrast, the importance of using 24-hour ambulatory BP monitoring (ABPM), home BP (HBP) monitoring, and ambulatory office-based BP (AOBP) monitoring has been recognized by the Centers for Medicare & Medicaid Services (CMS) and other organizations.[2,3,6] Regardless of the guideline and strategy implemented in practice, it is imperative that clinicians consider patient-specific characteristics and preferences among other considerations when establishing BP targets and drug selection.

EPIDEMIOLOGY

KEY CONCEPT Hypertension is widely prevalent and significantly contributes to cardiovascular-related morbidity, mortality, and associated health care costs. Globally, the estimated age-standardized prevalence of hypertension in adults (defined as SBP ≥ 140 mm Hg, diastolic DBP ≥ 90 mm Hg, and/or current use of antihypertensive medication) was 31.1% in 2010 with a modest decline in high-income countries and significant increase in low- and middle-income countries since 1975.[7] In the United States, nearly half (46%, 116.4 million) of adults greater than or equal to 20 years of age were estimated to be hypertensive when applying the definition of hypertension from the 2017 ACC/AHA guidelines.[1] The prevalence of hypertension differs based on age, sex, and ethnicity. As individuals age, risk of systolic hypertension increases. Eventually, more than 80% of the US population will have hypertension when aged 75 or older. Prior to age 64, women have a lower prevalence of hypertension than men but have a higher prevalence after age 65. Age-adjusted prevalence of hypertension is highest in non-Hispanic black individuals (56%–58.6%) when compared with non-Hispanic white individuals (41.3%–48.2%) and Mexican Americans (37.9%–44.4%).[1]

ETIOLOGY

KEY CONCEPT The cause of hypertension is usually unknown and referred to as primary hypertension in more than 90% of patients. However, in some patients there is an identifiable cause of hypertension, referred to as secondary hypertension. Causes of secondary hypertension include[2,8]:

More common (> 1%):

- Chronic kidney disease (CKD) (renal parenchymal disease)
- Drug-induced/related (Table 6–4)
- Obstructive sleep apnea
- Primary aldosteronism
- Renovascular hypertension or fibromuscular dysplasia

Less common (≤ 1%):

- Coarctation of the aorta
- Cushing syndrome and other glucocorticoid excess states
- Mineralocorticoid excess syndromes other than primary aldosteronism
- Genetic disorders (such as Liddle syndrome, Gordon syndrome, or Geller syndrome)
- Pheochromocytoma/paraganglioma
- Thyroid or parathyroid disease

The 2017 ACC/AHA guidelines recommend screening for secondary causes of hypertension in uncontrolled drug-resistant hypertension (three or more drugs), abrupt onset, age less than 30 years, excessive target organ damage, onset of diastolic hypertension in older adults, or in the presence of unprovoked or excessive hypokalemia.[2] In addition to primary and secondary hypertension, the clinician may encounter what is referred to as resistant hypertension. **KEY CONCEPT** Patients failing to achieve goal BP despite adherence to optimal doses of three antihypertensive agents of different classes (ideally, one being a diuretic) or those achieving goal BP on four or more antihypertensive medications have resistant hypertension and should be evaluated for secondary causes of hypertension.[9] Several causes of resistant hypertension are listed in Table 6–4 and should be carefully considered in such patients.[10] Additional consideration should be given to the clinical scenario of pseudohypertension, or elevated BP resulting from a myriad of potentiating factors including therapy nonadherence, white coat hypertension, or poor BP measurement technique.[9]

PATHOPHYSIOLOGY

KEY CONCEPT The pathophysiology of primary hypertension is heterogeneous but ultimately exerts its effects through two primary determinants of BP: cardiac output (CO) and peripheral vascular resistance (PVR). The processes influencing these two determinants are numerous and complex, and although the underlying cause of primary hypertension remains unknown, it is most likely multifactorial. As a review of these mechanisms is beyond the scope of this text, readers are referred to other sources.[8]

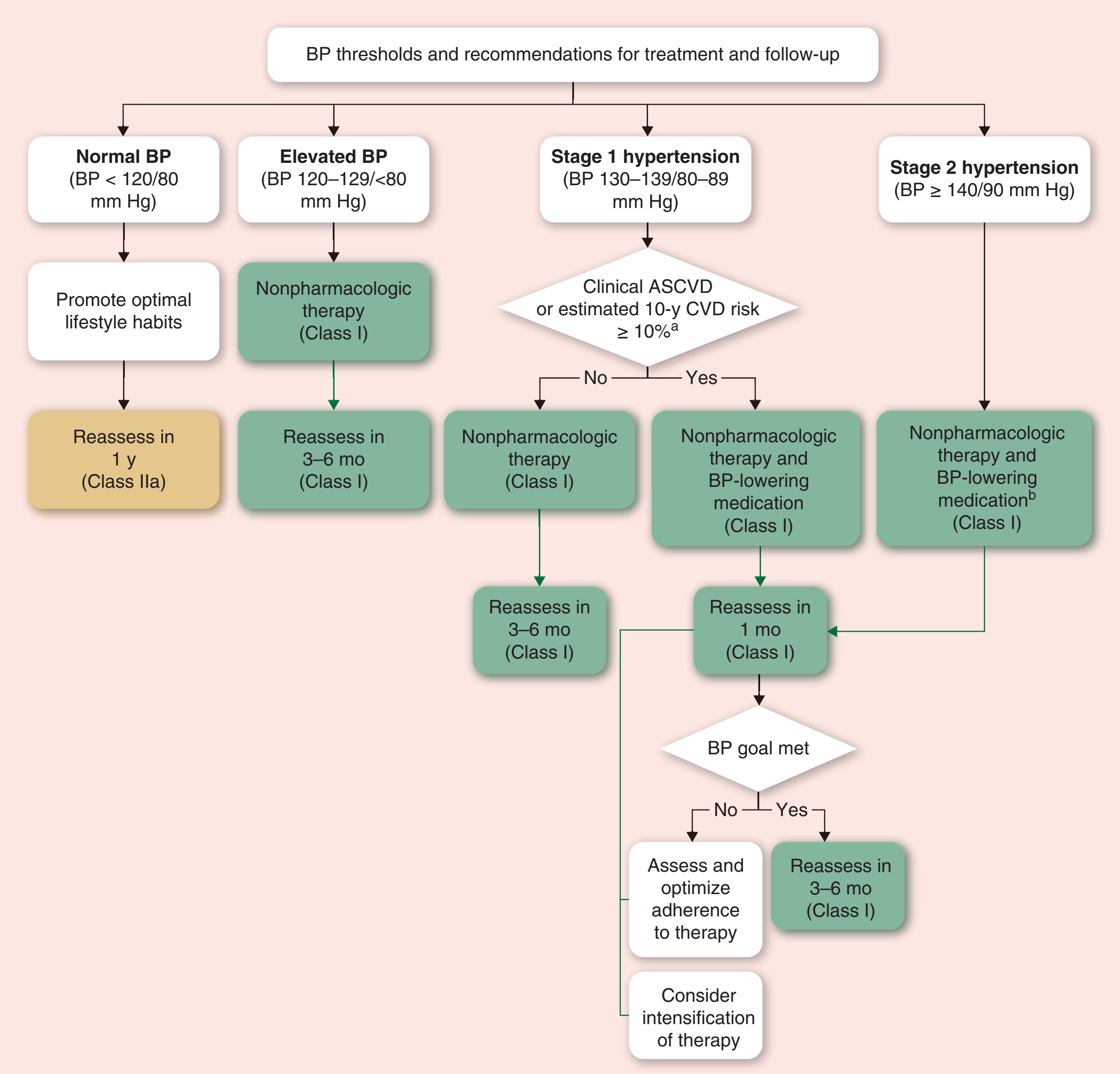

BP thresholds and recommendations for treatment and follow-up
Normal BP (BP < 120/80 mm Hg)
Elevated BP (BP 120–129/<80 mm Hg)
Stage 1 hypertension (BP 130–139/80–89 mm Hg)
Stage 2 hypertension (BP ≥ 140/90 mm Hg)
Promote optimal lifestyle habits
Nonpharmacologic therapy (Class I)
Clinical ASCVD or estimated 10-y CVD risk ≥ 10%a
No
Yes
Reassess in 1 y (Class IIa)
Reassess in 3–6 mo (Class I)
Nonpharmacologic therapy (Class I)
Nonpharmacologic therapy and BP-lowering medication (Class I)
Nonpharmacologic therapy and BP-lowering medicationb (Class I)
Reassess in 3–6 mo (Class I)
Reassess in 1 mo (Class I)
BP goal met
No
Yes
Assess and optimize adherence to therapy
Reassess in 3–6 mo (Class I)
Consider intensification of therapy

FIGURE 6–1. General recommendations for blood pressure (BP) threshold and recommendations for treatment and follow-up. Patients with elevated BPs should incorporate nonpharmacologic therapies to promote BP lowering. As BP reaches stage 1 hypertension, thresholds for therapy are guided based on a patient's level of risk as determined by baseline presence of cardiovascular disease (CVD), chronic kidney disease (CKD), or diabetes mellitus (DM) (all placing patient at higher risk) and CVD risk as calculated with the American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equations (values greater than or equal to 10% defining higher risk). Lower-risk patients are reasonable for an initial trial of nonpharmacologic therapies while those with higher risk or stage 2 hypertension are initially begun on BP-lowering medications. Consideration may be given in patients with stage 2 to the initiation of combination therapy at treatment onset. "Class" indicates the strength of the recommendation, with Class I considered the strongest. [a]Using the ACC/AHA Pooled Cohort Equations. Note that patients with DM or CKD are automatically placed in the high-risk category. For initiation of renin–angiotensin system (RAS) inhibitor or diuretic therapy, assess blood tests for electrolytes and renal function 2 to 4 weeks after initiating therapy. [b]Consider initiation of pharmacologic therapy for stage 2 hypertension with two antihypertensive agents of different classes. Patients with stage 2 hypertension and BP greater than or equal to 160/100 mm Hg should be promptly treated, carefully monitored, and subject to upward medication dose adjustment as necessary to control BP. Reassessment includes BP measurement, detection of orthostatic hypotension in selected patients (eg, older or with postural symptoms), identification of white coat hypertension or a white coat effect, documentation of adherence, monitoring of the response to therapy, reinforcement of the importance of adherence, reinforcement of the importance of treatment, and assistance with treatment to achieve BP target. (ASCVD, atherosclerotic cardiovascular disease; mo, month; y, year.) (Reprinted with permission from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Hypertension. 2017. https://doi.org/10.1161/HYP.0000000000000065.)

Table 6–3

Compelling Indications for Individual Drug Classes[2]

	Recommended Drug Class						
Compelling Indication	**Diuretic**	**Ald Ant**	**BB**	**CCB**	**ACE-I**	**ARB**	**Dir Vaso**
Heart failure with reduced ejection fraction	X	X	X		X	X	X
Heart failure with preserved ejection fraction	X		X		X	X	
Stable ischemic heart disease[a]	X	X	X	X	X	X	
Chronic kidney disease[b]					X	X	
Postrenal transplantation				X	X[c]		
Diabetes mellitus	X			X	X[d]	X[d]	
Secondary stroke prevention	X				X	X	
Atrial fibrillation						X	
Peripheral arterial disease	X			X	X	X	
Thoracic aortic disease			X				
Black race[e]	X			X			

[a] Recommended β-blockers for blood pressure (BP) control or angina relief include carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol. Avoid β-blockers with intrinsic sympathomimetic activity. Atenolol should not be used as it is less effective than placebo for reducing cardiovascular events. CCBs recommended (class I) if blood pressure goal not met with BB, ACE-I or ARBs, and angina pectoris present.

[b] Recommendations stronger (class IIa) for patients with chronic kidney disease (CKD) and albuminuria (≥ 300 mg/day or ≥ 300 mg/g creatinine [34 mg/mmol creatinine]) and weaker (class IIb) for CKD stage 3 or higher without albuminuria or stage 1 or 2 with albuminuria (≥ 300 mg/day or ≥ 300 mg/g creatinine [34 mg/mmol creatinine]).

[c] ACE-I may be reserved in the development of albuminuria or heart failure after transplantation.

[d] ACE-I or ARB may be considered in the presence of albuminuria.

[e] Black adults with or without diabetes mellitus but without heart failure or CKD.

ACE-I, angiotensin-converting enzyme inhibitor; Ald Ant, aldosterone antagonist; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; Dir Vaso, direct vasodilator.

Data from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. J Am Coll Cardiol. 2017. https://doi.org/10.1161/HYP.0000000000000065.

Patient Encounter 1

A 49-year-old man comes into your clinic with complaints of upper respiratory symptoms. Seated BP measured in the left arm is 148/96 mm Hg and 150/94 mm Hg in the right arm. The patient's physical examination was unremarkable. His past medical history is significant for dyslipidemia. He does not smoke tobacco or drink alcohol, and he walks daily for 30 minutes; however, he struggles with a heart healthy diet. He takes no medication on a chronic basis, but he reports taking an antihistamine/decongestant and ibuprofen for his current symptoms over the past several days. His cholesterol panel revealed a high-density lipoprotein (HDL) cholesterol level of 40 mg/dL (1.03 mmol/L), triglyceride level of 140 mg/dL (1.58 mmol/L), and total cholesterol of 198 mg/dL (5.12 mmol/L). Calculated low-density lipoprotein (LDL) cholesterol level is 130 mg/dL (3.36 mmol/L). All other laboratory values were within normal limits.

What steps are involved in assuring the patient's BP measurements are accurate?

Based on the information above, what stage of hypertension does this patient have?

What is the patient's BP target and threshold for antihypertensive therapy?

The development of primary hypertension involves interplay between genetic and environmental factors interacting with multiple physiological systems including neural, renal, hormonal, and vascular. Further complicating this is that an individual's phenotype of primary (or essential) hypertension (eg, systolic hypertension in teenagers and young adults, diastolic hypertension in middle-aged individuals, and isolated systolic hypertension in the elderly) may have different contributing mechanisms.[8] Because of these complexities, no final common pathway has been identified, and a single target for the treatment of primary hypertension remains elusive. Therefore, guidelines for the selection of specific therapeutic agents allow the clinician some flexibility in choices based on patient-specific factors.

Genetic Factors

Despite the identification of more than 1000 genetic loci associated with BP regulation, these loci together only explain about 5.7% of the variability of SBP, DBP, and pulse pressure.[11] However, rare monogenetic disorders can cause secondary hypertension in children, adolescents, or young adults, who typically have a suppressed PRA or plasma renin concentration (PRC). Environmental factors and gene-environment interactions, on the other hand, confer a larger effect on the pathophysiology of hypotension. Consequently, with very few exceptions, the information available to date is far from sufficient to provide any practical guidance for clinicians.[12] Nevertheless, these genetic associations reveal novel mechanisms and pathways regulating BP and may accelerate development of new drug therapies.

Table 6–4

Causes of Resistant Hypertension[10]

Apparent Resistance
- Improper blood pressure measurement
- Failure to receive or take antihypertensive medication appropriately (nonadherence)
- Inadequate doses (subtherapeutic)
- Improper antihypertensive selection or combination
- White coat hypertension

True Resistance
- Secondary hypertension
- Drug effects and interactions
  - Adrenal steroid hormones
  - Amphotericin B
  - Cocaine, amphetamines, and other illicit drugs
  - Cyclosporine and tacrolimus
  - Erythropoietin
  - Fluid retention from kidney disease or potent vasodilators (eg, minoxidil)
  - Herbal products (ma huang, guarana, bitter orange, blue cohosh)
  - Highly active antiretroviral therapy (HAART)
  - Inadequate diuretic therapy
  - Natural licorice (including some chewing tobacco)
  - Neurologic and psychiatric agents (eg, venlafaxine, lithium, thioridazine hydrochloride)
  - Nonsteroidal anti-inflammatory medications
  - Oral contraceptive hormones
  - Recent caffeine or nicotine intake
  - Sympathomimetics (decongestants, anorectics, and stimulants)
  - Vascular endothelial growth factor inhibitors (bevacizumab, sorafenib, sunitinib)
- Volume overload
- Excess sodium intake
- Comorbidities
  - Obesity
  - Excess alcohol intake
  - Chronic pain syndromes
  - Intense vasoconstriction (arteritis)
  - Anxiety-induced hyperventilation/panic attacks
- Genetic variation
  - Genetic differences in drug efficacy or metabolism

Environmental Factors

Environmental factors contributing to hypertension are well-characterized. Nicotine use (including cigars and smokeless tobacco) and caffeine cause transient increases in BP via norepinephrine release and, in the case of caffeine, by its antagonism of vasodilatory adenosine receptors.[2] Daily use of electronic cigarettes adds additional cardiovascular risks especially in the younger population in part because of the association with increased BP, higher sympathetic nerve activity, and increased myocardial infarction.[13] Acute alcohol ingestion may have a transient variable effect (increased due to sympathetic nerve activity or lowering due to vasodilation), whereas chronic heavy consumption of alcohol and binge drinking raises the risk of hypertension.[8] Many other environmental factors have been implicated in the development of hypertension. These include obesity, physical inactivity, adverse fetal environment, postnatal weight gain, premature birth and low birth weight, potassium and magnesium depletion, vitamin D deficiency, and environmental toxins (eg, lead).[8]

Neural Mechanisms

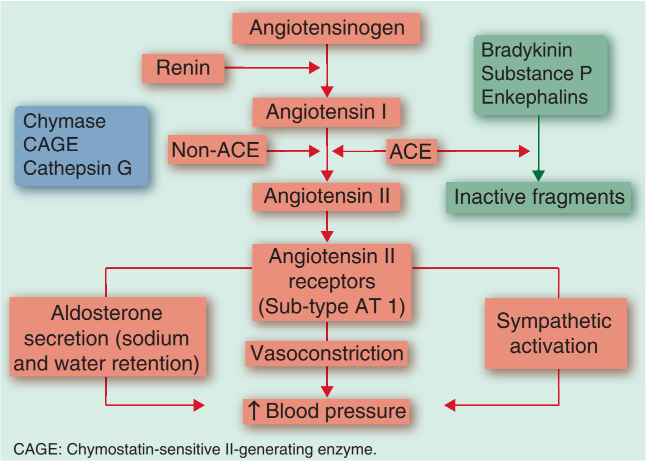
Overactivity of the sympathetic nervous system (SNS) in the early stages of primary hypertension manifests as increased heart rate, CO, and peripheral vasoconstriction. Despite this, outcome trials of agents targeting the SNS (α- and β-adrenergic blockers) have not performed as well as other drug classes. Nevertheless, strategies aimed at targeting the SNS continue with specific interest in invasive strategies aimed at resistant hypertension.[9]

Renal Mechanisms

The contribution of sodium to the development of primary hypertension is related to excess sodium intake and/or abnormal sodium excretion by the kidneys.[8] It is generally accepted that reducing dietary sodium intake while increasing dietary potassium intake reduces BP and cardiovascular disease (CVD).[14,15]

Hormonal Mechanisms

Renin is produced and stored in the juxtaglomerular cells of the kidney, and its release is stimulated by impaired renal perfusion, salt depletion, and β_1-adrenergic stimulation. The release of renin is the rate-limiting step in the eventual formation of angiotensin II, which is a potent vasoconstrictor (Figure 6–2).[8] The role of the renin-angiotensin-aldosterone system (RAAS) in primary hypertension is supported by the presence of high levels of renin, suggesting the system is inappropriately activated. Proposed mechanisms include increased sympathetic drive, defective regulation of the RAAS (nonmodulation), and the existence of a subpopulation of ischemic nephrons that release excess renin.[8] However, there are also patients with primary hypertension, and low levels of renin, which suggests alternative mechanisms, unrelated to renin levels or activity, may be in play. Thus, although



CAGE: Chymostatin-sensitive II-generating enzyme.

FIGURE 6–2. Diagram of the renin-angiotensin-aldosterone system (RAAS), a key system involved in the modulation of blood pressure. The diagram depicts the pathways involved in the action of various antihypertensive agents including angiotensin-converting enzyme (ACE) inhibitors, ARBs, diuretics, and aldosterone antagonists. By inhibiting the action of ACE, ACE inhibitors reduce both the formation of the vasoconstrictors angiotensin II and the degradation of vasodilating substances including bradykinin. ARBs primarily act through inhibition of the action of angiotensin II on the angiotensin-I receptors that modulate vasoconstriction. Aldosterone antagonists directly inhibit the action of aldosterone; diuretics affect sodium and water retention at a renal level. (ARB, angiotensin receptor blockers; AT1, angiotensin-1.) (From Victor RG, Kaplan NM. Kaplan's Clinical Hypertension, 10th ed. Philadelphia, PA: Wolters Kluwer Lippincott Williams & Wilkins Health; 2010, with permission.)

uncommon in general practice, PRA measurements may be utilized to guide antihypertensive therapy selection particularly in younger patients with genetic disorders. In fact, it has been demonstrated that patients with low PRA (< 0.65 ng/mL/hour [0.18 ng/L/s]) respond preferentially to diuretics, aldosterone antagonists, and calcium channel blockers (CCBs), whereas those with higher PRA levels respond preferentially to renin-mediated therapies such as β-blockers, angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and direct renin inhibitors.[16] However, use of PRA measurements to guide therapy is not without controversy, and the reader is referred to other sources for more information.[12]

Vascular Mechanisms

Elevated PVR is the hemodynamic hallmark of primary hypertension. The increase in PVR typically observed may be due to a reduction in arterial lumen size as a result of vascular remodeling. This remodeling, or change in vascular tone, may be modulated by various endothelium-derived vasoactive substances, growth factors, and cytokines. This increase in arterial stiffness or reduced compliance results in an incremental rise in systolic BP.[8]

Contributing Comorbidities

Several comorbidities have a high concurrence with the presence of hypertension leading to a higher risk of target organ damage, cardiovascular morbidity and mortality, and overall healthcare costs. Specifically, these include diabetes mellitus (DM), dyslipidemia, obesity, and CKD. As such, assessment of atherosclerotic cardiovascular disease (ASCVD) risk in all patients with hypertension should be part of the management plan while pursuing target BPs through nonpharmacologic and pharmacologic means.[2]

MEASUREMENT OF BLOOD PRESSURE

KEY CONCEPT Appropriate technique in measuring BP is a vital component to the diagnosis and management of hypertension. Accurate measurement of a patient's BP requires control of factors that may influence variability in the measure. Failure to consider these factors, including body position, cuff size, device selection, auscultatory technique, and dietary intake prior to the visit, may lead to misclassification and thus inaccurate assessments of risk. Clinicians should instruct patients to avoid exercise, alcohol, caffeine, or nicotine 30 minutes before BP measurement. Patients should be sitting comfortably with their back supported and arm free of constrictive clothing with legs uncrossed and feet flat on the floor for a minimum of 5 minutes before the first reading. Systolic and diastolic BP tend to increase when the cuff size is too small. Ideally, the cuff bladder should encircle at least 80% of the arm's circumference to ensure a more accurate measurement of BP.[2]

To reduce deviations in BP measurement in the clinic, the patient and clinician should not talk during measurement. The measurement arm should be supported and positioned at heart level. If a mercury or aneroid device is used, then the palpatory method (inflate the cuff to approximately 80 mm Hg rapidly while palpating the radial pulse, then increase pressure slowly by 10 mm Hg increment every two to three seconds until the radial pulse is no longer felt [estimated SBP]; the cuff is then inflated further until the pressure is about 30 mm Hg higher) must be used first to estimate the SBP.[2] If an automated device is used, this is not necessary. After the patient's cuff is inflated above the systolic pressure, the pressure indicator should drop at a rate of 2 to 3 mm Hg/s. A stethoscope placed over the brachial artery in the antecubital fossa identifies the first and disappearance of audible Korotkoff sounds, which should be taken as systolic and diastolic pressure, respectively. A minimum of two readings at least one minute apart are then averaged. If measurements vary by more than 5 mm Hg between the two readings, then one or two additional BP measurements are collected (at least one minute apart from each measurement) and the multiple readings averaged. BP classification is based on the average of two or more properly measured BP readings on each of two or more office visits. Details and further recommendations for accurate measurement of BP in special populations can be found elsewhere.[2,3] Finally, measurement of clinic or office BPs is often poorly correlated with assessments of BP in other settings. Consequently, under select circumstances, clinicians are increasingly using 24-hour ABPM, AOBP monitoring, and HBP monitoring. Corresponding values of systolic and diastolic BP for clinic, 24-hour ABPM, AOBP, and HBP measurements are provided in Table 6–5.[2] These methods of BP measurement are useful in identifying patients with white coat hypertension or in the case of 24-hour ABPM, elevations of BP during the night and masked hypertension, or hypertension not identified through traditional office measurement. They may also aid in the management of patients with refractory hypertension with minor target organ damage, suspected autonomic neuropathy, hypotensive symptoms, and patients with large differences between home and office BP measurements. Benefits derived from these additional methods of BP monitoring may be of greater prognostic significance than traditional office-based measurements.[7,16] Consequently, the 2017 ACC/AHA guidelines recommend utilizing out-of-office self-monitoring of BP to confirm hypertension diagnosis and for titration of BP-lowering medications in conjunction with clinic and telehealth counseling.[2]

Table 6–5

Corresponding Values (mm Hg) of Systolic BP/Diastolic BP for Various Methods of BP Measurement[2]

Clinic	HBPM[a]	Daytime ABPM[a]	Nighttime ABPM[a]	24-Hour (Overall) ABPM[a]
120/80	120/80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	145/90	145/90	140/85	145/90

[a] Average of recorded values.

ABPM, ambulatory BP measurement; BP, blood pressure; HBPM, home BP measurement.

Adapted from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Hypertension. 2017, with permission.

TREATMENT

Desired Outcomes

The goal of BP management is to reduce the risk of CVD-related morbidity and mortality manifested as target organ damage such as coronary artery disease (CAD), stroke, and kidney disease.

General Approach to Treatment

KEY CONCEPT Drug therapy for the management of patients with hypertension should be considered as adjunctive to

Clinical Presentation and Diagnosis of Primary Hypertension

General

Prevalence of hypertension is likely to be highest with middle-aged or older patients.

Gender: In the United States, hypertension is slightly more prevalent in men than women before the age of 35 years, similar between the ages of 35 and 64 years, and higher in women than men thereafter.

Symptoms

The patient with primary hypertension may be asymptomatic yet still have major CVD risk factors.

Signs

BP should be assessed as an average of two or more BP readings (SBP and DBP) on two or more occasions.

Classification of an individual's hypertension (Table 6–1) can be made based on the higher classification from either the SBP or DBP readings; for example, an individual whose readings are consistently 136/94 mm Hg would be classified as having stage 2 hypertension.

Basic Testing (facilitates CVD risk factor profiling, establishes a baseline for monitoring medication use, and facilitates screening for select secondary causes of hypertension):

- Fasting lipid panel (to determine ASCVD risk and those who may benefit from statin therapy as described in Chapter 13, "Dyslipidemias")
- Hemoglobin A_{1C} or fasting plasma glucose (to identify patients with impaired fasting glucose or diabetes as described in Chapter 44, "Diabetes Mellitus")
- Complete blood count
- Serum sodium, potassium, calcium, creatinine with estimated glomerular filtration rate (GFR; may all be included as part of a comprehensive metabolic panel)
- Thyroid-stimulating hormone (simple test and hypo- or hyperthyroidism are secondary causes of hypertension)
- Urinalysis
- Electrocardiogram (ECG)

Optional Testing (may provide information on target organ damage):

- Echocardiogram
- Uric acid
- Urinary albumin to creatinine ratio

The following abnormal tests may indicate hypertension-related damage:

- Serum creatinine elevated (> 1.2 mg/dL [106 μmol/L])
- Microalbuminuria, which is diagnosed either from a 24-hour urine collection (20–200 mcg/min) or from elevated concentrations (30–300 mg/L) on at least two occasions. Use of the albumin-to-creatinine ratio (ACR) in a spot urine sample is becoming more common, and **microalbuminuria** is defined by this measure as 30 to 300 mg/g creatinine (3.4–34 mg/mmol creatinine)

Common Comorbidities and Factors Contributing to Cardiovascular Risk

- DM
- Metabolic syndrome
- Insulin resistance
- Dyslipidemia
- Microalbuminuria/CKD
- Family history
- Central obesity
- Physical inactivity
- Tobacco use

Cardiovascular Risk Assessment

Calculate with risk assessment tools, such as the ACC/AHA ASCVD Risk Estimator (http://tools.acc.org/ascvd-risk-estimator/)

Target Organ Damage

- Cerebrovascular disease (eg, stroke or transient ischemic attack)
- Ocular (hypertensive retinopathy)
- Cardiac (left ventricular hypertrophy, left ventricular dysfunction, CAD, HF)
- CKD (eg, albuminuria, nephrosclerosis)
- Peripheral arterial disease

nonpharmacologic approaches for BP lowering. Ultimately, the attainment of target BP in many cases may be more important than the antihypertensive agent selected. Previous research has established the value of using individual antihypertensive drugs versus placebo to achieve reduction in morbidity and mortality by lowering BP. According to the 2017 ACC/AHA guidelines, the recommended BP target for the vast majority of patients is less than 130/80 mm Hg.[2] The BP threshold for treatment varies according to the patient's baseline cardiovascular risk. BP-lowering medications are recommended in patients with clinical CVD (defined as coronary heart disease (CHD), HF, or stroke) and an average SBP of 130 mm Hg or higher or an average DPB of 80 mm Hg or higher. In addition, BP-lowering medications are recommended for primary prevention in adults with an estimated 10-year ASCVD risk of 10% or higher and whose SBP/DBP exceeds 130/80 mm Hg. The recommended tool for calculating ASCVD risk is the ACC/AHA ASCVD Risk Estimator (http://tools.acc.org/ascvd-risk-estimator/). BP thresholds and goals for pharmacologic therapy in these patients and those with other clinical conditions are summarized in Table 6–2. Although these guidelines clearly recommend treatment thresholds for most individuals with or without CVD or select comorbidities, the benefits of aggressive BP control using pharmacotherapy remain debatable for certain patients. Examples where conflicting data require reconciliation include controlled studies, such as the SPRINT (Systolic Blood Pressure Intervention Trial),[17] ACCORD (Action to Control Cardiovascular Risk in Diabetes),[18] and SPS3 (Secondary Prevention of Small Subcortical Strokes; blood-pressure targets in patients with recent lacunar stroke)[19] trials, where improved outcomes across all major endpoints for patients achieving a more intensive

BP-lowering goal were not consistently observed. Although these inconsistencies underscore the need for additional high-quality research with the aim of determining the most appropriate BP targets for specific patient groups, the 2017 ACC/AHA guidelines were generated by inclusion of many associations and groups representing a wide array of specialty populations.[2]

Evidence supports the position that the main benefits of pharmacologic therapy are related to achievement of BP lowering and are generally independent of the selection of an individual drug regimen. Inherent in this position is the realization that lifestyle changes or nonpharmacologic approaches alone are rarely successful in attaining target BPs, and multidrug therapy (sometimes as many as three or more agents) is necessary for most patients.[20] Given the need for multiple medications to control hypertension, clinicians should work to minimize pill burden, frequency of administration, and cost. When possible and appropriate, selecting fixed-combination drug therapies, longer-acting formulations, and generic or formulary-based medications may optimize adherence. The 2017 ACC/AHA guidelines state that it is reasonable to initiate pharmacologic therapy with a single agent in patients with stage 1 hypertension.[2] In those with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target, it is recommended to start therapy simultaneously with two agents from different classes.[2] Furthermore, this guideline identifies black adults as a cohort who may be considered for two or more drugs to control hypertension. Both circumstances acknowledge the urgency to control hypertension with a high likelihood of needing multiple medications.

Another general consideration for antihypertensive therapy planning includes incorporation of chronotherapeutic principles. The timing of administration of antihypertensive medications may have relevance to the manifestations of adverse effects and/or optimizing therapeutic outcomes. A study of patients with CKD and diabetes demonstrated that moving the administration time of one antihypertensive agent to bedtime dosing significantly reduced composite cardiovascular events compared to administering all antihypertensive agents at one time in the morning.[21]

Nonpharmacologic Treatment

Therapeutic lifestyle modifications consisting of nonpharmacologic approaches to BP reduction should be part of all treatment plans. The most widely studied interventions demonstrating effectiveness include:

- Dietary sodium restriction
- Increasing dietary potassium intake
- Low-fat diet, high in vegetables and fruits
- Weight reduction in overweight or obese individuals
- Regular physical activity
- Moderation of alcohol consumption

KEY CONCEPT Implementation of these lifestyle modifications successfully lowers BP, often with results similar to those of therapy with a single antihypertensive agent.[2] Combining multiple lifestyle modifications can have even greater BP-lowering effects. Sodium restriction to 2.4 g (100 mmol) of elemental sodium (6 g of sodium chloride or one teaspoon of table salt) per day lowers BP and has been recommended for the general population, especially individuals with hypertension.[2] Although controversy surrounds the optimal level of sodium intake and its cardiovascular benefits and risks, adoption of an optimal dietary pattern that includes consuming fewer processed foods is expected to afford overall cardiovascular benefits.[22]

Compared to the general population, BP lowering through sodium restriction is more pronounced in salt-sensitive individuals (low PRA), persons with diabetes, metabolic syndrome, or CKD, as well as older individuals and black people.[5] Simple dietary advice and instructions on reading nutrition labels should be introduced to patients initially and assessed and reinforced at subsequent visits. A diet high in fruits, vegetables, and low-fat dairy products, along with a reduced intake of total and saturated fat, can significantly reduce BP in as little as 8 weeks.[23] See Table 6–6.[2]

Smoking cessation should be encouraged for overall cardiovascular health despite its lack of chronic effects on BP.[2] Although BP-lowering lifestyle modifications have never been documented to reduce cardiovascular morbidity and mortality in patients with hypertension, they do effectively lower BP in most hypertensive patients and exhibit a favorable effect on other risk factors including dyslipidemia and insulin resistance. This may eliminate the need for drug therapy in those with mild elevations in BP or minimize the doses or number of antihypertensive agents required in those on therapy.[2]

Table 6–6

Lifestyle Modifications to Manage Hypertension[a,2]

Modification	Recommendation	Approximate Systolic BP Reduction (Range)
Weight reduction	Maintain normal body weight (body mass index: 18.5–24.9 kg/m^2)	1 mm Hg/1 kg
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	11 mm Hg
Dietary sodium restriction	Reduce dietary sodium intake to no more than 2.4 g sodium or 6 g sodium chloride (100 mmol/day). If these targets cannot be achieved, an absolute reduction in 1 g sodium/day is recommended	5–6 mm Hg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min/day, most days of the week)	5–8 mm Hg
Moderation of alcohol consumption	Limit consumption to no more than two standard drinks per day in most men and to no more than one standard drink per day in women and lighter weight persons[b]	4 mm Hg

[a] For overall cardiovascular risk reduction, stop smoking. The effects of implementing these modifications are dose and time dependent and could be greater for some individuals.

[b] One standard drink is defined as 12 oz (355 mL) beer, 5 oz (148 mL) wine, or 1.5 oz (44 mL) 80-proof whiskey.

BP, blood pressure; DASH, dietary approaches to stop hypertension.

Pharmacologic Treatment

KEY CONCEPT An approach to selection of drugs for the treatment of patients with hypertension should be evidence-based with considerations regarding the individual's comorbidities, co-prescribed medications, and practical patient-specific issues including tolerability and cost. The evidence-based 2017 ACC/AHA guidelines recommend drug therapy that is largely grounded in the best available evidence for superiority in outcomes—specifically morbidity and mortality.[2] The approach is often tempered with practical considerations related to competing options for specific comorbidities and issues regarding a patient's experience or tolerance for side effects and, in some cases, the cost of medications.

Landmark trials such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) have provided some objective basis for comparisons between initiating antihypertensive drug therapy with one class of antihypertensives versus another; however, there is room for criticism of these studies.[20,24,25] Consequently, practical interpretations of their conclusions must leave room for individualization based on clinical judgment. Overall, current clinical guidelines provide a reasonable basis for guiding the selection of drug classes for individuals based on their stage of hypertension, comorbidities, and special circumstances. The following sections summarize key features of specific drug classes and guideline-based recommendations. An overview of specific oral antihypertensive drug classes in common use is summarized in Table 6–7.[2,26,27]

Diuretics

Diuretics are a heterogenous group of medications with different recommendations for use among each group. The four subtypes include thiazides/thiazide-like diuretics, loop diuretics, potassium-sparing agents, and aldosterone antagonists. Each diuretic subtype has properties that distinguish their role in select patient populations. Thiazide diuretics are by far the most commonly prescribed with the greatest number of outcome-based studies supporting their use. This type of diuretic inhibits the sodium-chloride symporter in the renal distal convoluted tubule, thus increasing sodium and chloride excretion. In the United States, hydrochlorothiazide and chlorthalidone represent the most commonly prescribed thiazide-type diuretics and have been the subject of large outcome-based studies. For example, in the ALLHAT trial, patients randomized to chlorthalidone, a thiazide-type diuretic, as initial antihypertensive therapy had similar CHD outcomes to those randomized to receive initial therapy with either amlodipine or lisinopril.[20] However, differences in outcomes for select secondary endpoints or special populations demonstrated superiority of chlorthalidone-based therapy over either ACE-I or CCB-based regimens. Criticisms of the different BPs achieved in the various treatment groups, the artificial construct guiding the use of add-on drugs to base therapy, and the overrepresentation of African Americans exhibiting select endpoints have weakened the interpretability of this trial.[20] Furthermore, other studies have challenged the status of diuretics as an ideal baseline choice for initial antihypertensive drug therapy for all patients[25,26] and even the choice of diuretic used,[28] supporting the debate over whether the means by which BP is lowered (specific drug selected) is more or less important than the extent and/or time taken to lower BP. Nonetheless, thiazide-type diuretics, specifically chlorthalidone, remain supported by many as acceptable baseline initial therapy for hypertensive patients without compelling indications for other agents.[2]

Key differences in the features of various thiazide diuretics may also play a role in selection. Practical differences among thiazides include their relative diuretic potency, with chlorthalidone being considered approximately 1.5 to 2 times more potent than hydrochlorothiazide for BP reduction.[28] Recent analyses have demonstrated superiority of chlorthalidone over hydrochlorothiazide,[28] leading the 2017 ACC/AHA guidelines to specifically recommend chlorthalidone over other diuretics.[2] Because the relationship between antihypertensive efficacy and metabolic (hyperlipidemia and hyperglycemia) and electrolyte-related (hypokalemia, hypomagnesemia, hyperuricemia, and hypercalcemia) side effects of thiazide diuretics are dose-related, attention to the differential in potency may be important. These effects may complicate the management of higher-risk patients with common comorbidities such as dyslipidemia or diabetes, or even those likely to be sensitive to complications from hyperuricemia and the potassium- or magnesium-wasting effects of diuretics such as patients with dysrhythmias or those taking digoxin. Thiazide diuretic-induced development of new-onset diabetes remains debatable since the ALLHAT and Systolic Hypertension in the Elderly Program (SHEP) demonstrated no significant adverse cardiovascular events from new diuretic-associated diabetes versus other trials contradicting this observation.[29] Nonetheless, clinicians should generally not exceed 25 to 50 mg/day of hydrochlorothiazide or 25 mg/day of chlorthalidone.[2] In addition, regardless of the dose used, careful assessment of the potential for metabolic- or electrolyte-based effects is essential.

Additionally, it is important to recognize that when estimated creatinine clearance approaches or is less than 30 mL/min (0.50 mL/s), thiazide diuretics have limited efficacy, rendering loop diuretics to be preferred. Clinicians are advised to reevaluate the use of thiazide diuretics prescribed to individuals whose renal function has been declining with age and whose risk for the consequences of metabolic effects may be more significant.[30]

Loop diuretics, such as furosemide, bumetanide, torsemide, and ethacrynic acid, have a common site of action in the thick ascending limb of the loop of Henle. As this region reabsorbs over 35% to 45% of filtered sodium, their diuretic efficacy is superior to that of thiazides, potassium-sparing diuretics, and aldosterone antagonists. With the exception of torsemide, which has a longer half-life, the loop diuretics should be administered twice daily (BID) when utilized primarily for their antihypertensive (vs diuretic) effect. Ethacrynic acid, unlike other loop diuretics, does not contain a sulfonamide moiety and as such may carry preference in patients with sulfonamide sensitivity. The most significant adverse effect of loop diuretic use is excessive diuresis leading to hyponatremia or hypotension. Additionally, hypokalemia, hypomagnesemia, and hypocalcemia may develop over time and contribute to the potential for cardiac arrhythmias. Overall, relevance of drug–drug interactions and potential for aggravating select conditions (hyperglycemia, dyslipidemias, and hyperuricemia) should be routinely monitored.[8]

Potassium-sparing diuretics that do not act through mineralocorticoid receptors include triamterene and amiloride. These agents are often prescribed in combination with potassium-wasting diuretics to mitigate potassium loss. When administered alone or as a combination product, these agents result in modest diuresis given their site of action on the distal tubule and collecting ducts has minimal impact on blocking sodium reabsorption. Their most significant risk is the potential for hyperkalemia. This is especially relevant in the context of those patients with moderate to severe renal impairment or those receiving nonsteroidal anti-inflammatory drugs (NSAIDs), potassium supplements, or

Table 6–7

Commonly Used Oral Antihypertensive Drugs by Pharmacologic Class[2,26,27]

Class	Brand	Usual Dose, Range (mg/day)	Frequency	Select Adverse Events	Comments[a]
Diuretics					
Thiazides and thiazide-like	Chlorthalidone (Hygroton)	12.5–25	QDay	Hypokalemia and other electrolyte imbalances Negative effect on glucose and lipids	Thiazide diuretics are generally more effective antihypertensive agents than loop diuretics Ineffective in patients with estimated CrCl < 30 mL/min (0.5 mL/s), except metolazone Not first-line agents in pregnancy, but may be used with close monitoring for hypokalemia Monitor electrolytes (ie, decreased serum potassium) and metabolic abnormalities (ie, dyslipidemia, hyperglycemia) Use caution in patients with gout and severe renal impairment Contraindications include hypersensitivity and anuria
	Hydrochlorothiazide (Esidrix, HydroDiuril, Microzide, Oretic)	12.5–50	QDay		
	Indapamide (Lozol)	1.25–2.5	QDay		
	Metolazone (Zaroxolyn)	2.5–10	QDay		
Loops	Bumetanide (Bumex)	0.5–2	QDay or BID	Hypokalemia and other electrolyte imbalances	Preferred diuretic class in patients with estimated CrCl < 30 mL/min (0.5 mL/s) Monitor electrolytes (ie, decreased potassium) and metabolic abnormalities (ie, dyslipidemia, hyperglycemia) Use with caution in patients with gout Contraindications include hypersensitivity, anuria, acute renal insufficiency
	Furosemide (Lasix)	20–80	BID		
	Torsemide (Demadex)	5–10	QDay		
Potassium-sparing	Amiloride (Midamor)	5–10	QDay or BID	Potassium-sparing diuretics may enhance hyperkalemic effects of drug therapies (eg, ACE inhibitor, aldosterone antagonist)	Reserved for patients with diuretic-induced hypokalemia Monitor electrolytes (ie, potassium) Contraindications include hypersensitivity, acute renal insufficiency, hyperkalemia Avoid in patients with estimated CrCl < 30 mL/min (0.5 mL/s)
	Triamterene (Dyrenium)	50–100	QDay or BID		
Aldosterone antagonists	Eplerenone (Inspra)	50–100	QDay or BID	Hyperkalemia Gynecomastia (spironolactone)	Eplerenone contraindicated as an antihypertensive in patients with estimated CrCl < 50 mL/min (0.83 mL/s) or serum creatinine > 1.8 mg/dL (159 µmol/L) for women or 2 mg/dL (177 µmol/L) in men as well as type 2 diabetes mellitus with microalbuminuria. Also contraindicated in patients concomitantly receiving strong CYP3A4 inhibitors or a serum potassium > 5.0 mEq/L (mmol/L) at initiation
	Spironolactone (Aldactone)	25–100	QDay		
β-Blocker					
Cardioselective	Atenolol (Tenormin)	25–100	QDay or BID	Bradycardia Heart block Heart failure Dyspnea, bronchospasm Fatigue, dizziness, lethargy, depression	Caution with heart rate < 60 and respiratory disease Selectivity of β_1 agents is diminished at higher doses Abrupt discontinuation may cause rebound hypertension May mask signs/symptoms of hypoglycemia in diabetic patients
	Bisoprolol (Zebeta)	2.5–10	QDay		
	Metoprolol tartrate (Lopressor)	100–200	BID		
	Metoprolol succinate (Toprol XL)	50–200	QDay		
Nonselective	Nadolol (Corgard)	40–120	QDay	Hyper-/hypoglycemia, hyperkalemia, hyperlipidemia	Contraindicated in hypersensitivity, sinus node dysfunction or severe sinus bradycardia (in the absence of a pacemaker), heart block (greater than first degree), cardiogenic shock, acute decompensated heart failure
	Nebivolol (Bystolic)	5–20	QDay		
	Propranolol (Inderal)	80–160	BID		
	Propranolol long-acting (Inderal LA, InnoPran XL)	80–160	QDay		
	Timolol (Blocadren)	10–40	QDay		
Mixed α- and β-blocker	Carvedilol (Coreg)	12.5–50	BID		
	Carvedilol CR (Coreg CR)	20–80	QDay		
	Labetalol (Trandate)	200–800	BID		

CCB					
Nondihydropyridines	Diltiazem long-acting (Cardizem SR, Cardizem CD, others)	120–360	QDay	Bradycardia, heart block (nondihydropyridines) Constipation (nondihydropyridines) Peripheral edema, headache, flushing	Caution with heart rate < 60 (verapamil, diltiazem) Use caution in concomitant use with β-blocker; may potentiate heart block Extended-release formulations are preferred for once- or twice-daily medication administration
	Verapamil sustained-release (Calan SR, Isoptin SR, Verelan)	120–360	QDay		
Dihydropyridines	Amlodipine (Norvasc)	2.5–10	QDay	Gingival hyperplasia (dihydropyridines) Reflex tachycardia (dihydropyridines)	Contraindicated in hypersensitivity, sinus node dysfunction, or severe sinus bradycardia (in the absence of a pacemaker) (nondihydropyridines), heart block (greater than first degree) in the absence of a pacemaker (nondihydropyridines), atrial fibrillation/flutter associated with accessory bypass tract (nondihydropyridines), reduced ejection fraction (most CCBs except amlodipine)
	Felodipine (Plendil)	2.5–10	QDay		
	Isradipine SR (DynaCirc SR)	5–10	BID		
	Nicardipine SR (Cardene SR)	60–120	BID		
	Nifedipine long-acting (Adalat CC, Procardia XL)	30–90	QDay		
	Nisoldipine (Sular)	17–34	QDay		
ACE inhibitors	Benazepril (Lotensin)	10–40	QDay or BID	Cough Hyperkalemia Renal insufficiency Angioedema	Monitor electrolytes (ie, serum potassium) Monitor renal function Initial dose may be reduced in renal impairment, the elderly, patients who are volume depleted or maintained on diuretic therapy Use with caution in patients with baseline hyperkalemia Contraindicated in pregnancy and hypersensitivity
	Captopril (Capoten)	25-150	BID or TID		
	Enalapril (Vasotec)	10–40	QDay or BID		
	Fosinopril (Monopril)	10–40	QDay		
	Lisinopril (Prinivil, Zestril)	10–40	QDay		
	Moexipril (Univasc)	7.5–30	QDay or BID		
	Perindopril (Aceon)	4–16	QDay		
	Quinapril (Accupril)	10–80	QDay or BID		
	Ramipril (Altace)	2.5–10	QDay or BID		
	Trandolapril (Mavik)	1–4	QDay		
ARBs	Azilsartan (Edarbi)	40–80	QDay	Hyperkalemia Renal function deterioration Angioedema Hypotension/syncope	Above comments to ACE inhibitors also apply to ARBs
	Candesartan (Atacand)	8–32	QDay or BID		
	Eprosartan (Teveten)	600–800	QDay or BID		
	Irbesartan (Avapro)	150–300	QDay		
	Losartan (Cozaar)	50–100	QDay or BID		
	Olmesartan (Benicar)	20–40	QDay		
	Telmisartan (Micardis)	20–80	QDay		
	Valsartan (Diovan)	80–320	QDay		
Direct renin inhibitors	Aliskiren (Tekturna)	150–300	QDay	Hyperkalemia Hypotension	Use caution in patients with severe renal impairment and in patients with deteriorating renal function or renal artery stenosis, both bi- and unilateral Contraindicated in combination with ACE-Is or ARBs in patients with diabetes
Central α_2-agonists	Methyldopa (Aldomet)	250–500	BID	Transient sedation initially Hepatotoxicity, hemolytic anemia, peripheral edema (methyldopa) Orthostatic hypotension (methyldopa, clonidine) Dry mouth, muscle weakness (clonidine)	First-line agent in pregnancy (methyldopa) Tolerance may occur 2–3 months after initiation of methyldopa; increase dose or add thiazide Contraindications include hypersensitivity, concurrent use of MAO inhibitor (methyldopa), hepatic disease (methyldopa), pheochromocytoma (methyldopa)
	Clonidine oral (Catapres)	0.1–0.8	BID		
	Clonidine patch (Catapres TTS)	0.1–0.3	Once weekly		
	Guanfacine (Intuniv)	0.5–2	QDay		

(Continued)

Table 6–7

Commonly Used Oral Antihypertensive Drugs by Pharmacologic Class[2,26,27] (*Continued*)

Class	Brand	Usual Dose, Range (mg/day)	Frequency	Select Adverse Events	Comments[a]
α_1-Blockers	Doxazosin (Cardura) Prazosin (Minipress) Terazosin (Hytrin)	1–16 2–20 1–20	QDay BID or TID QDay or BID	Syncope, dizziness, palpitations, orthostatic hypotension	Contraindicated in hypersensitivity
Direct vasodilator	Isosorbide dinitrate 20 mg and hydralazine 37.5 (BiDil)	20–120/37.5–225	TID	Edema, hypertrichosis (minoxidil) Tachycardia	Give minoxidil with diuretic and β-blocker to mitigate side effects Contraindicated in hypersensitivity, pheochromocytoma (minoxidil), increased intracranial pressure (isosorbide dinitrate + hydralazine)
	Hydralazine (Apresoline)	100–200	BID	Lupus-like syndrome (hydralazine)	
	Minoxidil (Loniten)	5–100	QDay or BID		
Peripheral sympathetic inhibitors	Reserpine (generic only)	0.05–0.25	QDay	Depression Orthostatic hypotension Nasal congestion, fluid retention, peripheral edema Diarrhea, increased gastric secretion	Contraindications include hypersensitivity, peptic ulcer disease or ulcerative colitis, history of mental depression or electroconvulsive therapy

[a] Comments listed are not intended to be inclusive of all adverse effects, monitoring parameters, cautions, or contraindications and may vary by source.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BID, twice daily; CCB, calcium channel blocker; CrCl, creatinine clearance; CYP, cytochrome P450; MAO, monoamine oxidase; QDay, once daily; TID, three times daily.

Modified from Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community. J Clin Hypertens. 2014;16(1):14–26; and Saseen JJ, Maclaughlin EJ. Hypertension. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York: McGraw-Hill; 2017:57–58.

other agents with potassium-sparing properties, such as ACE-Is or ARBs.[8]

Aldosterone Antagonists

Aldosterone antagonists such as spironolactone and eplerenone modulate vascular tone through a variety of mechanisms besides diuresis (Figure 6–2). Their potassium-sparing effects mediated through aldosterone antagonism counteract the potassium-wasting effects of other diuretics such as thiazide or loop diuretics. Patients with resistant hypertension (with or without primary aldosteronism) experience significant BP reductions with the addition of low-dose spironolactone (12.5–50 mg/day) to diuretics, ACE-Is, and ARBs.[31] Although a positive attribute, it is important to recognize the risk for hyperkalemia in patients with impaired or fluctuating renal function, or those who are receiving ACE-Is, ARBs, direct renin inhibitors, potassium supplements, potassium-containing salt substitutes, or NSAIDs. In addition, spironolactone is associated with gynecomastia, whereas eplerenone rarely causes this complication, presumably because of its greater aldosterone blocking specificity than spironolactone and minimal effects on androgens and progesterone.[8]

β-Blockers

Contemporary guidelines refrain from supporting the use of β-blockers as first-line antihypertensive agents.[2] The basis of this position varies but often cites studies indicating inferior outcomes and a lack of positive outcomes in elderly patients when compared to other antihypertensives.[32] These analyses were conducted with a limited number of β-blockers (usually atenolol), and thus their findings may or may not apply to newer formulations of existing agents (eg, metoprolol succinate) or agents with unique properties such as carvedilol or nebivolol.[32] However, the role of β-blockers in patients with specific select comorbidities is well-established (Table 6–3).[2] Specific studies conducted in patients with comorbidities such as CAD, HF with reduced ejection fraction (HFrEF), or recent MI have clearly demonstrated morbidity and mortality benefits from β-blocker use.[2] Their hemodynamic effects and antiarrhythmic properties make them desirable for hypertensive patients who suffer from ischemic conditions including acute coronary syndromes (ACS). The mechanisms through which β-blockers affect BP are complex but most certainly include their modulation of renin, which appears to result in a reduction in CO and/or reduction in PVR along with their negative inotropic/chronotropic actions (Figure 6–2).

The specific pharmacologic properties of β-blockers are varied and diverse. An understanding of these properties may assist in the selection of one agent over others given a patient's specific condition(s) or comorbidities. One of these properties is cardioselectivity: the property of some β-blockers that preferentially block the β_1-receptor versus β_2-receptor. Some β-blockers exhibit membrane stabilization activity, which relates to the β-blocker's capacity to exhibit certain antiarrhythmic properties. Some β-blockers, as shown in Figure 6–3, possess properties referred to as intrinsic sympathomimetic activity (ISA). β-Blockers possessing this property effectively block the β-receptor at higher circulating catecholamine levels, such as during exercise, while having modest β-blocking activity at times of lower catecholamine levels, such as at rest, but β-blockers with ISA are not recommended for use in the post-ACS patient.[33]

Cardioselectivity represents the most clinically relevant property of β-blockers. With regard to cardioselectivity, it is important to consider patients with asthma and/or chronic obstructive pulmonary disease. A β-blocker with relative cardioselectivity to block β_1-receptors may be more desirable in such a patient, whereas a nonselective β-blocker may be potentially disadvantageous. In such a patient, low doses of cardioselective β-blockers may achieve adequate blockade of β_1-receptors in the heart and kidneys while minimizing the undesirable effects of β_2-receptor blockade on the smooth muscle lining the bronchioles. In doing so, hypertension may be managed while avoiding complications of the coexisting reactive airway disease, which is mediated by β_2-receptor stimulation. Similarly, either because of a reduction in the β_2-mediated vascular blood flow or by enhanced unopposed α-agonist–mediated vasoconstriction, a patient with peripheral vascular disease and intermittent claudication may experience a worsening of symptoms with use of a nonselective β-blocker (Figure 6–3). It is important to remember that cardioselectivity depends on dose, with diminished selectivity exhibited with higher doses.

A limited number of β-blockers also possess vasodilatory properties that are either mediated through α_1-receptor blockade

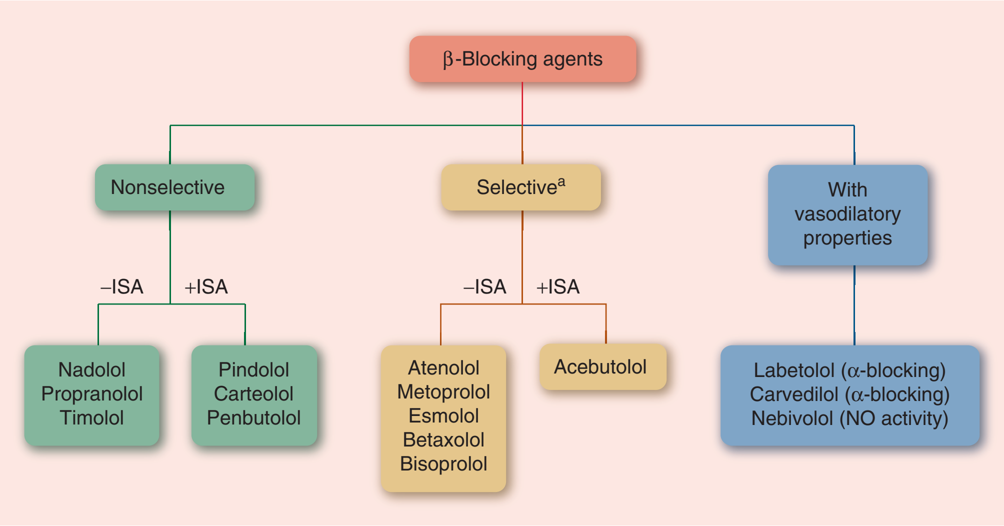


FIGURE 6–3. Flowchart listing various β-blocking agents separated by β-receptor activity and intrinsic sympathomimetic activity. [a]β-1 Cardioselective. (ISA, intrinsic sympathomimetic activity; NO, nitric oxide.)

(carvedilol, labetalol) or via L-arginine/nitric oxide–induced release from endothelial cells, with subsequent increased nitric oxide bioavailability in the endothelium (nebivolol). Although theoretically of benefit, there has been no proven evidence of superior outcomes from use of β-blockers with these vasodilatory properties.

The adverse effects of β-blockers follow their pharmacology. Their potential to precipitate bradycardia, various degrees of heart block, or signs and symptoms of HF may be of concern to those with a subclinical diagnosis of HF, the elderly, or those with reduced left ventricular ejection fraction (LVEF). Conversely, abrupt discontinuation of β-blockers has been cited as a precipitating factor in the development of ischemic syndromes, especially for those patients in whom β-blockers were used for extended periods of time, at higher doses, or who had underlying ischemic heart disease. In such cases, tapering the dose over a period of several days to one or even 2 week(s) is recommended. β-Blocker use in diabetics is usually a complex decision requiring consideration of their consequential effects on insulin, glucose availability, and blocking the signs and symptoms of hypoglycemia against their potential for morbidity/mortality benefits for select candidates with comorbidities such as HFrEF. Lastly, β-blockers, particularly first-generation agents (ie, those other than carvedilol and nebivolol), have a greater effect on glucose metabolism as well as other metabolic effects, and they should be used cautiously, if at all, with diuretics unless compelling indications exist for both.

The Food and Drug Administration (FDA)-approved drug labeling for metoprolol, carvedilol, nebivolol, and propranolol states that when coadministered with drugs that affect cytochrome P450 (CYP) 2D6 metabolic pathways, their efficacy and/or toxicity may be altered. However, specific recommendations vary by agent. For example, recommendations for metoprolol state that dose titration or an alternative agent should be considered for individuals classified as CYP2D6 poor, intermediate, and ultrarapid metabolizers. However, similar recommendations are not explicitly suggested for carvedilol, nebivolol, or propranolol.

Calcium Channel Blockers

Exhibiting considerable interclass diversity, CCBs are recognized as effective antihypertensives, particularly in the elderly.[2,30] The variety of pharmacologic properties among the subclasses of CCBs is significant and categorizes their expected effects on the cardiovascular system and potential risk of toxicities. Dihydropyridine CCBs such as nifedipine and amlodipine are recommended as potential first-line antihypertensive agents but are commonly associated with edema, especially when used at higher doses.[2] As previously reviewed, CCBs were found to be similar to chlorthalidone and lisinopril with regard to CHD events.[20] Nondihydropyridine CCBs such as verapamil and diltiazem are recognized for their electrophysiological effects and negative chronotropic and inotropic effects. These pharmacologic properties may be exploited for their specific clinical utility. Verapamil and diltiazem effectively block cardiac conduction through the atrioventricular node, exhibiting value in the management of patients with atrial fibrillation in addition to hypertension. However, their negative inotropic effects can be detrimental to patients with reduced LVEF and should be avoided. In contrast, the dihydropyridine subclass of agents has no utility for managing patients with atrial dysrhythmias but may be used safely (exception being nifedipine) in patients with reduced ejection fraction. Similarly, all CCBs possess some coronary vasodilating properties and, therefore, may be used in select patients for the management of patients with angina, in addition to their antihypertensive benefits.[8]

ACE Inhibitors

ACE-Is have been extensively studied for the treatment of hypertension, and outcome-based trials generally support their use for a wide array of patients, especially with select comorbidities. These compelling indications include their qualified role in managing patients with hypertension who have a history of type 1 or 2 DM, HF, MI, CKD, or stroke.[2] Comparative trials using either ACE-Is, diuretics, or CCBs as initial drug therapy have demonstrated similar primary outcomes.[20] It is therefore reasonable to conclude that diuretics, CCBs, and ACE-Is represent appropriate choices as first- or second-line antihypertensive therapies that effectively achieve a target BP goal for most patients with or without comorbidities.

Although generally well-tolerated, ACE-Is are associated with two hallmark side effects: hyperkalemia and a persistent dry cough. Modest elevations in serum potassium should be anticipated when starting or increasing the dose of an ACE-I, particularly in patients with compromised renal function and those receiving any concurrent NSAIDs, potassium supplements, or potassium-containing salt substitutes. Hyperkalemia is rarely a reason for discontinuation of therapy. Nonetheless, periodic monitoring of serum potassium is prudent for patients receiving ACE-Is. The dry cough associated with ACE-Is is thought to be caused by accumulation of bradykinin resulting from a direct effect of inhibiting ACE. If a cough jeopardizes compliance with the agent, ARBs should be considered as possible alternative agents because there is less incidence of cough.

Less common adverse effects of ACE-Is include acute kidney injury, particularly in patients with hemodynamically significant bilateral renal artery stenosis (or unilateral if one functioning kidney), preexisting kidney dysfunction, blood dyscrasias, or angioedema, the latter particularly in black African or African Caribbean origin.

In general, effects of ACE-Is on renal function and potassium can be predicted given an understanding of their pharmacologic actions (Figure 6–2). Inhibition of angiotensin II synthesis through ACE inhibition (or direct blockage of the angiotensin II receptor by ARBs) reduces the efferent renal artery tone, thereby changing the intraglomerular pressure. Although changes in the afferent renal artery tone also occur, the overall effects usually produce a reduction in GFR of up to 30%.[2,8] Such reductions in GFR are not usually indications to discontinue use of the ACE-I; however, continued monitoring for further decreases in GFR and consideration of dose reduction remain prudent. Alternatively, should declines in GFR exceed 30%, dose reduction or discontinuation is warranted until further evaluation can be made.

Angiotensin Receptor Blockers

ARBs are inhibitors of the angiotensin-1 (AT1) receptors (Figure 6–2). AT1 receptor stimulation evokes a pressor response via a host of accompanying effects on catecholamines, aldosterone, and thirst.[8] Consequently, inhibition of AT1 receptors directly prevents this pressor response and results in upregulation of the RAAS. Upregulation of the RAAS results in elevated levels of angiotensin II, which have the added effect of stimulating the angiotensin-2 (AT2) receptors. AT2-receptor stimulation is generally associated with antihypertensive activity; however, long-term effects of AT2-receptor stimulation on cellular growth and repair mechanisms are relatively unknown. While the pharmacologic differences between ARBs and ACE-Is are clear, the therapeutic relevance resulting from these differences remains ambiguous. Previously, the clinical benefits of ARBs were considered less robust as compared to ACE-Is, but the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) has demonstrated that in high-risk patients, telmisartan is noninferior to ramipril for the reduction of death from cardiovascular causes, MI, stroke, or hospitalization for HF.[34] This study also demonstrated that an ACE-I in combination with an ARB reduces proteinuria to a greater extent than either agent alone but increases the composite of dialysis, doubling of serum creatinine, and death.[35] Although better tolerated than ACE-Is, ARBs have not been shown to demonstrate superiority of outcomes relative to ACE-Is.

At this point, ARBs have emerged as an effective class of antihypertensives whose low incidence of side effects and demonstrated clinical role in patients with specific comorbidities have afforded them an attractive position in the antihypertensive armamentarium. However, as with ACE-Is, patients may develop angioedema. Although estimates of cross-reactivity are reportedly low,[36] one should always exercise caution when considering the use of an ARB in a patient with a known history of angioedema to an ACE-I. Like ACE-Is, the antihypertensive effectiveness of ARBs is greatly enhanced by combining them with diuretics. Combining an ACE-I with an ARB for treating hypertension should almost always be avoided. Overall, ARBs have proven their value as reasonable first-line agents for uncomplicated patients with hypertension, well-tolerated alternatives to ACE-Is for patients with select comorbidities (CKD, DM, and prior MI [Table 6–3]), and alternatives when ACE-Is are not well-tolerated.

Patient Encounter 2

A 65-year-old man returns to your clinic for a follow-up visit. During his previous visit 1 month ago, his BP measurements were 168/98 and 176/98 mm Hg. His seated BP measurements today are 170/92 and 178/94 mm Hg. His heart rate is 100 beats/min. He was prescribed amlodipine-benazepril 5–20 mg once daily and atorvastatin 10 mg once daily about 6 weeks ago. He states that he has been taking the medications only intermittently and not for the past 2 weeks due to complaints of a dry cough when he took the medications and that resolved when not taking. He has a previous history of heavy alcohol consumption and cigarette smoking (three packs per day), but states that he no longer smokes tobacco or consumes alcohol. The patient confirms smoking marijuana occasionally. He is fit-appearing, is able to tolerate exercise well, and states that he tries to maintain a well-balanced diet. The patient's past medical history is significant for a minor gastrointestinal (GI) bleed within the past month that has since resolved and has no past surgical history. Physical examination is unremarkable. Pertinent laboratory values include serum creatinine of 1.3 mg/dL (115 μmol/L), potassium of 4.1 mEq/L (mmol/L), sodium of 141 mEq/L (mmol/L), fasting glucose of 99 mg/dL (5.5 mmol/L), cholesterol of 157 mg/dL (4.06 mmol/L), HDL of 38 mg/dL (0.98 mmol/L), LDL of 89 mg/dL (2.3 mmol/L), and triglycerides of 148 mg/dL (1.67 mmol/L).

Based on the information provided, what is the best approach for managing hypertension in this patient? Create a care plan that includes (a) goals of therapy, (b) a patient-specific therapeutic plan, and (c) a plan for appropriate monitoring to achieve goals and avoid adverse effects.

Renin Inhibitors

Aliskiren is the only currently available agent in this class of antihypertensive agents. Although similar to ACE-Is and ARBs in that it acts within the RAAS, it is unique in that it directly blocks renin, thereby reducing PRA and subsequently AT1 and AT2 with a resultant reduction in BP. This disruption of the negative feedback loop results in a compensatory increase in prorenin and renin levels, the significance of which is not well-established. Aliskiren has been shown to be well-tolerated and effective in reducing BP when used as monotherapy and in combination with other antihypertensive agents, including thiazide diuretics, ARBs, and CCBs.[3] However, long-term clinical trials evaluating efficacy and safety have not been completed, and thus the effects of aliskiren on morbidity and mortality are unknown as yet. Additionally, the Aliskiren Trial In Type 2 Diabetes Using Cardio-renal End points (ALTITUDE) comparing ACE-I or ARB monotherapy to that in combination with aliskiren was stopped prematurely as the combination therapy did not reduce cardiovascular endpoints.[37] Therefore, combining two or more RAAS blocking agents (ACE-Is, ARBs, or renin inhibitors) for the treatment of hypertension is not recommended.[35,37] Because of aliskiren's role in the RAAS, recommendations and precautions for monitoring serum potassium and kidney function should be similar to those of ACE-Is and ARBs.

α_1-Blockers

Generally, α_1-blockers should not be used as monotherapy. Further, doxazosin is associated with an increase in cardiovascular and cerebrovascular events.[20] However, α_1-blockers may be considered as add-on therapy to other agents (eg, fourth or fifth line) when hypertension is not adequately controlled. In addition, they may have a specific role in the antihypertensive regimen for elderly men with **prostatism**; however, their use is often curtailed by complaints of transient dizziness, palpitations, or syncope following the first dose and **orthostatic hypotension** with chronic use. Due to their ability to cross blood–brain barrier, α_1-blockers can also cause asthenia, vivid dreams, and depression. In addition, **priapism** may occur. When selected, however, combination therapy with a thiazide is recommended to minimize potential edema resulting from the α_1-blocker's tendency to cause sodium and water retention. The roles of doxazosin, terazosin, and prazosin in management of patients with hypertension are limited due to the paucity of outcome data and absence of a unique role for special populations or compelling indications.[2,3]

Central α_2-Agonists

Limited by their tendency to cause **orthostasis**, sedation, dry mouth, and vision disturbances, clonidine, methyldopa, guanfacine, and guanabenz represent rare choices in contemporary treatment of patients with hypertension. However, adding clonidine to other antihypertensive agents may be used for individuals with resistant hypertension, and methyldopa is a viable option for pregnancy. Their central α_2-adrenergic stimulation is thought to reduce sympathetic outflow and enhance parasympathetic activity, thereby reducing heart rate, CO, and total PVR. Occasionally used for cases of resistant hypertension, these agents may have a role when other more conventional therapies appear ineffective. The availability of a transdermal clonidine patch applied once-weekly may offer an alternative to hypertensive patients with adherence problems. Of particular importance is the potential for severe rebound hypertension when clonidine is abruptly discontinued. Rather, clonidine's dose should be gradually reduced when being discontinued. In patients concurrently taking a β-blocker, the β-blocker should be tapered to discontinuation first, ideally several days before initiating the clonidine taper. Because clonidine withdrawal results in an increase in SNS activity, patients withdrawing from clonidine while on a β-blocker could experience unbalanced α-mediated vasoconstriction.[8]

Other Agents

Direct vasodilators such as hydralazine and minoxidil represent alternative agents used for patients with resistant hypertension. They primarily act to relax smooth muscles in arterioles and activate baroreceptors. Because of the reflex tachycardia and fluid retention they cause, their use in the absence of concurrently administered β-blockers and diuretics such as furosemide is uncommon. Other side effects associated with minoxidil include pericardial effusion, nonspecific T-wave change on the ECG, and hypertrichosis (excessive body hair), particularly in women. Rarely, hydralazine-induced lupus-like syndrome can occur in some patients. Although uncommon, females, those receiving doses in excess of 200 mg/day, individuals with slow hepatic acetylation capacity, or having certain immunogenic factors appear to be at greater risk.[38] Because slow acetylation can increase the bioavailability of hydralazine leading to adverse effects, in 2013 the FDA listed N-acetyltransferase-1 (*NAT1*) and *NAT2* genes as biomarkers for the effectiveness and/or toxicity of hydralazine. References describing the appropriate use and monitoring of these infrequently utilized agents should be consulted before use.[8] Finally, reserpine, although slow to act, reduces sympathetic tone and thus PVR by depleting norepinephrine from sympathetic nerve endings. Although included in the SHEP and ALLHAT trials,[20] reserpine's numerous side effects including gastric ulceration, depression, and sexual side effects have limited its utility. Two additional agents, guanethidine and guanadrel, act as postganglionic sympathetic inhibitors inhibiting the release of norepinephrine as well as depleting norepinephrine from these nerve terminals. However, these agents have little role in the management of hypertension because of significant adverse effects.[8]

Antihypertensive Toxicity and Management

Common adverse reactions and monitoring parameters with each class of antihypertensive agents are discussed in the earlier sections. Overdoses occurring from antihypertensive agents are relatively uncommon, but their consequences, especially those involving β-blockers, CCBs, and vasodilators, can be profound.[39] This contrasts with the toxicities observed from diuretics, ACE-Is, ARBs, and direct renin inhibitors, which are generally more limited. Early gastrointestinal decontamination followed by routine supportive care, including intravenous (IV) crystalloid boluses, airway protection, and/or vasopressor administration should be initiated in patients manifesting significant bradycardia, hypotension, and/or seizures. If unresponsive to standard supportive care, glucagon and/or high-dose insulin with glucose (if no response to glucagon) may be used when β-blocker toxicity is suspected or confirmed. The early use of high-dose insulin and IV calcium can be effective for CCB poisonings. While administering calcium, one should monitor the ECG, avoid rapid infusions, and never infuse calcium in the same line as phosphate-containing solutions to prevent precipitation. Patients who ingest sustained-release formulations may experience delayed responses and prolonged toxicity and require 24-hour observation, even if asymptomatic upon presentation.

Patient Encounter 3

A 61-year-old man with history of hypertension, gout, and HFrEF presents to clinic for his annual examination. Upon reviewing his medication history, you see the patient has been taking chlorthalidone 12.5 mg daily, lisinopril 40 mg daily, carvedilol 25 mg twice daily, potassium chloride 20 mEq daily, and allopurinol 200 mg daily. Physical examination is unremarkable and no edema is present, but he continues with class II HF symptoms (dyspnea with normal activity). Laboratory values are remarkable for potassium 3.8 mEq/L (mmol/L), serum creatinine 1.5 mg/dL (133 μmol/L), and serum uric acid 9.4 mg/dL (559 μmol/L). Patient's average seated BP is 132/81 mm Hg with heart rate of 76 beats/min.

Based on the 2017 ACC/AHA guidelines, is this patient achieving his BP goal?

Would you consider changes to current antihypertensive therapy given the patient's BP, laboratory values, and medical history?

How would you assess the effectiveness of your therapeutic recommendations for this patient?

SPECIAL PATIENT POPULATIONS

Compelling Indications and Special Considerations

KEY CONCEPT Specific comorbidities, patient factors, and clinical scenarios may direct therapeutic goals and approach to therapy. These additional factors to consider include:

Comorbidities:

- Stable ischemic heart disease (SIHD)
- HF
- Diabetes
- CKD
- Valvular heart disease
- Atrial fibrillation
- Cerebrovascular disease

Special populations:

- Advanced age
- Pediatrics
- Race and ethnicity

Clinical scenarios:

- Hypertensive crisis
- Isolated systolic hypertension
- Pregnancy

The treatment of hypertension requires the clinician to consider acute and chronic factors that may alter the general approach to setting goals and initiating therapy. Blood pressure treatment thresholds and goals are listed in Table 6–2, and compelling indications for specific drug therapies are summarized in Table 6–3.[2]

In patients with an ACS or stable angina and hypertension, β-blockers and possibly long-acting CCBs are indicated because of their antihypertensive and antianginal effects.[2] Nitrate therapy should also be considered in patients with persistent angina or in the setting of ACS for symptom control. In post-MI patients, especially those with reduced LVEF, β-blockers and ACE-Is or ARBs are indicated due to their proven reduction of cardiovascular morbidity/mortality in this population. Aldosterone antagonists are also indicated for the post-MI patient with reduced LVEF and either diabetes or symptoms of HF.[36] Patients with CAD were included in the SPRINT trial, which showed a reduction in major adverse cardiovascular events, including mortality, with intensive SBP reduction (< 120 mm Hg) versus standard treatment (< 140 mm Hg) as measured via AOBP.[17] It should be noted that serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or acute renal failure were more frequent in the intensive therapy arm and must weigh into decisions regarding application of the SPRINT findings. These data were considered by the 2017 ACC/AHA guidelines committee as part of the evidence and rationale to support a BP target of less than 130/80 mm Hg in this patient population.[2]

Patients with HF represent a heterogeneous cohort with specific recommendations for antihypertensive therapy depending on their classification. Current ACC/AHA guidelines recommend a BP target of less than 130/80 mm Hg for patients with HFrEF and HF with preserved ejection fraction (HFpEF).[2] Similarly, patients at risk for HF (stage A HF) are given a BP target recommendation of less than 130/80 mm Hg.[2] Patients with HFrEF and hypertension should be treated with evidence-based β-blockers (bisoprolol, carvedilol, or metoprolol succinate), ACE-Is or ARBs, and aldosterone antagonists as each has evidence supporting their morbidity/mortality benefits for such patients. In contrast, diuretics are recommended in HF patients with evidence of volume overload for symptom relief. African Americans with symptomatic HFrEF are ideal candidates for combination therapy with isosorbide dinitrate and hydralazine based on morbidity and mortality benefits and potential beneficial effects on lowering BP.[36] The dihydropyridine CCBs, amlodipine or felodipine, may be used in patients with HFrEF for uncontrolled BP; however, they offer no beneficial effect on morbidity and mortality and may increase the risk of edema.[36] For patients with HFpEF, use of non-dihydropiridine CCBs (diltiazem and verapamil) is not discouraged, in contrast to patients with HFrEF with whom they should not be used.[36] Updated HFpEF recommendations highlight the potential role for aldosterone antagonists in decreasing HF hospitalization in this cohort in addition to benefit as an antihypertensive if indicated.[40]

Initial drug therapy recommendations for patients with diabetes and hypertension without CKD (regardless of age) are dependent on if the patient is Black or non-Black.[2] Black patients with diabetes and no CKD should be treated initially with thiazide-type diuretics or CCBs alone or in combination. Alternatively, ACE-Is or ARBs, if ACE-I intolerant, should be considered for these patients when albuminuria (≥ 300 mg/day or ≥ 300 mg/g creatinine [34 mg/mmol creatinine]) is present. Non-Black patients with hypertension, diabetes, and no CKD are candidates for ACE-Is or ARBs as well as thiazide-type diuretics and CCBs for initial therapy.[2] In patients with CKD (stage 3 or higher or stage 1 or 2 with albuminuria (≥ 300 mg/day or ≥ 300 mg/g creatinine [34 mg/mmol creatinine])) and hypertension, ACE-Is, or ARBs if ACE-I intolerant, are recommended to slow progression of renal disease.[2] ACE-Is in combination with a thiazide diuretic are preferred in patients with a history of prior stroke or transient ischemic attack based on a reduced risk of recurrent stroke with the combination.

Hypertension in patients with asymptomatic aortic stenosis can be treated with standard pharmacologic therapy, but initiation of low doses and cautious titration should be observed. In patients with chronic aortic dissection, β-blockers were associated with improved survival, whereas ACE-Is were not.[2]

In patients with atrial fibrillation, ARB therapy is suggested for reduction in recurrence of atrial fibrillation.[2] This is based on comparisons of ARB versus CCB or β-blocker therapy where ARB therapy had clinical superiority with regard to atrial fibrillation recurrence.[2] Of note, no data on the role of ACE-Is in this situation are currently available.

Hypertensive crisis includes both hypertensive emergencies and hypertensive urgencies. A hypertensive emergency occurs when severe elevations in BP are accompanied by acute or life-threatening target organ damage such as ACS, unstable angina with dynamic ST changes, encephalopathy, intracerebral hemorrhage, acute left ventricular failure with pulmonary edema, dissecting aortic aneurysm, rapidly progressive renal failure, accelerated malignant hypertension with papilledema, and eclampsia, among others. BP is generally greater than 180/120 mm Hg, although a hypertensive emergency can occur at lower levels, particularly in individuals without previous hypertension. The goal in most hypertensive emergency cases is to reduce SBP by up to 25% in the first hour; if stable, then lower to 160/100–110 mm Hg over the next 2 to 6 hours; and then carefully lower to normal over the following 24 to 48 hours. For individuals with compelling conditions, including aortic dissection, severe preeclampsia or eclampsia, or pheochromocytoma crisis, a more aggressive BP-lowering approach (reduce SBP to < 140 mm Hg in the first hour and < 120 mm Hg in aortic dissection) should be taken.[2] IV therapy is generally required and may consist of the agents listed in Table 6–8. In the setting of spontaneous intracranial hemorrhage occurring within the previous 6 hours and SBP between 150 and 220 mm Hg, immediate lowering of SBP to less than 140 mm Hg failed to reduce rates of death and severe disability, and there have been suggestions of risks, such as renal adverse events, associated with such a strategy.[2] Alternatively, hypertensive urgency is manifested as a severe elevation in SBP greater than 180 mm Hg and/or DBP greater than 110 mm Hg without evidence of acute or life-threatening target organ damage.[2] In these individuals, BP can usually be managed by restarting or intensifying oral therapy and treating anxiety as needed with close follow-up in the ambulatory setting. Emergency department referral is not typically indicated for these patients.[2]

The target for BP in patients 65 years and older remains uncertain and in part depends on whether the patient is ambulatory, community dwelling, institutionalized, and able to tolerate therapy.[2] A target systolic BP of less than 130 mm Hg is recommended in noninstitutionalized ambulatory community dwelling patients. However, if the patient has a high burden of comorbidity and limited life expectancy, a patient-centered, team-based approach evaluating potential risks and benefits of therapy is warranted.[2] The treatment of patients 65 years of age and older with hypertension should follow the same approach as other populations, with the exception that lower starting doses may be warranted to avoid adverse effects. Special attention should be paid to postural hypotension. This includes careful assessment of orthostatic symptoms measuring BP in the upright seated position and upon standing for 1 and 3 minutes. Additionally, caution should be taken to avoid volume depletion and rapid titration of antihypertensive therapy. It should also be noted that in the Hypertension in the Very Elderly Trial (HYVET), which supports BP lowering in the elderly, patients were excluded if standing

Table 6–8

Parenteral Antihypertensive Agents for Hypertensive Emergency and Special Conditions [2,27]

Drug	Dose Range[a]	Onset	Duration	Adverse Effects[b]	Special Indications
Adrenergic inhibitors					
Esmolol hydrochloride	500–1000 mcg/kg/min IV over 1 minute, then 50 mcg/kg/min by infusion; may repeat bolus after 5 minutes at 50 mcg/kg/min increment; maximum 200 mcg/kg/min	1–2 minutes	10–20 minutes	Nausea, asthma, first-degree heart block, HF	Preferred agent for acute aortic dissection, ACS and perioperative hypertension. Avoid use in combination with other β-blocker therapy, bradycardia or decompensated HF.
Labetalol hydrochloride	0.3–1 mg/kg (maximum 20 mg) slow IV injection or 0.4–1 mg/kg/hour IV infusion up to 3 mg/kg/hour; may repeat every 4–6 hours; maximum total cumulative dose 300 mg	5–10 minutes	3–6 hours	Vomiting, scalp tingling, dizziness, asthma, COPD, nausea, heart block, orthostatic hypotension, HF	Most hypertensive emergencies, including eclampsia and preeclampsia. Avoid use in reactive airway disease, second- or third-degree heart block or bradycardia.
Phentolamine	5 mg IV bolus, may repeat every 10 minutes	1–2 minutes	10–30 minutes	Tachycardia, flushing, headache, nausea, vomiting	Catecholamine excess such as adrenergic crisis secondary to pheochromocytoma or cocaine or amphetamine overdose or clonidine withdrawal.
Angiotensin-converting enzyme inhibitors					
Enalaprilat	1.25 mg IV over 5 minutes, may increase to 5 mg and repeat every 6 hours	15–30 minutes	6–12 hours	Precipitous fall in pressure in high-renin states; variable response	High plasma renin activity; avoid in acute MI, bilateral renal stenosis, and pregnancy.
Dihydropyridine calcium channel blockers					
Clevidipine	Initial 1–2 mg/hour IV, doubling every 90 seconds until BP at target, then increasing by less than doubling every 5–10 minutes; maximum 32 mg/hour	2–4 minutes	5–15 minutes; maximum 72 hours	Atrial fibrillation, fever, insomnia, nausea, headache, vomiting, postprocedural hemorrhage, acute renal failure, respiratory failure	Most hypertensive emergencies. Avoid use if hypersensitivity to soy or egg products, pathological hyperlipidemia, lipoid nephrosis, or acute pancreatitis. Use low-end dose range for elderly.
Nicardipine hydrochloride	Initial 5 mg/hour IV, increasing by 2.5 mg/hour every 5 minutes; maximum 15 mg/hour	5–10 minutes	15–30 minutes, may exceed 4 hours	Tachycardia, headache, flushing, local phlebitis	Preferred agent for most hypertensive emergencies, pregnancy, except acute pulmonary edema. Avoid use in acute aortic dissection. No dose adjustment needed for elderly.
Dopamine$_1$-receptor agonist					
Fenoldopam mesylate	0.1–0.3 mcg/kg/min as IV infusion[c]	< 5 minutes	30 minutes	Tachycardia, headache, nausea, flushing	Preferred agent in acute renal failure. Avoid use in glaucoma, elevated intracranial pressure, and sulfite allergy.
Vasodilators					
Hydralazine hydrochloride	Initial 10 mg as slow IV push; maximum initial dose 20 mg; repeat every 4–6 hours as needed	10–20 minutes 20–30 minutes	1–4 hours IV	Tachycardia, flushing, headache, vomiting, aggravation of angina	Preferred agent in pregnancy. Not first line in most patients due to unpredictability of response and prolonged duration of action.

(Continued)

Table 6–8

Parenteral Antihypertensive Agents for Hypertensive Emergency and Special Conditions [2,27] (*Continued*)

Drug	Dose Range[a]	Onset	Duration	Adverse Effects[b]	Special Indications
Nitroglycerin	Initial 5 mcg/min as IV infusion; increase in increments of 5 mcg/min to achieve BP target; maximum dose 20 mcg/min	2–5 minutes	5–10 minutes	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Preferred agent in ACS, acute pulmonary edema, and perioperative hypertension. Use caution if use of phosphodiesterase type-5 inhibitors (see package inserts for formal recommendations)
Sodium nitroprusside	Initial 0.3–0.5 mcg/kg/min as IV infusion[d]; increase in increments of 0.5 mcg/kg/min to achieve BP target; maximum dose 10 mcg/kg/min	Immediate	1–2 minutes	Nausea, vomiting, muscle twitching, sweating, thiocyanate, and cyanide intoxication	Use low-dose range for elderly.

[a]These doses may vary from those in the *Physicians' Desk Reference.*

[b]Hypotension may occur with all agents.

[c]Requires special delivery system.

[d]Requires special delivery system. For infusion rates over or equal to 4–10 mcg/kg/min or duration more than 30 minutes, coadminister thiosulfate to prevent cyanide toxicity.

ACS, acute coronary syndrome; BP, blood pressure; COPD, chronic obstructive pulmonary disease; HF, heart failure; IV, intravenous; MI, myocardial infarction.

Data from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. J Am Coll Cardiol. 2017; and Saseen JJ, Maclaughlin EJ. Hypertension. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:74.

SBP at baseline was less than 140 mm Hg.[41] Newer data from SPRINT suggest that patients 75 years of age and older benefit in a similar fashion from intensive SBP reduction (< 120 vs < 140 mm Hg as measured by AOBP) as did patients less than 75 years of age with regard to cardiovascular morbidity and mortality risk reduction.[17] While some patients may benefit from pursuing intensive BP-lowering targets, tolerability must not be overlooked, and aspects of patient selection and safety considerations are paramount when considering any BP-lowering strategy in the elderly.

In individuals with isolated systolic hypertension (defined as elevated SBP [≥ 140 mm Hg] and low DBP [< 90 mm Hg]), the optimal level of diastolic pressure is not known, and although treated patients who achieve diastolic pressures less than 60 to 70 mm Hg had poorer outcomes in a landmark trial, their cardiovascular event rate was still lower than those receiving placebo.[30]

While the treatment approach of hypertension in minority populations is similar to other populations, special consideration should be paid to socioeconomic and lifestyle factors that may be important barriers to BP control. In addition, in patients of African origin, diminished BP responses have been seen with ACE-Is and ARBs compared with diuretics or CCBs.[2] A consensus document has also highlighted that long-acting CCBs and RAAS inhibitors with or without a diuretic should be used to improve outcomes in Asian patients.[42]

Hypertension in pregnancy is a major cause of maternal, fetal, and neonatal morbidity and mortality. There are four different categories of hypertension in pregnancy: preexisting chronic hypertension, gestational hypertension, preeclampsia–eclampsia, and preeclampsia superimposed on chronic hypertension. Each category is treated slightly differently. General recommendations for antihypertensive therapy in pregnancy favor methyldopa, nifedipine, and/or labetalol use versus other antihypertensives. Despite recommendations for use, these agents carry statements that “fetal risk cannot be ruled out” based on current FDA labelling recommendations and, as such, discussions regarding therapy should be had with all patients who are, or who may be planning to become, pregnant. Due to the known presence of fetal risk, ACE-Is, ARBs, or aliskiren should not be used in women who are pregnant. Readers are also referred to the American College of Obstetricians and Gynecologists task force on hypertension in pregnancy for detailed therapeutic options for guidelines on the diagnosis and management of gestational hypertension and preeclampsia.[43]

In children and adolescents, three or more BP readings are compared with tables listing the 90th, 95th, and 95th percentile + 12 mm Hg for BPs based on age, height, and gender that classify BP as normal, elevated, and stage 1 and stage 2 hypertension.[44] Prevalence of hypertension in adolescent populations is increasing. This, along with increases in obesity, sedentary lifestyle, or a positive family history, increases the risk of CVD. Clinicians should be aware that secondary causes are common in adolescents with hypertension, and identification and aggressive modification of risk factors with nonpharmacologic and pharmacologic interventions is paramount for risk reduction of target organ damage. The 2017 Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents published by the American Academy of Pediatrics provides specific recommendations to modify and treat risk factors in this population of patients.[44]

OUTCOME EVALUATION

Short-term goals are to achieve reduction in BP safely through the iterative process of using pharmacologic therapy, along with nonpharmacologic therapy and lifestyle changes. Key to achieving target BP goals is a comprehensive monitoring plan, which considers the following:

- In patients in whom healthy lifestyle changes alone are recommended (ie, elevated BP or stage 1 hypertension without clinical ASCVD, CKD, DM, and estimated 10-year CVD risk < 10%), BP should be reassessed every 3 to 6 months.
- In patients starting pharmacologic therapy, BP and HR should be measured at monthly intervals, or more frequently in patients with marked elevations or significant comorbidities (eg, HF, CKD) until BP goal is achieved.
- Monitor renal function and electrolytes within 2 to 4 weeks of initiating or increasing doses of antihypertensive therapy that may affect these parameters (eg, diuretics, aldosterone antagonists, ACE-Is, and ARBs). Earlier monitoring should be considered in those with CKD, baseline electrolyte abnormalities, or HF.

Patient Care Process

Collect Information:

- Perform a medication history including prescription and nonprescription medications, herbal products, and dietary supplements as well as history of allergies to medications or other substances.
- Obtain health data including personal and family medical history, past surgeries/procedures, immunization status, fall risk, health and wellness information, laboratory and physical assessment findings.
- Speak with patient and review records to obtain lifestyle habits (eg, sodium intake, cooking practices, physical activity, use of alcohol/tobacco/recreational drugs), preferences and beliefs, health literacy, cultural factors, health and functional goals, and socioeconomic factors that affect access to medications and other aspects of care.
- Document current BP and heart rate (office, HBP, or 24-hour ABPM or AOBP results if available).

Assess the Information:

- Identify any substances or lifestyle habits that could adversely affect BP control or negatively interact with current medications.
- Based on medical history, physical examination, laboratory results, and review of systems determine whether patient has any target organ damage or comorbidities related to or associated with high BP or if experiencing any signs or symptoms of high BP.
- Calculate patient's 10-year risk of a cardiovascular event to establish BP threshold for initiation of pharmacologic therapy if stage 1 hypertension and no clinical ASCVD, DM, or CKD, and candidacy for other cardioprotective therapies (eg, statin therapy, antiplatelet therapy).
- Establish an appropriate BP goal.
- Determine patient's awareness and knowledge (eg, health literacy) of health effects of high BP and benefits and risks of treatment.
- Identify compelling indications for specific antihypertensives (Table 6–3) or specific considerations (eg, pregnancy).
- Evaluate appropriateness, effectiveness, safety (adverse events, drug interactions), and patient adherence to current pharmacotherapy.
- Review immunization status and need for preventive care and other healthcare services, where appropriate.

Develop a Care Plan:

- Collaborate with patient to identify feasible lifestyle modifications (Table 6–6).
- If patient is not at BP goal, determine whether antihypertensive pharmacotherapy is indicated, and select appropriate therapy based on compelling indications (Tables 6–2 and 6–3), specific patient characteristics (eg, pregnancy), and patient preferences.
- Utilize medications with complementary mechanisms of action and at doses that are optimal for patient (Table 6–7).
- Determine affordability of medications (eg, insurance coverage) and availability on health care formulary, if applicable.
- Engage and empower the patient through education and self-management.

Implement the Care Plan:

- Educate and provide resources about implementing lifestyle modifications and changes in drug therapy including medication administration, storage, adherence, and potential adverse effects and their management.
- Help patient select a self-monitoring device and seek commitment on a mutually agreed upon frequency of measurements.
- Advise patient on how to monitor, document, and report BP measurements as well as when to seek medical advice or care.
- Address any patient concerns about management of hypertension.
- Arrange for preventive care (eg, immunizations) and other healthcare services that were previously identified as warranted.

Follow-up: Monitor and Evaluate:

- Follow at monthly intervals or more frequently in patients with marked elevations or significant comorbidities (eg, HF, CKD), until BP goal is achieved.
- Review medication and lifestyle adherence, BP measurements, adequacy of BP control, and laboratory and other diagnostic tests to assess changes in clinical status and target organ damage.
- Determine whether patient is experiencing any adverse reactions or drug interactions.
- Once BP is controlled, monitor patient every 3 to 6 months to assess BP control, electrolytes and renal function as appropriate, clinical status, and target organ damage.

- Increase the dose of initial drug (replace with an alternative if adverse event or no significant reduction in BP) or add an additional drug to current regimen if BP goal is not reached.
- Once BP target is achieved, monitor patient every 3 to 6 months to assess BP control, electrolytes and renal function as appropriate, clinical status and target organ damage.
- Implement lifestyle changes that address risk factors for CVD such as obesity, physical inactivity, insulin resistance, dyslipidemia, smoking cessation, need for low-dose aspirin, or statin therapy.
- Monitor for efficacy, adverse events, drug interactions, and adherence to therapy as keys to achieving the long-term goals of reducing risk of morbidity and mortality associated with CVD.

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Abbreviations Introduced in This Chapter

ABPM	Ambulatory blood pressure monitoring
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE-I	Angiotensin-converting enzyme inhibitor
ACC	American College of Cardiology
ACR	Albumin-to-creatinine ratio
ACS	Acute coronary syndromes
AHA	American Heart Association
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ALTITUDE	Aliskiren Trial in Type 2 Diabetes Using Cardiorenal End points
AOBP	Ambulatory office-based blood pressure
ARB	Angiotensin receptor blocker
ASCVD	Atherosclerotic cardiovascular disease
AT1	Angiotensin-1
AT2	Angiotensin-2
BID	Twice daily
BP	Blood pressure
CAD	Coronary artery disease
CCB	Calcium channel blocker
CHD	Coronary heart disease
CKD	Chronic kidney disease
CMS	Centers for Medicare & Medicaid Services
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CrCl	Creatinine clearance
CVD	Cardiovascular disease
CYP	Cytochrome P450
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic blood pressure
DM	Diabetes mellitus
ECG	Electrocardiogram
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
GI	Gastrointestinal
HAART	Highly active antiretroviral therapy
HBP/HBPM	Home blood pressure/home blood pressure measurement
HDL	High-density lipoprotein
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HYVET	Hypertension in the Very Elderly Trial
ISA	Intrinsic sympathomimetic activity
IV	Intravenous
LDL	Low-density lipoprotein
LVEF	Left ventricular ejection fraction
MAO	Monoamine oxidase
MI	Myocardial infarction
NAT1	N-acetyltransferase-1
NSAID	Nonsteroidal anti-inflammatory drug
ONTARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
PRA	Plasma renin activity
PRC	Plasma renin concentration
PVR	Peripheral vascular resistance
QDay	Once daily
RAAS	Renin-angiotensin-aldosterone system
SBP	Systolic blood pressure
SHEP	Systolic Hypertension in the Elderly Program
SIHD	Stable ischemic heart disease
SPRINT	Systolic Blood Pressure Intervention Trial
SPS3	Secondary Prevention of Small Subcortical Strokes
SNS	Sympathetic nervous system
TID	Three times daily

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7 Heart Failure

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Classify heart failure (HF) syndrome types into HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF), HF with mid-range ejection fraction (HFmrEF), and HF with recovered ejection fraction (HFrecEF).
2. Differentiate between the common underlying etiologies of HF, including ischemic, nonischemic, and idiopathic causes.
3. Describe the pathophysiology of HF as it relates to neurohormonal activation of the renin-angiotensin-aldosterone system, sympathetic nervous system, and endogenous counterregulatory vasodilatory peptide systems.
4. Identify signs and symptoms of HF and classify a given patient by New York Heart Association Functional Classification and American College of Cardiology/American Heart Association Heart Failure Stage.
5. Discuss and modify the goals of therapy for a patient with acute and/or chronic HF.
6. Create a strategy for the nonpharmacologic management of a patient with HF that includes patient education.
7. Develop an evidence-based pharmacologic treatment and monitoring plan for a patient with chronic HFrEF.
8. Design a pharmacologic treatment and monitoring plan for a patient with acute HF.
9. Formulate a therapeutic management plan for a patient with HFpEF.

INTRODUCTION

Heart failure (HF) is a syndrome defined as the inadequate ability of the heart to pump enough blood to meet the blood flow and metabolic demands of the body.[1] HF is most commonly a result of low **cardiac output** (CO) secondary to impaired cardiac function. High-output HF is characterized by an inordinate increase in the body's metabolic demands that outpaces an increase in CO of a generally normally functioning heart. The term *heart failure* refers to low-output HF for the purposes of this chapter.

HF can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to eject or fill with blood.[1] Apart from the clinical syndrome, it is commonly characterized by assessment of left ventricular (LV) function. Impairment in ventricular contraction (systolic dysfunction) and/or ventricular filling (diastolic dysfunction) can result in a similar decrease in CO. Ejection fraction (EF) is the fraction of the volume present at the end of diastole that is pushed into the aorta during systole. When the primary defect is LV systolic dysfunction, evidenced by a left ventricular ejection fraction (LVEF) of 40% (0.40) or less, and is accompanied by symptoms, it is referred to as HF with reduced ejection fraction (HFrEF). HFrEF can occur with or without a component of diastolic dysfunction, which coexists in up to two-thirds of patients. When the primary defect is LV diastolic dysfunction, evidenced by an LVEF of 50% (0.50) or greater along with other criteria to document impaired ventricular filling, and symptoms are present, it is referred to as HF with preserved ejection fraction (HFpEF). HFpEF occurs in approximately one-third to one-half of patients with HF, with long-standing hypertension being the leading cause. Patients with symptoms of HF and an LVEF between 41% and 49% (0.41 and 0.49) are termed to have HF with mid-range ejection fraction (HFmrEF). HF with recovered ejection fraction (HFrecEF) refers to patients who have an LVEF greater than 40% (0.40) but at one time had an LVEF less than or equal to 40% (0.40). Ventricular dysfunction can also reflect involvement of either the left or right ventricle (or both) and be referred to as left-sided or right-sided HF, respectively. This has implications for symptomatology because predominant right-sided failure manifests as systemic congestion, whereas predominant left-sided failure results in pulmonary symptoms.

In addition to derangement of cardiac function, HF is diagnosed by a history of specific signs and symptoms related to congestion and hypoperfusion. Because HF can occur in the presence or absence of fluid overload, the term *heart failure* is preferred over the former term *congestive heart failure*. The term *acute heart failure* (AHF) is used to signify either an acute decompensation of a patient with a history of chronic HF or to refer to a patient presenting with new-onset HF symptoms. Many disorders, such as those of the heart valves, pericardium, epicardium, endocardium, or great vessels, may lead to HF, but most patients develop symptoms due to impairment in LV function. Terms commonly associated with HF, such as *cardiomyopathy* and *LV dysfunction*, are not equivalent to HF but describe possible structural or functional reasons for the development of HF.

EPIDEMIOLOGY

HF is a major public health concern affecting approximately 6.2 million people in the United States. HF manifests most commonly in adults older than 60 years.[2] The growing prevalence of HF corresponds to advancements in evidence-based medical therapy in patients with risk factors for HF and increasing proportions of older adults. The relative incidence of HF is slightly higher in women compared to men; the prevalence of HF in women is also higher due to the greater incidence rate and longer life expectancy. Hospitalizations for HF have declined slightly in the past decade, to approximately 800,000 admissions annually in the United States.[2] According to national registries, patients presenting with HF are older and have numerous comorbidities such as coronary artery disease (CAD), renal insufficiency, diabetes, and obesity. Total estimated costs for managing both chronic and acute HF in the United States for 2012 was approximately $30.7 billion, of which more than two-thirds were attributable to direct medical costs. Globally, the cost of HF in that same year was estimated to be $108 billion.[3]

Prognosis remains poor, with the 5-year mortality rate for chronic HF greater than 50%.[2] Survival strongly correlates with severity of symptoms and functional capacity. For patients hospitalized for HF, the average hospital length of stay is estimated to be approximately 4 to 6 days, a number that has remained constant over the past decade.[4] In-hospital mortality rate has been estimated at approximately 4%, with ranges from 2% to 20%.[4] Readmissions are also high, with up to 30% to 60% of patients readmitted within 6 months of initial discharge date.[4]

ETIOLOGY

HF is the eventual outcome of numerous cardiac diseases or disorders (Table 7–1).[5] HF can be classified by the primary underlying etiology as ischemic or nonischemic, with the majority related to ischemia in the United States. KEY CONCEPT The most common causes of HF are CAD, hypertension, and *dilated cardiomyopathies*.

Table 7–1

Causes of Heart Failure

Heart failure with reduced ejection fraction (HFrEF)
- Coronary artery disease (eg, myocardial infarction or ischemia)
- Dilated cardiomyopathies (eg, drug-induced, viral infections, postpartum)
- Pressure overload (eg, systemic or pulmonary hypertension, aortic or pulmonic valve stenosis)
- Volume overload (eg, valvular regurgitation, shunts, high-output states)

Heart failure with preserved ejection fraction (HFpEF)
- Increased ventricular stiffness
  - Ventricular hypertrophy (eg, hypertrophic cardiomyopathy, hypertension)
  - Infiltrative myocardial diseases (eg, amyloidosis, sarcoidosis, endomyocardial fibrosis)
  - Myocardial infarction or ischemia
- Mitral or tricuspid valve stenosis
- Pericardial disease (eg, pericarditis, pericardial tamponade)

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PATHOPHYSIOLOGY

A basic grasp of normal cardiac function sets the stage for understanding pathophysiological processes contributing to HF development, progression, and management. CO is defined as the volume of blood ejected per unit of time (L/min) and is a major determinant of tissue perfusion. CO is the product of heart rate (HR) and stroke volume (SV): CO = HR × SV. The following sections describe how each parameter relates to CO.

HR is controlled by the autonomic nervous system, where sympathetic stimulation of β-adrenergic receptors results in an increase in HR and subsequent increase in CO in most instances. SV is the volume of blood ejected with each systole. SV is determined by factors regulating **preload**, **afterload**, and contractility. Preload is a measure of ventricular filling pressure at the end of diastole (also known as LV end-diastolic pressure) and is related to the volume of blood in the left ventricle just prior to systole (also known as LV end-diastolic volume). Preload is determined by venous return, ventricular relaxation, as well as atrial contraction. An increase in venous return to the left ventricle results in the stretch of cardiomyocyte sarcomeres (or contractile units) and a subsequent increase in the number of cross-bridges formed between actin and myosin myofilaments. In a healthy heart, this results in an increase in the force of contraction based on the **Frank-Starling mechanism**.[6] Afterload is the resistance to ventricular ejection and is regulated by ejection impedance, wall tension, and geometry. Thus, elevated aortic and systemic pressures result in an increase in afterload and reduced SV. Contractility, also known as the **inotropic** state of the heart, is an intrinsic property of cardiac muscle incorporating fiber shortening and tension development. Contractility is influenced to a large degree by adrenergic nerve activity and circulating catecholamines such as epinephrine and norepinephrine.

Compensatory Mechanisms

There are fundamental pathophysiological differences between HFrEF and HFpEF. This section will focus more on HFrEF, with specifics of HFpEF pathophysiology discussed later in this chapter. In the setting of a loss of myocardium (such as after an acute myocardial infarction [MI]), a number of adaptive and maladaptive mechanisms are activated in response to the reduced CO and increased hemodynamic burden. They include the Frank-Starling mechanism, tachycardia and increased afterload, and ventricular hypertrophy and cardiac remodeling (Table 7–2).[5,6]

▶ *Preload and the Frank-Starling Mechanism*

In the setting of a sudden decrease in CO, the body's natural response is to increase blood volume and prioritize perfusion of vital organs such as the heart and brain. Decreased renal perfusion activates the renin-angiotensin-aldosterone system (RAAS), triggering the production of angiotensin II and downstream synthesis and release of aldosterone. Aldosterone stimulates sodium and water retention, increasing intravascular volume and hence preload. In the absence of LV systolic dysfunction, increases in preload result in proportional increases in CO. However, in a failing heart, alterations in the contractile filaments reduce the ability of cardiomyocytes to adapt to increases in preload. Thus, an increase in preload can further impair contractile function and a further decline in CO. See Figure 7–1.

Table 7–2

Beneficial and Detrimental Effects of the Compensatory Responses in Heart Failure[5,6]

Compensatory Response	Beneficial Effects of Compensation	Detrimental Effects of Compensation
Increased preload (through sodium and water retention)	Optimizes stroke volume via Frank-Starling mechanism	Pulmonary and systemic congestion and edema formation Increased MVO_2
Vasoconstriction	Maintains BP and perfusion in the face of reduced cardiac output	Increased MVO_2 Increased afterload decreases stroke volume and further activates the compensatory responses
Tachycardia and increased contractility (due to SNS activation)	Increases cardiac output	Increased MVO_2 Shortened diastolic filling time β_1-Receptor downregulation, decreased receptor sensitivity Precipitation of ventricular arrhythmias Increased risk of myocardial cell death
Ventricular hypertrophy and remodeling	Maintains cardiac output Reduces myocardial wall stress Decreases MVO_2	Diastolic dysfunction Systolic dysfunction Increased risk of myocardial cell death Increased risk of myocardial ischemia Increased arrhythmia risk

BP, blood pressure; MVO_2, myocardial oxygen consumption; SNS, sympathetic nervous system.

▶ *Tachycardia and Increased Afterload*

An increase in HR is another mechanism to increase CO, especially when contractility is reduced. This is achieved through sympathetic nervous system (SNS) activation and the agonist effect of norepinephrine on cardiac β-adrenergic receptors. SV is relatively fixed in HF; thus, HR becomes a major determinant of CO. Although this mechanism increases CO acutely, the chronotropic and inotropic responses to sympathetic activation increase myocardial oxygen demand, worsen underlying ischemia, contribute to proarrhythmia, and further impair both systolic and diastolic function.

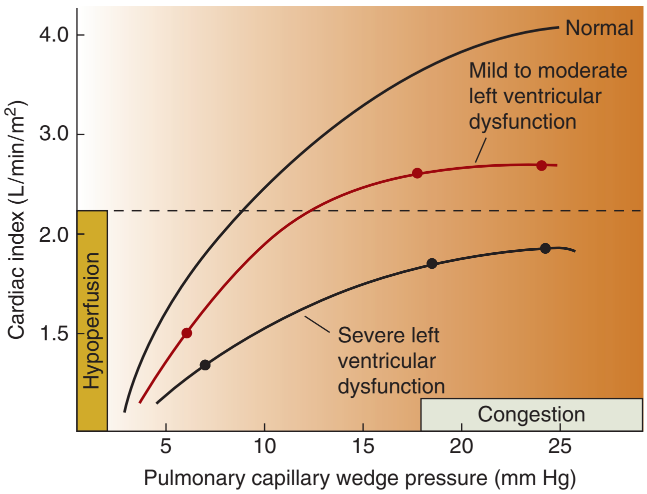

FIGURE 7–1. Relationship between cardiac output (shown as cardiac index) and preload (shown as pulmonary capillary wedge pressure). Cardiac index is expressed in conventional units of $L/min/m^2$ and can be converted to SI units of $L/s/m^2$ by multiplying by 0.0167. (Reproduced with permission from Parker RB, Nappi JM, Cavallari LH. Chronic heart failure. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:83.)

Activation of both the RAAS and SNS also contributes to vasoconstriction in an attempt to redistribute blood flow from peripheral organs to coronary and cerebral circulation.[6] However, arterial vasoconstriction and the resulting increase in afterload may further impair SV. Therefore, arterial vasoconstriction is maladaptive in the failing heart, contributing to a further decrease in CO, continued stimulation of compensatory responses, and a vicious cycle of neurohormonal activation.

▶ *Cardiac Remodeling and Ventricular Hypertrophy*

Cardiac remodeling is a compensatory adaptation to a change in wall stress and is largely regulated by neurohormonal activation, with angiotensin II and aldosterone being key stimuli.[6] The process entails changes in myocardial and extracellular matrix composition and function that result in both structural and functional alterations to the heart. In HF, the changes in cardiac size, shape, and composition are detrimental to heart function. In addition to myocyte size and extracellular matrix changes, heart geometry shifts from an elliptical to a less efficient spherical shape. These changes can occur acutely or manifest over time. After remodeling, the heart can maintain CO for many years. However, function generally continues to deteriorate until progression to clinical HF.

Ventricular hypertrophy, an adaptive increase in ventricular muscle mass due to the growth of existing myocytes, occurs in response to an increased hemodynamic burden such as volume or pressure overload.[5] Hypertrophy can be concentric or eccentric. Concentric hypertrophy occurs in response to pressure overload such as in long-standing hypertension or pulmonary hypertension, whereas eccentric hypertrophy occurs after an acute MI. Eccentric hypertrophy involves an increase in myocyte size in a segmental fashion, as opposed to the global hypertrophy occurring in concentric hypertrophy. Hypertrophy is commonly a component of cardiac remodeling. Although hypertrophy may reduce cardiac wall stress in the short term, continued hypertrophy accelerates myocyte cell death through an overall increase in myocardial oxygen demand. Maladaptive ventricular hypertrophy is also a major contributor to diastolic dysfunction.

Neurohormonal Model of Heart Failure

KEY CONCEPT Development and progression of HF is also intimately linked to neurohormonal pathways activated as a compensatory response to a decline in CO. Activated pathways include those with pathological consequences such as the RAAS, SNS, endothelin, and vasopressin, as well as counterregulatory pathways such as the natriuretic peptides and nitric oxide. This model is the basis for many of the current guideline-directed medical therapies (GDMT) for HFrEF.

▶ *Angiotensin II*

Angiotensin II is a key neurohormone in the pathophysiology of HF. Angiotensin II contributes to an increase in systemic vascular resistance (SVR) and blood pressure (BP) through vasoconstriction. The resulting increase in afterload increases myocardial oxygen demand and opposes the desired increase in SV. In the kidneys, angiotensin II acutely raises intraglomerular pressure through constriction of the efferent arterioles.[6] However, the increase in glomerular filtration pressure may be offset by a reduction in renal perfusion secondary to angiotensin II's influence over the release of other vasoactive neurohormones such as vasopressin and endothelin-1 (ET-1). Angiotensin II also potentiates the release of aldosterone from the adrenal glands and norepinephrine from adrenergic nerve terminals. Additionally, angiotensin II induces vascular hypertrophy and remodeling in both cardiac and renal cells.

▶ *Aldosterone*

Aldosterone's contribution to HF pathophysiology is multifaceted. Renally, aldosterone stimulates sodium and water retention to increase intravascular volume and preload. This mechanism is maladaptive as it exacerbates the already elevated ventricular filling pressures. Aldosterone also contributes to electrolyte abnormalities, especially hypokalemia and hypomagnesemia, which increase the risk for arrhythmias. Aldosterone is an etiological factor in cardiac remodeling through promotion of myocardial fibrosis by causing increased extracellular matrix collagen deposition and inflammation.[6] Aldosterone also potentiates SNS activation. The combination of these effects increases the risk of sudden cardiac death in HF. Elevated aldosterone concentrations are associated with a poorer prognosis in HF.

▶ *Norepinephrine*

Norepinephrine is a classic marker for SNS activation. It plays an adaptive role in the failing heart by increasing HR and myocardial contractility to augment CO and mediating vasoconstriction to maintain organ perfusion. However, excess levels are directly cardiotoxic. Sympathetic activation also increases the risk for arrhythmias and ischemia and accelerates myocyte cell death through increased myocardial workload and apoptosis. Ventricular hypertrophy and remodeling are also influenced by norepinephrine.[6]

Plasma norepinephrine concentrations are elevated proportionally to HF severity, with highest levels correlating to the poorest prognosis. HF is also characterized by diminished responsiveness to catecholamines.[6] Adrenergic receptor desensitization and downregulation (decreased receptor number and post-receptor responses and signaling) occur under sustained sympathetic stimulation. The desensitization is another driver for heightened norepinephrine release.

▶ *Endothelin*

Endothelin-1 is one of the most potent physiological vasoconstrictors.[6] ET-1 binds to two G-protein–coupled receptors, endothelin-A (ET-A) and endothelin-B (ET-B). ET-A receptors mediate vasoconstriction and are prevalent in vascular smooth muscle and cardiac cells. ET-B receptors are expressed on the endothelium and in vascular smooth muscle, and receptor stimulation mediates vasodilation and endothelin clearance. Levels of ET-1 correlate with HF functional class and mortality. However, endothelin receptor antagonists have failed to improve long-term outcomes of patients with HFrEF.

▶ *Arginine Vasopressin*

Vasopressin exerts its effects through vasopressin type 1a (V_{1a}) and vasopressin type 2 (V_2) receptors.[5,6] V_{1a} stimulation leads to vasoconstriction and trophic effects on the heart, whereas actions on the V_2 receptor cause free water retention through aquaporin channels in the renal collecting duct. Vasopressin increases preload, afterload, and myocardial oxygen demand in the failing heart. Higher vasopressin concentrations are linked to dilutional hyponatremia and a poorer prognosis in HF. Vasopressin receptor antagonists have not been shown to improve HFrEF prognosis when added to established therapies.

▶ *Counterregulatory Hormones (Natriuretic Peptides, Bradykinin, and Nitric Oxide)*

Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are endogenous neurohormones, synthesized mainly from the atria and ventricles, respectively, that regulate sodium and water balance. Natriuretic peptides decrease sodium reabsorption in the collecting duct of the kidney and cause vasodilation through the cyclic guanosine monophosphate (cGMP) pathway.[6] They are degraded by an enzyme called neprilysin, which has become an important therapeutic target in the management of HFrEF. Release of ANP and BNP is stimulated by increased cardiac chamber wall stretch usually indicative of volume load. Higher concentrations of natriuretic peptides correlate with a more severe HF functional class and prognosis. Plasma concentrations of BNP are used as a diagnostic biomarker in HF.[6]

Bradykinin is part of the kallikrein-kinin system, which shares a link to the RAAS through angiotensin-converting enzyme (ACE). Bradykinin is a vasodilatory peptide that is released in response to a variety of stimuli, including neurohormonal and inflammatory mediators known to be activated in HF.[6] As a consequence, bradykinin levels are elevated in HF patients and thought to partially antagonize the vasoconstrictive peptides.

Nitric oxide, a vasodilatory hormone released by the endothelium, is found in higher concentrations in patients with HF and provides two main benefits: vasodilation and neurohormonal antagonism of endothelin.[6] Nitric oxide's production is affected by the enzyme inducible nitric oxide synthase (iNOS), which is upregulated in the setting of HF likely in response to activation of angiotensin II, norepinephrine, and multiple cytokines. In HF, the physiological response to nitric oxide appears to be blunted, which contributes to the imbalance between vasoconstriction and vasodilation. Other vasodilatory peptides (eg, adrenomedullin, substance P) also have a putative role in the pathophysiology of HF and remain in investigation as potential targets for pharmacologic therapy development.

▶ *Proinflammatory Cytokines*

Inflammatory cytokines have been implicated in the pathophysiology of HF.[6] Several proinflammatory cytokines (eg, tumor necrosis factor [TNF]-α, interleukin [IL]-1, IL-6, and interferon-γ) and anti-inflammatory cytokines (eg, IL-10) are overexpressed in the failing heart. The most is known about

TNF-α, a pleiotropic cytokine that acts as a negative inotrope, stimulates cardiac cell apoptosis, uncouples β-adrenergic receptors from adenylyl cyclase, and is related to cardiac cachexia. The exact role of cytokines and inflammation in HF pathophysiology continues to be studied.

▸ *Other Prognostic Biomarkers*

Aside from natriuretic peptides having both diagnostic and prognostic implications, other novel biomarkers are linked to HF prognosis.[7] Soluble suppression of tumorigenicity-2 (sST2) is a biomarker for myocardial fibrosis and has prognostic value for both chronic and acute HF. Galectin-3 (Gal-3) is a member of the lectin family found to play a role in ventricular remodeling and fibrosis through stimulation of the transforming growth factor-β (TGF-β) signaling pathway. Myocardial Gal-3 levels are upregulated in patients with HF; however, the association between plasma and myocardial Gal-3 levels remains under investigation. Neutrophil gelatinase-associated lipocalin (NGAL) is a protein that is highly expressed in the kidneys and is being studied as a marker of acute kidney injury and prognosis in HF. Other prognostic biomarkers include high-sensitivity troponin (hsTn) and midregional proadrenomedullin (MR-proADM).[7] The guidelines suggest measurement of these biomarkers in chronic HF may provide value for added risk stratification.

Precipitating and Exacerbating Factors in Heart Failure

HF patients exist in one of two clinical states. When a patient's volume status and symptoms are stable, their HF condition is said to be "compensated." In situations of volume overload or other worsening symptoms, the patient is considered "decompensated." Acute decompensation can be precipitated by numerous etiologies (Table 7–3).[5]

KEY CONCEPT The clinician must identify potential reversible causes of HF exacerbations including prescription and nonprescription drug therapies, dietary indiscretions, and medication nonadherence. Nonadherence with dietary restrictions or chronic HF medications deserves special attention because it is the most common cause of acute decompensation and can be prevented. As such, an accurate history regarding diet, food choices, and the patient's knowledge regarding sodium and fluid intake (including alcohol) is valuable in assessing dietary indiscretion. Nonadherence with medical recommendations such as laboratory and other appointment follow-up can also be indicative of nonadherence with diet or medications.

Table 7–3

Exacerbating or Precipitating Factors in Heart Failure[5]

Cardiac	Metabolic	Patient-Related
Acute ischemia	Anemia	Dietary/fluid nonadherence
Arrhythmia	Hyperthyroidism/thyrotoxicosis	HF therapy nonadherence
Endocarditis	Infection	Use of cardiotoxins (cocaine, chronic alcohol, amphetamines, sympathomimetics)
Myocarditis	Pregnancy	Offending medications (NSAIDs, COX-2 inhibitors, steroids, lithium, β-blockers, calcium channel blockers, antiarrhythmics, alcohol, thiazolidinediones)
Pulmonary embolus	Worsening renal function	
Uncontrolled hypertension		
Valvular disorders		

COX-2, cyclooxygenase-2; HF, heart failure; NSAID, nonsteroidal anti-inflammatory drug.

CLINICAL PRESENTATION AND DIAGNOSIS OF HEART FAILURE

In low-output HF, symptoms are generally related to either congestion behind the failing ventricle(s) or hypoperfusion (decreased tissue blood supply), or both. Congestion is the most common finding in HF. Elevated filling pressure in the left ventricle (left-sided HF) causes fluid to back up in the lungs causing pulmonary symptoms, whereas elevated right ventricular filling pressure (right-sided HF) leads to systemic symptoms of congestion. Symptoms of left-sided HF include dyspnea, orthopnea, and paroxysmal nocturnal dyspnea (PND), whereas symptoms of right-sided HF include peripheral edema, gastrointestinal (GI) bloating, and fatigue. Although most patients initially have left ventricular failure (LVF), both ventricles will eventually be involved leading to pulmonary and systemic symptoms. Because of the complex nature of this syndrome, it has become more difficult to attribute a specific sign or symptom as caused by either right ventricular failure (RVF) or LVF. Symptoms related to hypoperfusion of peripheral tissues include decreased urine output, mental confusion, and cold extremities.

General Signs and Symptoms

Refer to the Clinical Presentation and Diagnosis of Chronic Heart Failure textbox for descriptions of signs and symptoms. Patients can experience a variety of symptoms related to buildup of fluid. The most recognized finding of systemic venous congestion is peripheral edema. It usually occurs in dependent areas of the body, such as the ankles (pedal edema) for ambulatory patients or sacral region for bedridden patients. Lower extremity edema should be quantified by how far it extends, that is, feet, ankles, calves, or thighs. Pitting edema is graded on a scale from 0 (no edema) to 4+ (severe edema) and is based on the depth and duration of the indentation that occurs upon releasing digital pressure over the site. Abdominal congestion may cause bloating, pain, early satiety, nausea, anorexia, and constipation. Intestinal edema may delay absorption of oral medications, including diuretics used to treat congestion. Often patients may have difficulty fitting into their shoes or pants due to edema. Weight gain often precedes signs of overt peripheral edema. Therefore, it is crucial for patients to weigh themselves daily even in the absence of symptoms to assess fluid status.

A clinically validated measure of venous congestion is assessment of the jugular venous pressure (JVP). This is performed by examining the right internal jugular vein for distention or elevation of the pulsation while reclining at a 45-degree angle (angle may be adjusted if the pulsation is not visible). A JVP more than 4 cm above the sternal angle is indicative of elevated right atrial pressure. JVP may be normal at rest, but if application of pressure to the abdomen can elicit a sustained elevation of JVP, this is defined as hepatojugular reflux (HJR). A positive finding of HJR indicates splanchnic congestion and results from displacement of volume from the abdomen into the jugular vein because the right atrium is unable to accept this additional blood. Hepatic congestion can cause abnormalities in liver function, which can be evident in liver function tests and/or clotting times. Development of hepatomegaly occurs infrequently and is caused by long-term systemic venous congestion.

Clinical Presentation and Diagnosis of Heart Failure

General

Patient presentation may range from asymptomatic to cardiogenic shock.

Symptoms

- Dyspnea, particularly on exertion
- Orthopnea
- Shortness of breath (SOB)
- Paroxysmal nocturnal dyspnea
- Exercise intolerance
- Tachypnea
- Cough
- Fatigue
- Nocturia and/or polyuria
- Hemoptysis
- Abdominal pain
- Anorexia
- Nausea
- Bloating
- Ascites
- Mental status changes (confusion, hallucinations)
- Weakness
- Lethargy
- Insomnia

Signs

- Pulmonary rales or crackles
- Pulmonary edema
- S_3 gallop
- Pleural effusion
- Cheyne-Stokes respiration
- Tachycardia
- Cardiomegaly
- Peripheral edema (eg, pedal edema, which is swelling of feet and ankles)
- Jugular venous distension (JVD)
- Hepatojugular reflux (HJR)
- Hepatomegaly
- Cyanosis of the digits
- Pallor or cool extremities

Laboratory Tests

- BNP greater than 100 pg/mL (ng/L; 28.9 pmol/L) or N-terminal proBNP (NT-proBNP) greater than 300 pg/mL (ng/L; 35.4 pmol/L) in acute HF setting; BNP greater than 35 pg/mL (ng/L; 10.1 pmol/L) or NT-proBNP greater than 125 pg/mL (ng/L; 14.7 pmol/L) in nonacute HF setting
- Electrocardiogram (ECG): May be normal or could show numerous abnormalities including acute ST-T–wave changes from myocardial ischemia, atrial fibrillation, bradycardia, and LV hypertrophy.
- Serum creatinine: May be increased owing to hypoperfusion; preexisting renal dysfunction can contribute to volume overload.
- Complete blood count: Useful to determine if HF is due to reduced oxygen-carrying capacity. Anemia is common in patients with HF.
- Chest x-ray: Useful for detection of cardiac enlargement, pulmonary edema, and pleural effusions.
- Echocardiogram: Used to assess LV size, valve function, pericardial effusion, wall motion abnormalities, and ejection fraction.

In chronic severe HF, unintentional weight loss can be an indicator of cardiac cachexia, defined as a nonedematous weight loss more than 6% of the previous normal weight over a period of at least 6 months. HF prognosis worsens considerably once cardiac cachexia has been diagnosed. This results from several factors including loss of appetite, malabsorption due to GI edema, elevated metabolic rate, and elevated levels of norepinephrine and proinflammatory cytokines. Absorption of fats is especially affected, leading to deficiencies of fat-soluble vitamins.

Dyspnea, or shortness of breath (SOB), can result from pulmonary congestion or systemic hypoperfusion due to LVF. Exertional dyspnea occurs when patients experience breathlessness induced by physical activity or a lower level of activity than previously. Patients often state that activities such as stair climbing, carrying groceries, or walking a particular distance cause SOB. In severe HF, dyspnea is present even at rest.

Orthopnea is dyspnea that is positional. Orthopnea is present if a patient is unable to breathe comfortably while lying flat (ie, in recumbent position). It manifests within minutes of a patient lying down and is relieved immediately when the patient sits upright. Patients can relieve orthopnea by elevating their head and shoulders with pillows. The practitioner should inquire as to the number of pillows needed to prevent dyspnea as a marker of worsening HF. PND occurs when patients awaken suddenly with a feeling of breathlessness and suffocation. PND is caused by increased venous return and mobilization of interstitial fluid from the extremities leading to alveolar edema, and usually occurs within 1 to 4 hours of sleep. In contrast to orthopnea, PND is not relieved immediately by sitting upright and often takes up to 30 minutes for symptoms to subside.

Pulmonary congestion may also cause a nonproductive cough that occurs at night or with exertion. Not all patients with LVF will exhibit signs of pulmonary congestion if lymphatic clearance is intact. In cases of pulmonary edema, the most severe form of pulmonary congestion, patients may produce pink frothy sputum and experience extreme breathlessness and anxiety due to feelings of suffocation and drowning. Severe pulmonary edema can progress to respiratory failure, necessitating mechanical ventilation.

Patient History

A thorough history is crucial to identify cardiac and noncardiac disorders or behaviors that may lead to or accelerate the development of HF. Past medical history, family history, and social history are important for identifying comorbid illnesses that are risk factors for development of HF or underlying etiological factors. A complete medication history (including prescription and nonprescription drugs, herbal therapy, and vitamin supplements) should be obtained each time a patient is seen to evaluate adherence, assess appropriateness of therapy, eliminate drugs that may be harmful in HF (Table 7–4), and determine additional monitoring requirements.[5] For newly diagnosed HF, previous exposure to radiation or chemotherapeutic agents as well as current or past use of alcohol and illicit drugs should be assessed. For patients with a known history of HF, questions related to symptomatology and exercise tolerance are essential for assessing any clinical status changes that may warrant further evaluation or adjustment of medications.

Heart Failure Classification

There are two common systems for categorizing patients with HF. The New York Heart Association (NYHA) Functional Classification (FC) system is based on the patient's activity and exercise tolerance. Patients in functional class I exhibit no symptoms or limitations of daily activities, while patients in functional class IV are symptomatic at rest (Table 7–5). The NYHA FC system reflects a subjective assessment by a healthcare provider and can

Table 7–4

Drugs That May Precipitate or Exacerbate Heart Failure

Negative Inotropic Effect
- Antiarrhythmics (eg, disopyramide, dronedarone, flecainide, propafenone, sotalol)
- β-Blockers (eg, propranolol, metoprolol, carvedilol)
- Calcium channel blockers (eg, verapamil, diltiazem)
- Itraconazole

Cardiotoxic
- Doxorubicin, daunorubicin, epirubicin, idarubicin
- Daunomycin
- Cyclophosphamide
- Pertuzumab
- Trastuzumab
- Bevacizumab
- Mitoxantrone
- Ifosfamide
- Mitomycin
- Lapatinib
- Sunitinib
- Sorafenib
- Imatinib
- Carbamazepine
- Ethanol
- Amphetamines (eg, cocaine, methamphetamine)

Sodium and Water Retention
- NSAIDs
- COX-2 inhibitors
- Rosiglitazone and pioglitazone
- Glucocorticoids
- Androgens and estrogens
- Salicylates (high dose)
- Sodium-containing drugs (eg, carbenicillin disodium, ticarcillin disodium)

Uncertain Mechanism
- TNF-α (adalimumab, infliximab, etanercept)
- Dipeptidyl peptidase-4 (DPP-4) inhibitors (eg, saxagliptin)

COX-2, cyclooxygenase-2; NSAID, nonsteroidal anti-inflammatory drug; TNF, tumor necrosis factor.

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Patient Encounter Part 1

A 65-year-old man with a history of hypertension, dyslipidemia, and coronary artery disease presents for follow-up. The patient noticed increasing shortness of breath when doing daily chores and quite a bit of swelling in his legs by midday. He complains of waking up at night intermittently because of difficulty breathing that takes a while to improve after sitting up. He has also needed to sleep on several pillows to get adequate rest. He used to be able to walk a few blocks and three flights of stairs comfortably before getting breathless, but now has to rest going up one flight of stairs. Additionally, his belly feels swollen and tight. He has been eating more take-out fast food lately because he always feels tired.

What information is suggestive of a diagnosis of HF?

What are potential etiologies or contributing factors for HF in this patient?

What additional information should be gathered during the interview of this patient that may relate to the development of HF symptoms?

Table 7–5

New York Heart Association (NYHA) Functional Classification and American College of Cardiology/American Heart Association (ACC/AHA) Staging

NYHA Functional Class	ACC/AHA Stage	Description
N/A	A	Patients at high risk for heart failure but without structural heart disease or symptoms of heart failure.
I	B, C	Patients with structural heart disease but without limitations of physical activity or symptoms of heart failure. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	C	Patients with structural heart disease that results in slight limitations of physical activity or symptoms of heart failure. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	C	Patients with structural heart disease that results in marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.
IV	C, D	Patients with structural heart disease that results in an inability to carry on physical activity without discomfort. Symptoms of heart failure are present at rest. Stage D refers to end-stage heart failure patients.

change frequently (improve or worsen) over short periods of time. In general, anticipated survival declines in conjunction with a decline in functional ability.

The American College of Cardiology/American Heart Association (ACC/AHA) developed a staging system based on the development and progression of the HF syndrome. Patients are placed into stages A through D (Table 7–5).[1] The staging system proposes management strategies for each stage including risk factor modification to guide best practices for preventing further progression. The staging system complements the NYHA FC system; however, patients can move between NYHA functional classes as symptoms improve with treatment, whereas HF staging does not reverse (eg, stage C patients will never revert to stage B, even after treatment). Functional classification and staging allow for longitudinal assessment of a patient's risk and prognosis, disease progression, and requirements for and response to nonpharmacologic and pharmacologic therapies.

TREATMENT OF CHRONIC HEART FAILURE

Desired Therapeutic Outcomes

There is no cure for HF. **KEY CONCEPT** The general therapeutic management goals for chronic HF include preventing the onset of clinical symptoms or reducing symptoms, preventing or reducing hospitalizations, slowing progression of the disease, improving quality of life, and prolonging survival. The ACC/AHA staging system provides a guide for application of these goals based on clinical progression for a given patient. Goals are additive as one moves from stage A to stage D.[1] For stage A, risk factor management is the primary goal to reduce onset of structural heart disease. Stage B emphasizes pharmacologic therapies to reduce further myocardial damage and slow progression to the onset of clinical symptoms. Stage C involves additional therapies that control symptoms and decrease morbidity and mortality. Finally, in stage D, the focus shifts toward palliative care and other quality-of-life–related issues. Only with aggressive management throughout all the stages can the odds of survival be improved. Attainment of these goals is based on designing a therapeutic plan that encompasses strategies to treat contributing disorders (ie, comorbidities), nonpharmacologic interventions, and optimization of GDMT.[8]

Control and Treatment of Contributing Disorders

All patients presenting with HF must be assessed to determine the etiology of cardiac dysfunction. The most common etiology of HF in the United States is ischemic heart disease. An ischemic workup that includes echocardiography, stress testing with imaging, and/or coronary angiography is warranted in all patients presenting with reduced LVEF regardless of the presence of traditional CAD risk factors or CAD history. Revascularization of patients with obstructive CAD and reversible ischemic defects may help restore some cardiac function and improve survival. Aggressive control of hypertension (goal BP of < 130/80 mm Hg), diabetes, obesity, and sleep-disordered breathing (eg, obstructive sleep apnea) is also essential because each of these conditions can contribute to further cardiac damage. Surgical repair of valvular disease or congenital malformations may be warranted if detected. Clinical HF partly depends on metabolic processes, so correction of imbalances such as thyroid disease, anemia, and nutritional deficiencies is important. Identifying and discontinuing medications that can exacerbate HF is also mandated.

Nonpharmacologic Interventions

It is imperative that patients recognize the role of self-management in HF. **KEY CONCEPT** Nonpharmacologic treatment involves dietary modifications such as sodium and fluid restriction, as well as risk factor reduction, including smoking cessation, timely immunizations, and supervised regular physical activity. These interventions help slow disease progression and prevent AHF exacerbations.

Patients should be educated and encouraged to become involved in their own care, including self-monitoring. Fluid status should be monitored daily by assessing weight, peripheral edema, and exercise tolerance. Daily weights should be performed first thing in the morning upon arising and before any food intake to maintain consistency, recorded in a journal, and brought to each scheduled provider appointment. Changes in weight can indicate fluid retention prior to onset of peripheral or pulmonary congestive symptoms. Individuals who have an increase of 3 lb (1.4 kg) in a single day or 5 lb (2.3 kg) over a week should alert their HF provider. Some patients may be educated about self-adjusting diuretic doses based on daily weights. In addition to weight changes, a marked decline in exercise tolerance should also be reported to the HF provider.

Nonadherence is a leading cause for AHF exacerbations. Ensuring an understanding of the importance of each medication, proper administration, and potential adverse effects may improve adherence. Stressing the rationale for each medication is especially important for NYHA FC I or ACC/AHA stage B patients who are asymptomatic yet started on medications. A clinician's involvement in medication adherence and intensive follow-up care has been shown to reduce HF hospitalizations.

Dietary modifications in HF consist of initiation of an AHA step II diet as part of cardiac risk factor reduction, sodium restriction, and sometimes fluid restriction. Because sodium and water retention is a compensatory mechanism that contributes to volume overload in HF, restriction is often necessary to help minimize congestion. The normal American diet includes 3 to 6 g of sodium per day. Most patients with stage C or D HF should limit salt intake to a maximum of 3 g/day. Patients should minimize cooking with salt and limit intake of foods with high salt content, such as fried or processed food (lunch meats, soups, cheeses, salted snack foods, and canned food). Sodium restriction can be challenging, and drastic dietary changes may lead to nonadherence. Sodium restriction may be more effective if implemented slowly over time. Salt substitutes should be used judiciously because many contain significant amounts of potassium that may increase the risk of hyperkalemia. Fluid restriction may not be necessary in many patients. When applicable, fluid intake is generally limited from all sources to less than 2 L/day. A referral to a registered dietician may also be warranted.

Exercise is recommended in patients with compensated HF. Exercise improves peripheral muscle conditioning and efficiency in the setting of low CO, which contributes to better exercise tolerance. Regular low-intensity, aerobic exercise (eg, light house/yard work, walking, swimming, or riding a bike) is encouraged; heavy weight training is discouraged. The prescribed exercise regimen should be tailored to individual functional ability, and thus it is recommended patients initially participate in cardiac rehabilitation programs. It is important that patients do not overexert themselves to fatigue or exertional dyspnea.

Modification of classic risk factors, such as tobacco and alcohol consumption, is important to prevent further cardiac damage. All patients with HF who smoke should be counseled on tobacco

Patient Encounter Part 2

Medical History, Physical Examination, and Diagnostic Tests

PMH: Hypertension × 20 years, dyslipidemia × 20 years, coronary artery disease (myocardial infarction 10 years ago), glucose intolerance, depression (untreated)

Allergies: No known drug allergies

Meds: Aspirin 81 mg once daily, atenolol 25 mg once daily, hydrochlorothiazide 25 mg once daily, simvastatin 20 mg once daily at bedtime, coenzyme Q10 100 mg twice daily, naproxen 250 mg twice daily as needed for pain

FH: Father had MI at 55 years of age

SH: He is married, has one child, and runs his own business; quit smoking 10 years ago, but drinks three beers daily

PE:

BP 146/88 mm Hg, pulse 89 beats/min and regular, respiratory rate 16 breaths/min, Ht 5 ft 8 in (173 cm), Wt 251 lb (114 kg), body mass index (BMI): 38.1 kg/m^2

Lungs: Bibasilar rales, decreased breath sounds at the bases, no wheezes

CV: JVP 15 cm above sternal angle. Regular rate and rhythm with normal S_1 and S_2; there is an S_3 and a soft S_4 present; there is a 2/6 systolic ejection murmur heard best toward the apex of the heart; point of maximal impulse displaced laterally

Abd: Tense and distended, and bowel sounds are present, (+) hepatomegaly

Ext: 2+ pitting edema extending to below the knees is observed

Chest x-ray: Cardiomegaly, pulmonary congestion

Echocardiogram: EF = 35% (0.35)

Laboratory Values:

Hct: 41.1% (0.411)

WBC: $7.3 \times 10^3/\mu L$ ($7.3 \times 10^9/L$)

Sodium: 137 mEq/L (mmol/L)

Potassium: 3.6 mEq/L (mmol/L)

Bicarbonate: 22 mEq/L (mmol/L)

Chloride: 98 mEq/L (mmol/L)

Magnesium: 1.5 mEq/L (0.75 mmol/L)

Fasting blood glucose: 120 mg/dL (6.7 mmol/L)

Uric acid: 6 mg/dL (357 μmol/L)

BUN: 40 mg/dL (14.3 mmol/L)

SCr: 1.6 mg/dL (141 μmol/L)

Alk Phos: 120 IU/L (2.0 μkat/L)

Aspartate aminotransferase: 100 IU/L (1.67 μkat/L)

Total bilirubin: 0.6 mg/dL (10.3 μmol/L)

What other laboratory or diagnostic tests are required for assessment of the patient's condition?

How would you classify his NYHA FC and ACC/AHA HF stage?

Classify the clinical presentation of the patient in terms of HF signs and symptoms.

What are your treatment goals for the patient?

cessation and offered a referral to a cessation program. Patients with alcoholic cardiomyopathy should abstain from alcohol. Whether patients with other etiologies of HF should abstain from any alcohol intake remains controversial. Proponents of moderation of alcohol base their rationale on the potential cardioprotective effects. However, opponents to any alcohol intake point out that alcohol is potentially cardiotoxic.

In general, it is suggested patients remain up-to-date on standard immunizations, including vaccinations for influenza and pneumococcal infections.

Pharmacologic Treatment

The ACC/AHA staging system delineates specific pharmacotherapy options based on disease progression.[1] For patients in stage A (risk factors for structural heart disease), every effort is made to minimize the impact of diseases that can damage the heart. Antihypertensive and lipid-lowering therapies should be utilized when appropriate to decrease the risk for stroke, MI, and HF. ACE inhibitors or angiotensin receptor blockers (ARBs) should be considered in patients at high risk for vascular disease. For patients in stage B (structural heart disease but asymptomatic), therapy targets preventing or slowing disease progression by interfering with neurohormonal pathways that lead to cardiac damage and mediate pathological remodeling. The goal is to prevent or delay the onset of HF symptoms. Therapies include ACE inhibitors or ARBs and β-adrenergic blockers (β-blockers). For patients in stage C (symptomatic LV systolic dysfunction, EF ≤ 40% [0.40]), goals focus on alleviating congestion, improving functional ability, slowing disease progression, and reducing risk for hospitalizations and death. Treatment entails a strategy that combines diuretics to control intravascular fluid balance with neurohormonal antagonists (including ACE inhibitors or ARBs or angiotensin receptor neprilysin inhibitor [ARNI], β-blockers, and aldosterone receptor antagonists) to minimize the detrimental effects of the RAAS and SNS. In patients of African American descent or patients with an intolerance to ACE inhibitor/ARB, combination hydralazine and isosorbide dinitrate is a reasonable alternative regimen. Both digoxin and ivabradine may be added to improve symptoms in patients receiving GDMT. Dosing and monitoring of pharmacologic agents for HF are described in Tables 7–6 and 7–7. Patients with stage D HF are offered more modest goals, such as improvement in quality of life. Enhancing quality of life is often achieved at the expense of expected survival. Treatment options include mechanical support, transplantation, and continuous use of intravenous (IV) vasoactive therapies, in addition to maintaining an optimal regimen of chronic oral medications as possible.

▸ *Diuretics*

Diuretics have been the mainstay for HF symptom management for many years. KEY CONCEPT Diuretics are used for relief of acute symptoms of congestion and maintenance of euvolemia. These agents increase urinary sodium and free water excretion. The primary role for diuretic therapy is maintenance of euvolemia in symptomatic or stages C and D HF. Diuretics are recommended for all patients with clinical evidence of fluid overload.

Table 7–6

Drug Dosing in the Pharmacologic Treatment of Heart Failure

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comments
Loop Diuretics					
Furosemide	Lasix	20–40 mg once or twice daily	20–160 mg once or twice daily	CrCl 20–50 mL/min (0.33–0.83 mL/s): 160 mg once or twice daily CrCl < 20 mL/min (0.33 mL/s): 400 mg daily	Single doses exceeding those listed are unlikely to elicit additional response
Bumetanide	Bumex	0.5–1.0 mg once or twice daily	1–2 mg once or twice daily	CrCl 20–50 mL/min (0.33–0.83 mL/s): 2 mg once or twice daily CrCl < 20 mL/min (0.33 mL/s): 8–10 mg daily	Single doses exceeding those listed are unlikely to elicit additional response
Torsemide	Demadex	10–20 mg once daily	10–80 mg once daily	CrCl 20–50 mL/min (0.33–0.83 mL/s): 40 mg once daily CrCl < 20 mL/min (0.33 mL/s): 200 mg daily	Single doses exceeding those listed are unlikely to elicit additional response
ACE Inhibitors					
Captopril	Capoten	6.25 mg three times daily	50 mg three times daily[a]		
Enalapril	Vasotec	2.5 mg twice daily	10–20 mg twice daily[a]		
Lisinopril	Zestril, Prinivil	2.5–5.0 mg once daily	20–40 mg once daily[a]		
Quinapril	Accupril	5 mg twice daily	20–40 mg twice daily		
Ramipril	Altace	1.25–2.5 mg once daily	10 mg once daily[a]		
Fosinopril	Monopril	5–10 mg once daily	40 mg once daily		Undergoes both hepatic and renal elimination
Trandolapril	Mavik	1.0 mg once daily	4 mg once daily[a]		Undergoes both hepatic and renal elimination
Perindopril	Aceon	2 mg once daily	8–16 mg once daily		Undergoes both hepatic and renal elimination
Angiotensin Receptor Blockers					
Candesartan	Atacand	4–8 mg once daily	32 mg once daily[a]		
Valsartan	Diovan	20–40 mg twice daily	160 mg twice daily[a]		
Losartan	Cozaar	25–50 mg once daily	150 mg once daily[a]		
Angiotensin Receptor Neprilysin Inhibitor (ARNI)					
Sacubitril/valsartan	Entresto	49/51 mg sacubitril/valsartan twice daily	97/103 mg sacubitril/valsartan twice daily[a]	For patients taking a low dose of or not taking an ACE inhibitor or ARB or if eGFR is < 30 mL/min/1.73 m^2, the starting dose is 24/26 mg sacubitril/valsartan twice daily	Discontinue ACE inhibitors at least 36 hours before initiating sacubitril/valsartan treatment; allow 36 hours between discontinuing ARNI and starting ACE inhibitor
β-Blockers					
Bisoprolol	Zebeta	1.25 mg once daily	10 mg once daily[a]		
Carvedilol	Coreg	3.125 mg twice daily	25 mg twice daily[a]	Target dose for patients weighing > 85 kg (187 lb) is 50 mg twice daily	Take with food
Carvedilol phosphate	Coreg CR	10 mg once daily	80 mg once daily[a]		Take with food
Metoprolol succinate CR/XL	Toprol-XL	12.5–25 mg once daily	200 mg once daily[a]		
Aldosterone Receptor Antagonists					
Spironolactone	Aldactone	eGFR > 50 mL/min/1.73 m^2: 12.5–25 mg once daily	25–50 mg once daily[a]	eGFR 30–49 mL/min/1.73 m^2: 12.5 mg once daily or every other day	Risk of hyperkalemia increases if serum creatinine is > 1.6 mg/dL (141 μmol/L). Avoid if baseline potassium is > 5 mEq/L (mmol/L)

(Continued)

Table 7–6

Drug Dosing in the Pharmacologic Treatment of Heart Failure (*Continued*)

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comments
Eplerenone	Inspra	eGFR > 50 mL/min/1.73 m^2: 25 mg once daily	50 mg once daily[a]	eGFR 30–49 mL/min/1.73 m^2: 25 mg every other day	Risk of hyperkalemia increases if serum creatinine is > 1.6 mg/dL (141 μmol/L). Avoid if baseline potassium is > 5 mEq/L (mmol/L)
Other					
Hydralazine-isosorbide dinitrate	Bidil	Hydralazine 37.5 mg three times daily; isosorbide dinitrate 20 mg three times daily	Hydralazine 75 mg three times daily[a]; isosorbide dinitrate 40 mg three times daily[a]		Indicated in conjunction with standard heart failure therapy to improve survival and reduce hospitalizations in self-identified African American patients
Digoxin	Lanoxin	0.125–0.25 mg once daily	0.125–0.25 mg once daily	Reduce dose in elderly patients with low lean body mass and patients with impaired renal function	Target plasma concentration range is 0.5–0.9 ng/mL (mcg/L; 0.6–1.2 nmol/L). Not shown to improve survival in patients with HFrEF
Ivabradine	Corlanor	5 mg twice daily	5–7.5 mg twice daily	Avoid if resting heart rate < 60 BPM before treatment	Indicated to reduce the risk of hospitalization in patients with HFrEF, in normal sinus rhythm, with a resting heart rate > 70 BPM receiving maximally tolerated β-blocker doses. Take with meals

[a] Regimens proven in large clinical trials to reduce mortality.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BPM, beats per minute; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction.

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Diuretics may be used on an as-needed basis in patients with mild congestion; however, scheduled doses will be required once edema is persistent.

Diuretics used for volume management in HF are thiazide and loop diuretics. Thiazide diuretics such as hydrochlorothiazide, chlorthalidone, and metolazone (thiazide-like diuretic) block sodium and chloride reabsorption in the distal convoluted tubule. Thiazides are weaker than loop diuretics for increasing urine output and therefore are not utilized frequently as monotherapy. Thiazides are optimally suited for patients with hypertension who have mild congestion. Additionally, the efficacy of thiazides is limited in patients with renal insufficiency (creatinine clearance [CrCl] < 30 mL/min [0.50 mL/s]) due to reduced tubular secretion. An exception is metolazone, which retains its action in renal insufficiency and is often used in combination with loop diuretics when patients exhibit diuretic resistance (edema unresponsive to escalating doses of loop diuretics alone).

Loop diuretics are the most widely used diuretics in HF. Loop diuretics, including furosemide, bumetanide, torsemide, and ethacrynic acid, block the $Na^+/K^+/2Cl^-$ cotransporter in the thick ascending loop of Henle. Loop diuretics are not filtered through the glomerulus but, instead, undergo active transport into the tubular lumen via the organic acid pathway. As a result, drugs that compete for this active transport (eg, probenecid and organic by-products of uremia) can lower the efficacy of loop diuretics. Loop diuretics increase sodium and water excretion and induce a prostaglandin-mediated increase in renal blood flow that contributes to natriuresis. Unlike thiazides, they retain their diuretic effect in the setting of reduced renal function. The various loop diuretics are equally effective when used at equipotent doses, although there are intrinsic differences in pharmacokinetics and pharmacodynamics (Table 7–6).[5] The choice of loop diuretic and route of administration depends on clinical factors such as the presence of intestinal edema and desired rapidity of effect. Oral efficacy may vary based on differing bioavailability, which is almost complete for bumetanide and torsemide but is approximately 50% for furosemide. Oral torsemide is a reasonable alternative to IV administration for patients who do not respond to oral furosemide. Onset of effect is slightly delayed with oral administration but occurs within minutes with IV administration. Consequently, bioequivalent doses of IV furosemide are half the oral dose, whereas bumetanide and torsemide IV doses are generally equivalent to the oral doses (note: torsemide IV is currently not available in the United States).

Table 7–7

Drug Monitoring

Drug Class	Adverse Effect	Monitoring Parameters	Comments
ACE inhibitors	Angioedema, cough, hyperkalemia, hypotension, renal dysfunction	BP, electrolytes, BUN, and creatinine	Contraindicated in patients with bilateral renal artery stenosis, history of angioedema, or pregnancy. Assess BP, BUN, creatinine, and electrolytes at baseline and 1–2 weeks after initiation or increase in dose. Goal is target dose from clinical trials or highest tolerated.
Angiotensin receptor blockers (ARBs)	Hyperkalemia, hypotension, renal dysfunction	BP, electrolytes, BUN, and creatinine	Contraindicated in patients with bilateral renal artery stenosis or pregnancy. Assess BP, BUN, creatinine, and electrolytes at baseline and 1–2 weeks after initiation or increase in dose. Use with caution in patients with a history of ACE inhibitor-associated angioedema. Goal is target dose from clinical trials or highest tolerated.
Sacubitril/valsartan	Angioedema, hyperkalemia, hypotension, dizziness, renal dysfunction	BP, electrolytes, BUN, and creatinine	Contraindicated in patients with a history of angioedema associated with ACE inhibitor or ARB therapy or in pregnancy. Assess BP, BUN, creatinine, and electrolytes at baseline and 1–2 weeks after initiation or increase in dose. Start with a low dose and double the dose every 2–4 weeks as tolerated based on BP, serum potassium, and renal function. Goal is target dose from clinical trials or highest tolerated.
Aldosterone receptor antagonists	Gynecomastia/breast tenderness/menstrual irregularities (spironolactone), hyperkalemia, worsening renal function	BP, electrolytes, BUN, and creatinine	Assess BP, BUN, creatinine, and electrolytes at baseline. Check potassium 3 days and 1 week after initiation and then monthly for the first 3 months, then every 3 months. Change to eplerenone if gynecomastia develops with spironolactone.
β-Blockers	Bradycardia, heart block, bronchospasm, hypotension, worsening HF	BP, HR, ECG, signs and symptoms of worsening HF, blood glucose	Start with low dose and titrate upward no more often than every 2 weeks as tolerated based on BP, HR, and symptoms. Goal is target dose from clinical trials or highest tolerated. Patients may feel worse before they feel better.
Digoxin	GI and CNS adverse effects, brady- and tachyarrhythmias	Electrolytes, BUN, creatinine, HR, ECG, serum digoxin concentration	Target serum digoxin concentration 0.5–0.9 ng/mL (mcg/L; 0.6–1.2 nmol/L).
Ivabradine	Bradycardia, hypertension, atrial fibrillation, luminous phenomena (phosphenes, transiently enhanced brightness in a portion of the visual field)	BP, HR, ECG	Start with 5 mg twice daily and after 2 weeks adjust dose to achieve a resting HR 50–60 BPM. Only use in patients in sinus rhythm.
Diuretics	Hypovolemia, hypotension, hyponatremia, hypokalemia, hypomagnesemia, hyperuricemia, renal dysfunction, thirst	BP, electrolytes, BUN, creatinine, glucose, uric acid, changes in weight, JVD	Dose should be adjusted based on volume status, renal function, electrolytes, and BP. Reassess these parameters 1–2 weeks after dose changes. Goal is lowest dose that maintains euvolemia.
Hydralazine	Hypotension, headache, rash, arthralgia, lupus, tachycardia	BP, HR	
Nitrates	Hypotension, headache, light-headedness	BP, HR	

ACE, angiotensin-converting enzyme; BP, blood pressure; BPM, beats per minute; BUN, blood urea nitrogen; CNS, central nervous system; ECG, electrocardiogram; GI, gastrointestinal; HF, heart failure; HR, heart rate; JVD, jugular venous distention.

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The lowest effective dose of diuretic should be used since they are used to improve symptoms and morbidity, not mortality. Once diuretic therapy is initiated, dosage adjustments are based on symptomatic improvement, net fluid balance, and daily body weight. Because body weight changes are a sensitive marker of fluid retention or loss, patients should weigh themselves daily. Once euvolemia ("dry weight") is achieved, diuretics may be tapered to a maintenance regimen. Select patients with mild volume retention may not require a scheduled diuretic. In stable, educated, and adherent patients, another option is self-adjusted diuretic dosing. Based on daily body weight, patients may temporarily increase their diuretic regimen to reduce the incidence of overt edema. Self-adjustment also avoids overuse of diuretics and possible complications of overdiuresis such as hypotension, fatigue, electrolyte imbalances, and renal impairment.

The maximal response to diuretics is reduced in chronic HF, creating a "ceiling dose" above which there is limited added benefit. This diuretic resistance is due to a compensatory increase in sodium reabsorption in the distal tubules, which decreases the effect of blocking sodium reabsorption in the loop of Henle. In addition, there is a simultaneous increase in the reabsorption of sodium from the proximal tubule, allowing less to reach the site of action for loop diuretics. Apart from increasing diuretic doses, strategies to improve diuretic efficacy include increasing the frequency of dosing to two or three times daily, and/or combining a loop diuretic with a thiazide diuretic. The latter strategy theoretically prevents sodium and water reabsorption at both the loop of Henle and the compensating distal convoluted tubule. Metolazone is used most often for this purpose because it retains its activity in settings of renal impairment. Metolazone can be dosed daily or as little as once weekly due to its long half-life. Clinicians must use metolazone cautiously because its potent activity predisposes to metabolic abnormalities as outlined next.

Diuretics cause numerous adverse effects and metabolic abnormalities, with severity linked to diuretic potency (Table 7–7). A particularly worrisome adverse effect is hypokalemia, which can predispose patients to arrhythmias and sudden death. Hypomagnesemia often occurs concomitantly with diuretic-induced hypokalemia, and therefore both should be assessed and replaced in patients needing correction of hypokalemia. Magnesium is an essential cofactor for movement of potassium intracellularly to restore body stores. Patients taking diuretics are also at risk for renal insufficiency due to overdiuresis and reflex activation of the renin-angiotensin system. The potential reduction in renal blood flow and glomerular pressure is amplified by concomitant use of ACE inhibitors or ARBs.

▶ *Neurohormonal Blocking Agents*

KEY CONCEPT Agents with proven benefits in improving symptoms, slowing disease progression, and improving survival in chronic HF target neurohormonal activation. These include ACE inhibitors, ARBs, ARNIs, β-blockers, and aldosterone receptor antagonists (Tables 7–6 and 7–7). The combination of hydralazine and isosorbide dinitrate is also discussed in this section based on their potential place in therapy although the proposed mechanisms of benefit do not directly target neurohormonal activation.

Angiotensin-Converting Enzyme Inhibitors ACE inhibitors are the cornerstone of treatment for HF. ACE inhibitors target RAAS activation by blocking the conversion of angiotensin I to angiotensin II. Simultaneously, ACE inhibition also prevents the breakdown of bradykinin, which enhances the release of vasodilatory prostaglandins and histamines. This results in arterial and venous dilation, reduction in preload and afterload, and a decrease in myocardial work. ACE inhibitors demonstrate favorable effects on cardiac hemodynamics such as improvement in **cardiac index** (CI), SV index, SVR, and mean arterial pressure.

There is extensive clinical experience with ACE inhibitors in HFrEF. Numerous studies show ACE inhibitor therapy is associated with improvements in clinical symptoms, exercise tolerance, NYHA FC, LV size and function, and quality of life as compared with placebo.[9-11] ACE inhibitors slow the development or progression of HF regardless of underlying disease severity or etiology. ACE inhibitors prevent HF development in high-risk patients (stage A). Studies in acute MI patients show a reduction in new-onset HF and death with ACE inhibitors whether they are initiated early (within 36 hours) or started later. ACE inhibitors decrease the risk of HF hospitalization and mortality through the entire HFrEF spectrum from asymptomatic LV dysfunction (stage B) to symptomatic HF (stages C and D). Mechanisms for improved prognosis are postulated to involve both the hemodynamic improvement and the inhibition of angiotensin II's growth promoting and remodeling effects. Therefore, all patients at risk for or with documented LV systolic dysfunction, regardless of existing HF symptoms (stages A to D), should receive an ACE inhibitor unless a contraindication or intolerance is present.

The benefit of ACE inhibitors is considered a class effect (no evidence that one ACE inhibitor is preferred over another). ACE inhibitors should be initiated using low doses and titrated up to target doses over several weeks depending on tolerability. The 2013 ACC/AHA HF guidelines advocate using doses that were proven to decrease mortality in clinical trials as the target doses (Table 7–6).[1] If the target dose cannot be attained, the highest tolerated dose should be used. Although there is incremental benefit with higher doses of ACE inhibitors, lower doses still provide much of the benefit.[12] Because ACE inhibitors are only one component of GDMT for HFrEF, targeting a high ACE inhibitor dose should not preclude starting a β-blocker or aldosterone receptor antagonist on the grounds of limited blood pressure.

Absolute contraindications to ACE inhibitors include a history of angioedema, bilateral renal artery stenosis, and pregnancy (Table 7–7). Relative contraindications include unilateral renal artery stenosis, renal insufficiency, hypotension, hyperkalemia, and cough. Relative contraindications should not preclude the use of ACE inhibitors in most patients considering their substantial benefit.

Renal insufficiency remains a concern. Note that ACE inhibitors can potentially contribute to both the preservation or decline of renal function depending on the clinical scenario. Through preferential efferent arteriole vasodilation, ACE inhibitors reduce intraglomerular pressure. Reduced glomerular pressures are renoprotective chronically; however, in situations of diminished or fixed renal blood flow this can lead to decreased filtration. In general, ACE inhibitors can be used in patients with serum creatinine less than 2.5 to 3.0 mg/dL (221–265 μmol/L). In HF, ACE inhibition can improve renal function through an increase in CO and renal perfusion. Although a small increase in serum creatinine (< 0.5 mg/dL [44 μmol/L]) is possible with the addition of an ACE inhibitor, it is usually transient or becomes the patient's new serum creatinine baseline level. However, ACE inhibition can cause acute worsening of renal function in the setting of reduced CO as glomerular filtration is maintained through angiotensin II's constriction of the efferent arteriole. Patients most dependent on angiotensin II for maintenance of glomerular filtration pressure, and hence most susceptible to ACE inhibitor worsening of renal function, include those with hyponatremia, severely depressed LV function, or dehydration. The most common reason for creatinine elevation in a patient without a history of renal dysfunction is overdiuresis. Therefore, consider decreasing or holding diuretic doses if an elevation in serum creatinine occurs concomitantly with a rise in blood urea nitrogen (BUN) or other evidence of hemoconcentration is present.

Hypotension occurs most commonly with initiation of therapy or with dosage escalation. Risk of hypotension is increased in the setting of volume depletion such as when ACE inhibitors are initiated or used concomitantly with high doses of diuretics. Therefore, in euvolemic patients, diuretic doses may often be decreased or withheld during ACE inhibitor dose titration. Initiating at a low dose and titrating slowly can also minimize hypotension. In patients at risk for hypotension, it may be advisable to initiate a short-acting ACE inhibitor, such as captopril, and subsequently switch to a longer-acting agent, such as lisinopril or enalapril, once the maximally tolerated dose is established.

Hyperkalemia results from reduced angiotensin II–stimulated aldosterone release. Risk of hyperkalemia with ACE inhibitors is also increased in HF due to a propensity for impaired renal function and additive effects with aldosterone receptor antagonists. ACE inhibitor doses may be reduced or withheld if serum potassium increases above 5 mEq/L (mmol/L). Persistent hyperkalemia in the setting of renal insufficiency may preclude use of an ACE inhibitor or consideration for the addition of a potassium-binder (eg, patiromer, sodium zirconium cyclosilicate) approved for chronic use. Assessment of potential causes of hyperkalemia should include dietary intake as well as potassium-containing salt substitutes.

Cough is commonly seen with ACE inhibitors (5%–15%) and may be related to accumulation of tissue bradykinins.[5] It can be challenging to distinguish a cough from ACE inhibition from pulmonary congestion. A productive or wet cough usually signifies congestion, whereas a dry, hacking cough is more indicative of a drug-related etiology. If a cough is determined to be ACE inhibitor–induced, its severity should be evaluated before deciding on a course of action. If the cough is truly bothersome, switching to an ARB is warranted.

Angiotensin Receptor Blockers ARBs selectively antagonize the effects of angiotensin II directly at the angiotensin type 1 (AT_1) receptor. AT_1 receptor stimulation is associated with vasoconstriction, release of aldosterone, and ventricular remodeling effects. The angiotensin type 2 (AT_2) receptor mediates vasodilation and inhibition of ventricular remodeling. Therefore, selective blockade at the AT_1 receptor blocks the detrimental effects of angiotensin II while sparing the compensatory actions at the AT_2 receptor. ARBs are considered an equally effective replacement for ACE inhibitors in patients who are intolerant or have a contraindication to an ACE inhibitor.

Clinical evidence suggests the efficacy of ARBs is similar to ACE inhibitors for reduction of hospitalizations for HF, sudden cardiac death, and all-cause mortality.[13-15] ARBs produce more complete inhibition of angiotensin II's detrimental effects than ACE inhibitors; however, ACE inhibitors also exert additional effects on the kallikrein-kinin system. Although ARBs produce clinical benefits equivalent to ACE inhibitors, they are considered second-line therapy due to the overwhelming clinical trial experience with ACE inhibitors.

Because the mechanism for long-term benefit appears different for ACE inhibitors and ARBs, their combination was studied for additive effect. The combination of an ACE inhibitor and ARB may reduce risk of HF hospitalizations but not mortality over ACE inhibition alone. However, since other therapies provide additional mortality advantages (eg, addition of mineralocorticoid receptor antagonists or switching to valsartan/sacubitril), the combination of ACE inhibitor and ARB has fallen out of favor and is not widely applied.[1]

ARBs show similar tolerability to ACE inhibitors with regard to hypotension and hyperkalemia but are less associated with cough because ARBs do not induce accumulation of bradykinin. ARBs can be considered in patients with ACE inhibitor–induced angioedema but should be initiated cautiously as cross-reactivity has been reported. Other considerations for use of ARBs are similar to those of ACE inhibitors, including the need for monitoring renal function, BP, and potassium. Contraindications are similar to ACE inhibitors (Table 7–7). In patients intolerant or contraindicated to ACE inhibitors or ARBs, the combination of hydralazine and isosorbide dinitrate should be considered.

Sacubitril/Valsartan Sacubitril/valsartan (formerly known as the compound, LCZ696) is a first in class ARNI.[16] Neprilysin is a neutral endopeptidase responsible for the breakdown of natriuretic peptides, in addition to substance P, adrenomedullin, bradykinin, and angiotensin II. Blockade of neprilysin increases circulating natriuretic peptide levels. Because neprilysin inhibition alone would also result in elevated levels of angiotensin II, combination of a neprilysin inhibitor with an ARB prevents this potentially deleterious effect. Sacubitril/valsartan is a crystalline complex composed of equal parts of the neprilysin inhibitor sacubitril and the ARB valsartan. Shortly after ingestion, sacubitril/valsartan breaks apart into sacubitril, a prodrug which is then cleaved to the active form of sacubitril and valsartan. The target dose is 97/103 mg twice daily, which was found to reduce the composite end point of cardiovascular death or hospitalization for HF by 20% compared to enalapril 10 mg twice daily in patients with symptomatic HF and reduced LVEF.[17] As such, the 2017 ACC/AHA/Heart Failure Society of America Focused Update of the 2013 American College of Cardiology Foundation/AHA Guideline for the Management of Heart Failure recommends that in patients with symptomatic HFrEF who are tolerating an ACE inhibitor or an ARB, replacement with sacubitril/valsartan is warranted to further reduce morbidity and mortality.[18] Compared to enalapril, patients taking sacubitril/valsartan experienced more symptomatic hypotension, necessitating caution with initiating or switching to this medication in patients with lower BP. Sacubitril/valsartan is contraindicated for use with an ACE inhibitor due to an increased risk for angioedema (Table 7–7), and a 36-hour washout period is necessary when switching to sacubitril/valsartan from an ACE inhibitor, or vice versa. The starting dose of sacubitril/valsartan is 49/51 mg twice daily, unless the patient has not previously been on an ACE inhibitor or ARB, or is taking a low dose of an ACE inhibitor, in which case the recommended initial dose is 24/26 mg twice daily (Table 7–6). Given the benefit observed in clinical trials, titration to a goal dose of 97/103 mg twice daily is recommended.

Hydralazine and Isosorbide Dinitrate Complementary hemodynamic actions originally led to the combination of nitrates and hydralazine. Nitrates reduce preload by causing primarily venous vasodilation through activating guanylate cyclase and a subsequent increase in cGMP in vascular smooth muscle. Hydralazine reduces afterload through direct arterial smooth muscle relaxation via an unknown mechanism. More recently, nitric oxide has been implicated in modulating numerous pathophysiological processes in the failing heart including inflammation, cardiac remodeling, and oxidative damage. Supplementation of nitric oxide via administration of nitrates has also been proposed as a mechanism for benefit from this combination. The beneficial effect of an exogenous nitric oxide source may be more apparent in the African American population, which appears to be predisposed to having an imbalance in nitric oxide production. In addition, hydralazine may reduce the development of nitrate tolerance when nitrates are given chronically.

The combination of hydralazine and isosorbide dinitrate was the first therapy shown to improve long-term survival in patients with HFrEF but was inferior with respect to mortality reduction when compared to the ACE inhibitor enalapril.[19,20] An additional niche for this combination was established in a prospective clinical trial in patients of African American descent.[21] **KEY CONCEPT** Combination therapy with hydralazine and isosorbide dinitrate is an appropriate substitute for angiotensin II antagonism in those unable to tolerate an ACE inhibitor or ARB (usually secondary to renal impairment, hyperkalemia, or angioedema) or as add-on therapy in African Americans. The 2013 ACC/AHA HF guidelines recommend considering the addition of hydralazine and isosorbide dinitrate in African Americans already on ACE inhibitors or ARBs.[1]

Combination therapy with hydralazine and isosorbide dinitrate should be initiated and titrated similarly to ACE inhibitors. Low doses are used to initiate therapy with subsequent titration toward target doses based on tolerability. Adverse effects such as hypotension and headache cause frequent discontinuations in patients taking this combination, and full doses often cannot be tolerated. Patients should be monitored for headache, hypotension, and tachycardia (Table 7–7). Hydralazine is also associated with a dose-dependent risk for lupus.

The frequent dosing of isosorbide dinitrate is not conducive to patient adherence; therefore, a once-daily isosorbide mononitrate is commonly substituted for isosorbide dinitrate to simplify the dosing regimen with the caveat that this form of oral nitrate has not been studied in a large outcome trial in HFrEF, and a clear target dose has not been established.

β-Adrenergic Antagonists β-Adrenergic antagonists, or β-blockers, competitively block the influence of the SNS at β-adrenergic receptors. β-blockers were previously thought to be detrimental in HFrEF due to their negative inotropic actions, potentially worsening symptoms. However, the benefits of inhibiting the SNS clearly outweigh the acute negative inotropic effects if used judiciously. Chronic β-blockade improves cardiac function through reverse modeling and has been shown to reduce ventricular mass, improve ventricular shape, and reduce LV end-systolic and diastolic volumes.[6] β-blockers also exhibit antiarrhythmic effects, decrease myocyte death from catecholamine-induced necrosis or apoptosis, and prevent myocardial fetal gene expression. Consequently, β-blockers improve LVEF, reduce all-cause and HF-related hospitalizations, and decrease all-cause mortality in patients with HFrEF (including sudden cardiac death and death due to progressive pump failure).[22-24]

The 2013 ACC/AHA HF guidelines recommend β-blockers be initiated in all HF patients with NYHA FC I to IV or ACC/AHA stages B through D if clinically stable.[1] Unlike with RAAS inhibition, the mortality reduction with β-blockers is not considered a drug class effect, and has only been demonstrated with the selective β_1-antagonists bisoprolol and metoprolol succinate and the nonselective β_1-, β_2-, and α_1-antagonist carvedilol.[22-24] Only metoprolol succinate and carvedilol have been approved by the Food and Drug Administration (FDA) to improve outcomes in patients with HFrEF. Other β-blockers either have not been studied or shown to reduce mortality for HFrEF. Nebivolol is approved for HFrEF in several countries outside of the United States.

Bisoprolol is not as commonly used since it does not carry an FDA-approved indication for HFrEF. Although metoprolol succinate and carvedilol are more commonly used, it is unknown whether one agent should be considered first line. Carvedilol was shown to lower all-cause mortality significantly more than metoprolol tartrate, but carvedilol has not yet been directly compared to metoprolol succinate.[25]

The key to utilizing β-blockers in HFrEF is initiation with low doses and slow titration to target doses over weeks to months. It is important the β-blocker be initiated when a patient is clinically stable and euvolemic. Volume overload at the time of β-blocker initiation increases the risk for worsening symptoms. β-Blockade should begin with the lowest possible dose (Table 7–6), after which the dose may be doubled every 2 to 4 weeks depending on patient tolerability. β-Blockers may cause an acute decrease in LVEF and short-term worsening of HF symptoms upon initiation and at each dosage titration. After each dose titration, if the patient experiences symptomatic hypotension, bradycardia, orthostasis, or worsening symptoms, further increases in dose should be withheld until the patient stabilizes. After stabilization, attempts to increase the dose should be reinstituted. If mild congestion ensues as a result of the β-blocker, an increase in diuretic dose may be warranted. If moderate or severe symptoms of congestion occur, a reduction in β-blocker dose should be considered. Dose titration should continue until target doses are achieved (Table 7–6) or until limited by repeated hemodynamic or symptomatic intolerance. Patient education regarding the possibility of acutely worsening symptoms but improved long-term function and survival is essential to ensure adherence.

Factors potentially affecting the selection of β-blockers for use in HFrEF include β-receptor selectivity, patient comorbidity, and pharmacokinetics. Carvedilol exhibits a more pronounced BP-lowering effect as a consequence of its α_1-receptor blocking activities and thus causes more frequent dizziness and hypotension. In patients predisposed to symptomatic hypotension, metoprolol succinate may be the more desirable whereas in patients with uncontrolled hypertension, carvedilol may be preferred. Patients with reactive airway disease may still use β-blockers; however, considerable caution should be made in those who display active respiratory symptoms. A selective β_1-blocker such as metoprolol succinate is a reasonable option for patients with reactive airway disease. The risk–benefit profile of using any β-blocker in peripheral vascular disease must be weighed based on the severity of the peripheral disease, and a selective β_1-blocker may be preferred. Both metoprolol and carvedilol are metabolized by the liver through cytochrome P-450 (CYP) 2D6 and undergo extensive first-pass metabolism. Therefore, β-blockers should be used cautiously in patients with severe hepatic failure.

As the guidelines recommend both an ACE inhibitor and β-blocker as initial therapy, a common question is whether it matters if one drug class is started before the other. A study evaluated whether the order of initiation affects all-cause mortality or hospitalization and found no difference. However, there were more events during the 6-month single-treatment phase of the study,[26] reinforcing the importance of having both ACE inhibition and β-blockade if possible. As such, dose titration of the agent initiated first should not prohibit initiation of the second class of agent (eg, having low doses of both an ACE inhibitor and β-blocker is generally regarded as providing greater benefit than having a high dose of only one drug class).

Mineralocorticoid Receptor Antagonists (MRAs) Both MRAs currently available, spironolactone and eplerenone, are inhibitors of aldosterone that produce weak diuretic effects while sparing potassium (potassium-sparing diuretics). Eplerenone is selective for the mineralocorticoid receptor and hence does not cause the endocrine adverse effects commonly seen with spironolactone. The rationale for specifically targeting aldosterone for treatment of HFrEF is based on knowledge that ACE inhibitors do not suppress the chronic production and release of aldosterone. Aldosterone is a key pathological neurohormone that exerts multiple detrimental effects in HF, most notably promoting fluid retention, cardiac fibrosis, and electrolyte abnormalities that predispose to arrhythmias (hypokalemia and hypomagnesemia). Similar to norepinephrine and angiotensin II, aldosterone levels are increased in HF and correlate with disease severity and poorer patient outcomes.

MRAs improved clinical outcomes, including mortality, across the spectrum of HFrEF in three separate clinical trials. These comprised patients who were post-MI with LVEF less than 40% (0.40), patients with NYHA FC II HF, and patients with NYHA FC III through IV HF.[27-29] It is postulated that MRAs reduce mortality at least in part through prevention of sudden cardiac death. The 2013 ACC/AHA HF guidelines recommend MRAs in symptomatic patients (NYHA FC II–IV) with LVEF less than or equal to 35% (0.35), or in patients post-MI with LVEF less than or equal to 40% (0.40) who develop symptoms of HF or have diabetes, unless contraindicated. For individuals with mild symptoms (NYHA FC II), it is recommended they also have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels.[1]

The major risk related to MRAs is hyperkalemia (Table 7–7). Therefore, balancing the benefit of decreasing death and hospitalization from HF and the potential risks of life-threatening hyperkalemia must always be weighed. Serum potassium and renal function (or serum creatinine to estimate glomerular filtration rate [GFR]) should be assessed before, at day 3, and 1 week after initiating an MRA. MRAs should not be initiated in patients with serum potassium concentrations greater than 5 mEq/L (mmol/L). Likewise, these agents should not be given when estimated GFR is less than 30 mL/min/1.73 m^2 or serum creatinine is greater than 2.5 mg/dL (221 μmol/L) in men or 2 mg/dL (177 μmol/L) in women. In patients without contraindications, spironolactone is initiated at a dose of 12.5 to 25 mg daily (Table 7–6), or occasionally on alternate days for patients with baseline renal insufficiency. Eplerenone is initiated at 25 mg daily, with a target dose of 50 mg daily. Doses should be halved or switched to alternate-day dosing if the estimated GFR falls below 50 mL/min/1.73 m^2. Potassium supplementation is often decreased or discontinued after MRAs are initiated, and patients should be counseled to avoid high-potassium foods. At any time after initiation of therapy, if potassium concentrations exceed 5.5 to 6 mEq/L (mmol/L), MRA dose should be reduced or discontinued until the potassium falls to below 5 mEq/L (mmol/L). In addition, worsening renal function dictates consideration for stopping the MRA. Other adverse effects observed mainly with spironolactone include gynecomastia for men, and breast tenderness and menstrual irregularities for women. Gynecomastia leads to discontinuation in up to 10% of patients on spironolactone. Eplerenone is a CYP3A4 substrate and should not be used concomitantly with strong inhibitors of CYP3A4.

▸ *Digoxin*

Digoxin has been used for several decades in the treatment of HF. Traditionally, it was considered useful for its positive inotropic effects, but more recently its benefits are thought to be related to neurohormonal modulation. Digoxin exerts positive inotropic effects through inhibition of the sodium- and potassium-activated adenosine triphosphate (ATP) pumps, leading to increased intracellular sodium concentrations and subsequently more available intracellular calcium during systole. The mechanism of digoxin's neurohormonal blocking effect is less well understood but may be related to restoration of baroreceptor sensitivity and reduced central sympathetic outflow.[5]

The exact role of digoxin in therapy remains controversial largely due to disagreement on the risk versus benefit of routinely using this drug in patients with HFrEF. Digoxin has been shown to decrease HF-related hospitalizations but does not improve survival.[30] Moreover, digoxin is associated with an increased risk for concentration-related toxicity and numerous adverse effects. Post hoc analyses of the pivotal digoxin clinical trial in HFrEF demonstrated a clear relationship between digoxin plasma concentration and outcomes. Concentrations below 1 ng/mL (mcg/L; 1.3 nmol/L) were associated with no apparent adverse effect on survival, whereas higher concentrations increased the relative risk of mortality.[31] The current guidelines state that if digoxin is used, serum concentrations should be kept below 1 ng/mL (mcg/L; 1.3 nmol/L).

Current recommendations are to consider the addition of digoxin to decrease hospitalizations in patients who remain symptomatic despite optimal GDMT. In patients with concomitant atrial fibrillation, digoxin may occasionally be added to slow ventricular rate; however, β-blockers are more effective at controlling ventricular rate, especially in the setting of exercise. Clinicians may also consider adding digoxin in patients with severe HF who have not responded symptomatically to neurohormonal blockade.

Digoxin is initiated at a dose of 0.125 to 0.25 mg daily depending on age, renal function, weight, and risk for toxicity (Table 7–6). The lower dose should be used if the patient satisfies any of the following criteria: older than 65 years of age, CrCl less than 60 mL/min (1 mL/s), or ideal body weight less than 70 kg (154 lb). The 0.125-mg daily dose is adequate in most patients. Doses are halved or switched to alternate-day dosing in patients with moderate to severe renal failure. The desired concentration range for digoxin in HFrEF is 0.5 to 0.9 ng/mL (mcg/L; 0.6–1.2 nmol/L), preferably with concentrations at or less than 1 ng/mL (mcg/L; 1.3 nmol/L). Routine monitoring of serum drug concentrations is not required but recommended in those with changes in renal function, suspected toxicity, or after addition or subtraction of an interacting drug. Digoxin levels should be drawn at steady state (after three to five elimination half-lives) and a minimum of 6 to 8 hours after the administration of the last dose.

Digoxin toxicity may manifest as nonspecific findings such as fatigue or weakness and other central nervous system (CNS) effects such as confusion, delirium, and psychosis (Table 7–7). GI manifestations include nausea, vomiting, or anorexia, and visual disturbances may occur such as halos, photophobia, and color perception problems (red-green or yellow-green vision). Cardiac findings include numerous types of arrhythmias related to enhanced automaticity, slowed or accelerated conduction, or delayed after-depolarizations. These include ventricular tachycardia and fibrillation, atrioventricular nodal block, and sinus bradycardia. Risk of digoxin toxicity, in particular, the cardiac manifestations are increased with electrolyte disturbances such as hypokalemia, hypercalcemia, and hypomagnesemia. To reduce the proarrhythmic risk of digoxin, serum potassium and magnesium should be monitored closely and supplemented when appropriate to ensure adequate concentrations (potassium > 4 mEq/L [mmol/L] and magnesium > 2 mEq/L [1 mmol/L]). In patients with life-threatening digoxin toxicity due to cardiac or other findings, administration of digoxin-specific Fab antibody fragments usually reverses adverse effects within an hour in most cases.

▸ *Ivabradine*

In patients with HFrEF, an elevated resting HR is associated with higher rates of morbidity and mortality. Ivabradine is a novel HR-lowering medication that blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel, which inhibits the I_f current (otherwise referred to as the "funny" current) in the sinoatrial node. A major advantage of ivabradine is its ability to lower sinus HR without affecting BP or contractility. In the main study leading to ivabradine's approval for HF, ivabradine was shown to reduce the composite of cardiovascular death or hospitalization for HF, although results were mainly driven by a reduction in hospitalizations.[32] Ivabradine is indicated in patients with HFrEF with an LVEF less than or equal to 35% (0.35), NYHA FC II and III, in normal sinus rhythm (without atrial fibrillation), taking maximally tolerated doses or have a contraindication to β-blockers, and who have an HR 70 beats/min or greater. The current guidelines recommend considering ivabradine for patients already optimized on GDMT who meet the specific indication parameters. It is important the β-blocker is optimized prior to initiating therapy with ivabradine as β-blockers have proven benefits in lowering mortality; thus, reaching target doses of a β-blocker takes priority. The starting dose of ivabradine is 5 mg twice daily (or 2.5 mg twice daily in those with conduction defects or in whom a low HR could result in hemodynamic compromise), which may be titrated to 7.5 mg twice daily after 2 weeks (Table 7–6). Ivabradine is contraindicated for use in patients concomitantly taking strong CYP3A4 inhibitors. Frequently observed adverse effects in clinical trials included bradycardia, atrial fibrillation, hypertension, and visual phenomena (Table 7–7). Termed "phosphenes," these visual disturbances consist of temporarily enhanced brightness, usually in response to sudden variations in light (ie, headlights from other cars while driving). These occur in limited areas of the visual field and may also include halos, image decomposition (stroboscopic or kaleidoscopic effects), or colored bright lights. These visual effects may reduce in severity after a few months of therapy.

▶ *Calcium Channel Blockers*

Treatment with nondihydropyridine calcium channel blockers (diltiazem and verapamil) may worsen HF and increase the risk of death in patients with advanced LV systolic dysfunction due to their negative inotropic effects. Conversely, dihydropyridine calcium channel blockers, although negative inotropes in vitro, do not appear to decrease contractility in vivo. Amlodipine and felodipine are the two most extensively studied dihydropyridine calcium channel blockers for HFrEF.[33,34] These two agents have not been shown to alter patient survival, either positively or negatively. As such, they are not routinely recommended as part of a standard HF regimen; however, amlodipine and felodipine can safely be used in patients with HF to treat uncontrolled hypertension or angina if required.

▶ *Antiplatelets and Anticoagulants*

Patients with HFrEF are at increased risk of thromboembolic events as a result of increased activity of prothrombotic molecules such as fibrinogen and von Willebrand factor, stasis of blood within the cardiac chambers and peripheral blood vessels, and endothelial damage or dysfunction. However, clinical trials randomizing patients with HFrEF to aspirin and/or anticoagulation have not shown improved outcomes. In fact, aspirin use may be associated with an increased risk of HF hospitalizations due to a potential interaction with RAAS inhibitors. Therefore, aspirin is generally used in HF patients with an underlying ischemic etiology, a history of ischemic heart disease, or other compelling indications such as a history of embolic stroke. In patients with HFrEF, warfarin and non–vitamin K oral anticoagulants (NOACs) are mainly used in those with a compelling indication such as atrial fibrillation. NOACs are still being studied; however, the first trial, which was conducted in HF patients with concomitant ischemic heart disease, failed to demonstrate a reduction in any cardiovascular events.[35] The choice of anticoagulant (warfarin vs NOAC) should be individualized and based on risk factors, tolerability, cost, patient preference, and potential for drug–drug interactions.

▶ *Emerging Therapies for HFrEF*

The therapeutics of HFrEF are rapidly evolving. Promising data exist for soluble guanylate cyclase (sGC) stimulators, sodium glucose cotransporter-2 (SGLT2) inhibitors, and myosin ATPase activators (omecamtiv mecarbil).

Heart Failure With Preserved Left Ventricular Ejection Fraction

It is now recognized that up to half of patients exhibiting HF symptoms have relatively preserved LV systolic function and primarily impaired diastolic function (impaired ventricular relaxation and filling) characterized by an LVEF 50% (0.50) or greater, a syndrome commonly referred to as HF with preserved EF (HFpEF). Patients with HFpEF tend to be older, with hypertension being the greatest contributing etiology. Mortality rate is slightly lower, though the proportion of patients requiring hospitalizations for decompensations is greater in HFpEF compared to HFrEF. Importantly, the reasons for decompensations are more commonly due to noncardiovascular causes which contribute pathophysiologically to a greater degree in HFpEF. An assessment for HFpEF should be performed in any patient who presents with signs and symptoms consistent with HF. A diagnosis is based on echocardiographic evidence of preserved LVEF and elevated natriuretic peptides in the absence of ventricular dilation, valvular disease, or cardiac ischemia.[36] Once HFpEF is diagnosed, further workup (commonly requiring cardiac magnetic resonance imaging) is directed at determining the etiology for this heterogenous disorder. Common etiologies include hypertensive heart disease, hypertrophic cardiomyopathy, cardiac amyloidosis, and connective tissue disorders like scleroderma.

Unlike HFrEF, no therapies have been shown to improve survival in HFpEF. Studies conducted with ACE inhibitors, β-blockers, nitrates, phosphodiesterase-5 inhibitors, digoxin, and ivabradine have all failed to demonstrate improvement in outcomes in HFpEF. Agents that may be of benefit are ARBs and MRAs, which were found to modestly decrease risk of hospitalizations in clinical trials.[37,38] Potential emerging therapies currently being studied for HFpEF include sGC stimulators, SGLT2 inhibitors, and treatments targeting transthyretin cardiac amyloidosis (ATTR) (eg, tafamidis, diflunisal, patisiran).

The guideline recommended treatment approach for patients with HFpEF is (a) correction or control of underlying etiologies/comorbidities (including optimal management of hypertension, CAD, and atrial fibrillation) and (b) optimization of volume status with diuretics. Consideration for use of ARBs and MRAs to possibly reduce hospitalization is mentioned but with a lower strength of recommendation. Although diuretics are recommended to attenuate signs and symptoms of congestion, their use in HFpEF differs slightly from HFrEF. In HFpEF, the less compliant and stiffened LV results in a steeper pressure–volume relationship.

Patient Encounter Part 3

Based on the information presented and your problem-based assessment, create a care plan for the patient's HF. Your plan should include:

- Nonpharmacologic treatment options.
- Acute and chronic treatment plans to address symptoms and prevent disease deterioration.
- Monitoring plan for acute and chronic treatments.

Therefore, small increases in volume can lead to large increases in LV filling pressure and the development of HF symptoms. As a result, management of volume status in the setting of HFpEF can be difficult as these patients are very sensitive to changes in volume, and diuresis goals may need to be more conservative than for HFrEF.

Outcome Evaluation of Chronic Heart Failure

- Evaluation of therapy is influenced by the ability of treatment to successfully reduce symptoms, improve quality of life, decrease frequency of hospitalizations for AHF, reduce disease progression, and prolong survival (Figure 7–2).
- The major outcome parameters focus on (a) volume status, (b) exercise tolerance, (c) overall symptoms/quality of life, (d) adverse drug reactions, and (e) preservation of cardiac function.
- Assess quality of life by evaluating patients' ability to continue their activities of daily living.
- Assess for symptoms of HF, including those related to both congestion and hypoperfusion.
- If diuretic therapy is warranted, monitor for therapeutic response by assessing weight and improvement of edema, as well as orthopnea and PND.
- Once therapy for preventing disease progression is initiated, continue to monitor for symptomatic improvement.
- Keep in mind that patients' symptoms can initially worsen with β-blockers, and it may take weeks or months before patients notice improvement.
- Monitoring for adverse drug reactions is especially important since patients tend to be on multiple medications that can affect BP, electrolytes, and kidney function.
- Occasional exercise testing or repeat echocardiography is conducted to ascertain disease prognosis or suitability for heart transplant. Keep in mind that improvement in symptoms does not always correlate directly to or necessitate improvement in cardiac function.

ACUTE AND ADVANCED HEART FAILURE

Clinical Presentation and Diagnosis of Acute Heart Failure

The 2019 ACC Expert Consensus Decision Pathway on Risk Assessment, Management, and Clinical Trajectory of Patients Hospitalized With Heart Failure provides the framework for management of AHF.[39] Patients with AHF present with symptoms of worsening fluid retention or decreasing exercise tolerance and fatigue (typically worsening of symptoms presented in

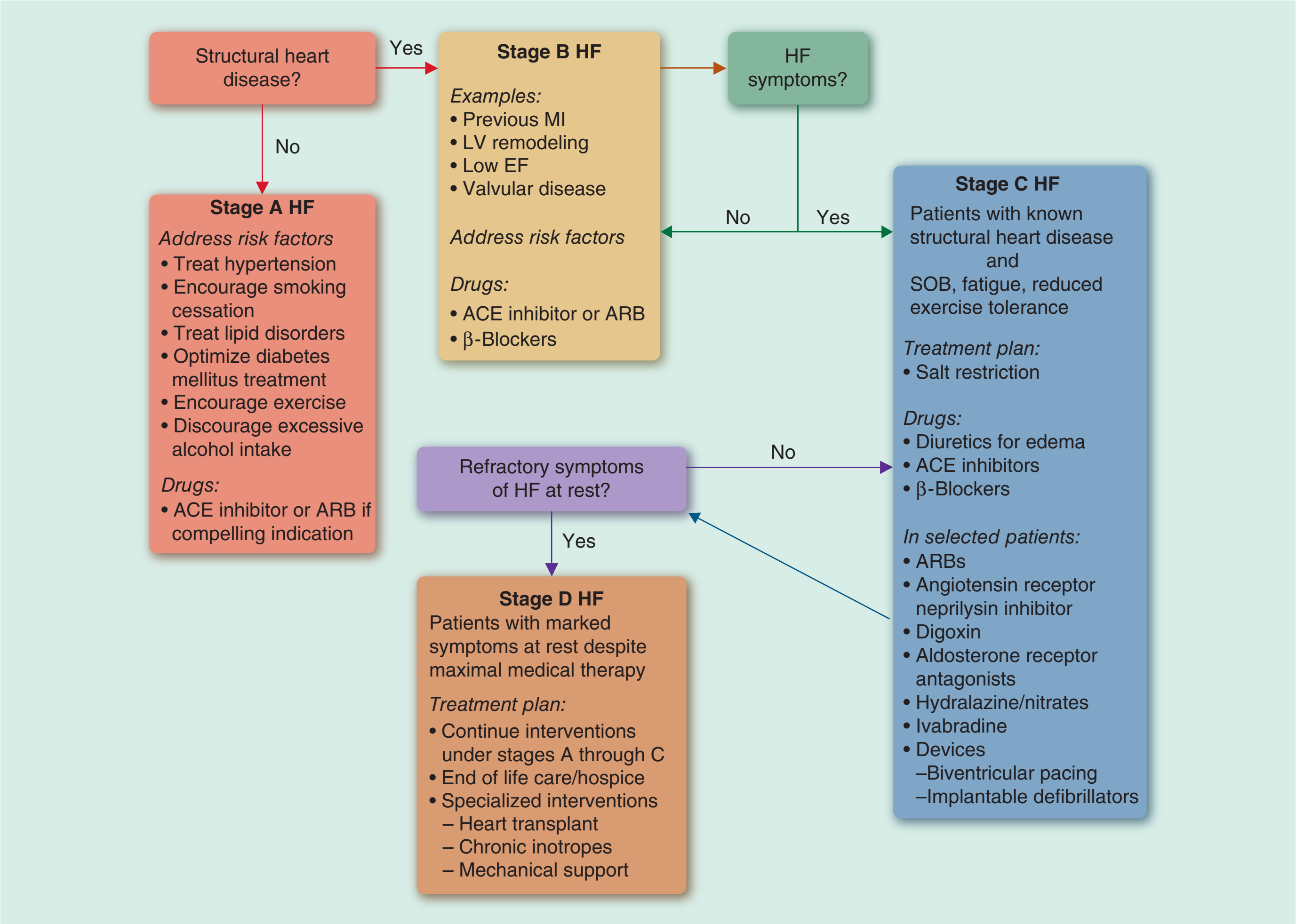
Structural heart disease?
Yes
No
Stage A HF
Address risk factors
• Treat hypertension
• Encourage smoking cessation
• Treat lipid disorders
• Optimize diabetes mellitus treatment
• Encourage exercise
• Discourage excessive alcohol intake
Drugs:
• ACE inhibitor or ARB if compelling indication
Stage B HF
Examples:
• Previous MI
• LV remodeling
• Low EF
• Valvular disease
Address risk factors
Drugs:
• ACE inhibitor or ARB
• β-Blockers
HF symptoms?
No
Yes
Stage C HF
Patients with known structural heart disease and SOB, fatigue, reduced exercise tolerance
Treatment plan:
• Salt restriction
Drugs:
• Diuretics for edema
• ACE inhibitors
• β-Blockers
In selected patients:
• ARBs
• Angiotensin receptor neprilysin inhibitor
• Digoxin
• Aldosterone receptor antagonists
• Hydralazine/nitrates
• Ivabradine
• Devices
–Biventricular pacing
–Implantable defibrillators
Refractory symptoms of HF at rest?
No
Yes
Stage D HF
Patients with marked symptoms at rest despite maximal medical therapy
Treatment plan:
• Continue interventions under stages A through C
• End of life care/hospice
• Specialized interventions
– Heart transplant
– Chronic inotropes
– Mechanical support

FIGURE 7–2. Treatment algorithm for heart failure with reduced ejection fraction. (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; EF, ejection fraction; HF, heart failure; LV, left ventricular; MI, myocardial infarction; SOB, shortness of breath.) Table 7–5 describes the staging of heart failure.

the chronic HF clinical presentation textbox). These symptoms reflect congestion behind the failing ventricle and/or hypoperfusion. Patients can be categorized into hemodynamic subsets based on assessment of physical signs and symptoms of congestion and/or hypoperfusion.[40] Patients can be described as "wet" or "dry" depending on volume status as well as "warm" or "cool" based on adequacy of tissue perfusion. "Wet" refers to patients with volume/fluid overload (eg, edema and JVD), whereas "dry" refers to euvolemic patients. "Warm" refers to patients with adequate CO to perfuse peripheral tissues (skin will be warm to touch), whereas "cool" refers to patients with evidence of hypoperfusion (skin cool to touch with diminished pulses). Additionally, invasive hemodynamic monitoring can be used in some cases to provide objective data for assessing volume status (pulmonary capillary wedge pressure [PCWP]) and perfusion (CO). A CI below 2.2 L/min/m^2 (0.037 L/s/m^2) is consistent with reduced contractility and hypoperfusion, and a PCWP above 15 to 18 mm Hg (2–2.4 kPa) is indicative of elevated LV preload and congestion. The four possible hemodynamic subsets a patient may fall into are "warm and dry," "warm and wet," "cool and dry," or "cool and wet."

▶ *Precipitating Factors*

KEY CONCEPT It is important for the clinician to identify the cause(s) of AHF to maximize treatment efficacy and reduce future disease exacerbations. Cardiovascular, metabolic, and lifestyle factors can all precipitate AHF. The most common precipitating factors for acute decompensation and how they contribute pathophysiologically are listed in Tables 7–3 and 7–4.

▶ *Laboratory Assessment*

Routine laboratory testing of patients with AHF includes electrolytes and blood glucose, as well as serum creatinine and BUN to assess renal function. Complete blood cell count is measured to determine if anemia or infection is present. Troponin concentrations are prognostic and also used to diagnose possible acute myocardial injury. Liver function tests can help determine if congestive hepatopathy and/or hepatocellular necrosis may be present due to either congestion or hypoperfusion. Thyroid function tests are measured to assess hyperthyroidism or hypothyroidism as causes of AHF. Lactate levels may be increased in the setting of cardiogenic shock and are a marker of hypoperfusion that may indicate poor prognosis. A urinalysis is attained in patients with an unknown history of renal disease to rule out nephrotic syndrome. Lastly, a toxicology screen is obtained in patients in whom the use of illicit drugs is suspected.

Measuring BNP or its degradation product NT-proBNP is advocated in the current guidelines. BNP is synthesized, stored, and released from the ventricles in response to increased ventricular filling pressures, hence plasma levels of BNP can be used as a marker for volume overload. The most widely accepted indication for BNP measurement is as an adjunctive aid for diagnosing a cardiac etiology for dyspnea.[41] The current values for ruling out a cardiac etiology for dyspnea in the acute setting are a BNP less than 100 pg/mL (ng/L; 28.9 pmol/L) or NT-proBNP less than 300 pg/mL (ng/L; 35.4 pmol/L). BNP measurements require cautious interpretation because numerous conditions can also elevate BNP concentrations. These include older age, renal dysfunction, pulmonary embolism, and chronic pulmonary disease. Treatment with sacubitril/valsartan would also be expected to raise BNP levels based on the drug's inhibition of neprilysin. As such, monitoring of NT-proBNP should be utilized instead of BNP in patients taking sacubitril/valsartan as NT-proBNP is not a substrate for neprilysin. Natriuretic peptide levels may also be obtained to aid in further risk stratification, although it remains controversial whether they provide added value when titrating GDMT.

▶ *Other Diagnostic Tests*

Other diagnostic tests should also be obtained to rule out precipitating factors (chest radiograph, ECG) and to evaluate cardiac function (transthoracic echocardiogram). Invasive hemodynamic monitoring in patients with HF entails placement of a right heart catheter or pulmonary artery catheter (PAC). The catheter is inserted percutaneously through a central vein and advanced through the right side of the heart to the pulmonary artery. Inflation of a balloon proximal to the end port allows the catheter to "wedge," yielding the PCWP, which estimates pressures in the left ventricle during end diastole. Additionally, CO can be estimated and SVR calculated (Table 7–8).

There are no universally accepted guidelines dictating when invasive monitoring in HF is required, and invasive monitoring has not been shown to improve mortality or reduce hospitalizations. Nonetheless, the use of a PAC remains helpful in the assessment of hemodynamics when volume status and/or cardiac output is uncertain, or when there is disagreement between signs

Table 7–8

Hemodynamic Monitoring: Normal Values

Hemodynamic Variable	Normal Value
Central venous (right atrial) pressure, mean	< 5 mm Hg[a] (0.7 kPa)
Right ventricular pressure (systolic/diastolic)	25/0 mm Hg[a]
Pulmonary artery pressure (systolic/diastolic), PAS/PAD	25/10 mm Hg[a]
Pulmonary arterial pressure, mean, PAP	< 18 mm Hg[a] (2.4 kPa)
Pulmonary capillary wedge pressure, PCWP	< 12 mm Hg[a,b] (1.6 kPa)
Systemic arterial pressure (systolic/diastolic), SBP/DBP	120/80 mm Hg[a]
Mean arterial pressure, MAP = (DBP+[1/3(SBP−DBP])	70–110 mm Hg[a] (9.3–14.6 kPa)
Cardiac output, CO	4–6 L/min (0.07–0.10 L/s)
Cardiac index, CI = CO/BSA	2.8–4.2 L/min/m^2 (0.047–0.070 L/s/m^2)
Systemic vascular resistance, SVR = ([MAP−CVP]×80)/(CO)	900–1400 dyn·s·cm^{-5}[c] (90–140 MPa·s·m^{-3})
Pulmonary vascular resistance, PVR = ([PAP−CVP]×80)/(CO)	150–250 dyn·s·cm^{-5}[c] (15–25 Mpa·s·m^{-3})
Arterial oxygen saturation	90%–95% (0.90–0.95)
Mixed venous oxygen saturation	60%–80% (0.60–0.80)

[a] 1 mm Hg = 0.133 kPa; 1 mL/beat per square meter = 0.001 L·beat^{-1}·m^{-2}.

[b] A higher than normal PCWP (ie, 15–18 mm Hg or 2–2.4 kPa) is often accepted in patients with heart failure.

[c] 1 dyn·s·cm^{-5} = 0.1 MPa·s·m^{-3}; 1 mL/dL = 10 mL/L.

BSA, body surface area; CVP, central venous pressure; DBP, diastolic blood pressure; PAD, pulmonary artery diastolic; PAP, pulmonary arterial pressure; PAS, pulmonary artery systolic; SBP, systolic blood pressure.

Reproduced with permission from Reed BN, Rodgers JE. Acute decompensated heart failure. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020.

and symptoms and clinical response. In patients requiring IV vasoactive therapies such as inotropes and vasopressors, invasive hemodynamic monitoring is useful to guide dose titration and offers the advantage of immediate hemodynamic assessment of an intervention and prompt adjustments. However, use of these agents does not mandate the need for invasive monitoring. Risks with PACs include infection, bleeding, thrombosis, catheter malfunction, and ventricular ectopy.

Desired Therapeutic Outcomes

The goals of therapy for AHF are to (a) correct the underlying precipitating factor(s); (b) relieve patient symptoms; (c) improve or normalize hemodynamics; (d) optimize GDMT; and (e) educate the patient, reinforcing adherence to lifestyle modifications and the drug regimen. The ultimate goal for a patient hospitalized for AHF is return to a compensated HF state and transition to the outpatient setting on oral medications.[39] Only through aggressive management to achieve all of these goals will a patient's prognosis be improved and future hospitalizations for acute decompensations be prevented.

Clinical Presentation of Acute Heart Failure

Subset I (Warm and Dry)

- CI *greater than* 2.2 L/min/m^2 (0.037 L/s/m^2), PCWP *less than* 18 mm Hg (2.4 kPa)
- Patients considered well compensated and perfused, without evidence of congestion
- No immediate interventions necessary except optimizing oral medications and monitoring

Subset II (Warm and Wet)

- CI *greater than* 2.2 L/min/m^2 (0.037 L/s/m^2), PCWP *greater than* or equal to 18 mm Hg (2.4 kPa)
- Patients adequately perfused and display signs and symptoms of congestion
- Main goal is to reduce preload (PCWP) carefully with loop diuretics and vasodilators

Subset III (Cool and Dry)

- CI *less than* 2.2 L/min/m^2 (0.037 L/s/m^2), PCWP *less than* 18 mm Hg (2.4 kPa)
- Patients are inadequately perfused and not congested
- Hypoperfusion leads to increased mortality, elevating death rates fourfold compared with those who are adequately perfused
- Treatment focuses on increasing CO with positive inotropic agents and/or replacing intravascular fluids
- Fluid replacement must be performed cautiously because patients can rapidly become congested

Subset IV (Cool and Wet)

- CI *less than* 2.2 L/min/m^2 (0.037 L/s/m^2), PCWP *greater than* 18 mm Hg (2.4 kPa)
- Patients are inadequately perfused and congested
- Classified as the most complicated clinical presentation of AHF with the worst prognosis
- Most challenging to treat; therapy targets alleviating signs and symptoms of congestion by increasing CI as well as reducing PCWP while maintaining adequate mean arterial pressure
- Treatment involves a delicate balance between diuretics, vasodilators, and inotropic agents
- Use of vasopressors is sometimes necessary to maintain BP

Removal or control of precipitating factors is essential for an optimal response to pharmacologic therapy. Relief of symptoms should occur rapidly to minimize length of hospitalization. Although a rapid discharge from the hospital is desirable, a patient should not be discharged before ensuring that he or she is in a euvolemic, or nearly euvolemic, state with a body weight and functional capacity similar to before the acute decompensation. Oral agents such as β-blockers, ACE inhibitors or ARBs (and possibly an ARNI), and MRAs should be initiated as soon as possible during the hospitalization. These chronic oral medications not only improve mortality and prevent readmissions, but acutely also contribute to improvement in hemodynamics. Patient education prior to discharge from the hospital is recommended to assist in minimizing adverse effects and nonadherence. Dissemination of written information, in addition to verbal information, is helpful for patient comprehension and retention. This can include therapy goals, lifestyle modifications, drug regimen, dosage information, and relevant adverse effects, as well as symptom and diary cards. The addition of a transitions of care program in this patient population is particularly important in reducing 30-day readmission rates.

Pharmacologic Treatment

KEY CONCEPT Treatment of AHF targets relief of congestion and optimization of CO utilizing oral or IV diuretics, IV vasodilators, and when appropriate, inotropes based on presenting hemodynamics. Optimizing hemodynamics results in improved symptomology and preservation of organ function. A specific treatment approach is formulated depending on the patient's symptoms (congestion vs hypoperfusion) and hemodynamic indices (CI and PCWP).[42] If the patient primarily exhibits signs and symptoms of congestion, treatment entails use of diuretics as first-line agents to relieve congestion (reduce PCWP) by decreasing preload. IV vasodilators may be considered in patients with moderate to severe congestion to provide more rapid relief of congestion (and reduction in PCWP) by decreasing both preload and afterload. Reducing congestion in the heart (analogous to reducing LV filling pressure) indirectly may lead to improved contractile function increases in SV and CO and hence perfusion to vital organs. The patient's presenting BP can also help guide the clinician on choice of diuretic, vasodilator, or both. For the patient with a systolic BP of 120 to 160 mm Hg in the setting of progressive worsening of chronic HF with pulmonary and systemic congestion, aggressive diuresis can be beneficial. In the patient with systolic BP greater than 160 mm Hg and abrupt onset of pulmonary congestion, IV vasodilators may be indicated in addition to diuretics. For patients primarily displaying symptoms of hypoperfusion, treatment relies on use of agents that increase cardiac contractility, known as positive inotropes. Some patients present with both symptoms of congestion and hypoperfusion, often requiring a combination of therapies. One of the current challenges to the treatment of AHF is achieving hemodynamic improvement without adversely affecting organ function. In the case of inotropes, the increased contractility occurs at the expense of an increase in cardiac workload and potential for proarrhythmia.

Therefore, inotropes should only be used when absolutely necessary and for the shortest duration possible to establish hemodynamic stability. High-dose diuretic therapy is associated with a risk for acute worsening of kidney function (as indicated by increases in serum creatinine) and possibly neurohormonal activation, although whether this indicates permanent kidney injury or poorer patient outcomes remains an area of debate.

▶ *Diuretics*

Loop diuretics, including furosemide, bumetanide, and torsemide, are the diuretics of choice in the management of AHF. Diuretics decrease preload by functional venodilation within 5 to 15 minutes of administration and subsequently by an increase in sodium and water excretion. This may provide rapid improvement in symptoms of pulmonary congestion, although achieving euvolemia will generally take time depending on how volume overloaded the patient is and the negative fluid balance achieved. The reduction in preload will result in a decrease in PCWP, but diuresis alone generally does not increase CI like positive inotropes and arterial vasodilators. Patients who have significant volume overload often have impaired absorption of oral loop diuretics because of intestinal edema or altered transit time. Therefore, for patients in AHF, loop diuretics are usually administered via IV boluses or continuous IV infusions (Table 7–9). Higher doses may be required for patients with renal insufficiency due to decreased drug delivery to the site of action in the loop of Henle. A good rule of thumb is to initiate the IV diuretic at 1 to 2.5 times the outpatient oral dose. Data suggest doses 2.5 times the home oral dose given intravenously may be associated with better diuresis compared to simply using the home dose intravenously.[43]

There is limited evidence comparing the benefit of diuretics with other therapies for symptom relief or long-term outcomes. Careful monitoring of diuresis is needed as excessive preload reduction can lead to a decrease in CO, resulting in a reflex increase in sympathetic activation, renin release, and the expected consequences of vasoconstriction, tachycardia, and increased myocardial oxygen demand. Routine monitoring of serum electrolytes, serum creatinine, and BUN should be performed at a minimum of every 24 hours, and more frequently in patients undergoing more aggressive diuresis (eg, every 6–12 hours).

Occasionally, patients with HF do not respond to a diuretic, defined as failure to achieve a negative net fluid balance of at least 500 mL or greater depending on clinical need after several increasing bolus doses. Several strategies are used to overcome diuretic resistance. These include using larger doses, converting to IV administration after failing to respond to oral doses, increasing the frequency of administration, or using a combination of loop and thiazide diuretic. Current data suggest there is little difference in diuretic efficacy whether the loop diuretic is administered via a continuous infusion or intermittent boluses.[43] (See Table 7–9.) An effective strategy for overcoming diuretic resistance is combining two diuretics with different sites of action within the nephron. The most common combination is the use of a loop diuretic with a thiazide or thiazide-like diuretic such as metolazone. Diuretic resistance commonly occurs due to adaptation of the kidney to chronic inhibition of sodium reabsorption in the ascending limb of the loop of Henle by enhancing sodium reabsorption in the distal portion of the nephron. Therefore, adding a thiazide that acts in the distal nephron provides sequential blockade of sodium reabsorption and enhanced diuresis. Combining diuretics should be done cautiously due to an increased risk for cardiovascular collapse from rapid intravascular volume depletion and electrolyte wasting (especially potassium and magnesium). Diuretic resistance may also be a result of poor CO and diminished renal perfusion. In these patients, it may become necessary to add vasodilators or inotropes to enhance perfusion to the kidneys. Care must be taken because vasodilators can decrease renal blood flow despite increasing CO through dilation of central and peripheral vascular beds.

▶ *Vasodilators*

Vasodilators are commonly used in patients presenting with AHF accompanied by moderate to severe congestion, although their routine addition to diuretics has not been shown to improve outcomes in AHF. This class includes nitroglycerin, nitroprusside, and nesiritide. Hemodynamic effects and dosages for these agents are included in Tables 7–10 and 7–11, respectively. IV vasodilators cause a rapid decrease in arterial tone, resulting in a decrease in SVR and a potential increase in SV and CO. Additionally, vasodilators also cause venodilation, reducing ventricular filling pressures (PCWP) within 24 to 48 hours, and potentially reducing myocardial oxygen consumption (MVO_2) and ventricular workload. Although IV vasodilators are generally safe and effective, identification of the proper patient for use is important to minimize the risk of significant hypotension. In addition, vasodilators are contraindicated in patients whose cardiac filling (and hence CO) depends on venous return or intravascular volume, as well as in patients who present with cardiogenic shock. The 2013 ACC/AHA HF guidelines recommend considering IV vasodilators in addition to diuretic therapy for relief of dyspnea in patients with acutely decompensated HF and not symptomatically hypotensive.

Nitroglycerin Nitroglycerin acts as a source of nitric oxide, which through a cGMP pathway induces smooth muscle relaxation in venous and arterial vascular beds. Nitroglycerin is primarily a venous vasodilator at lower doses but can exert potent arterial vasodilatory effects at higher doses. At lower doses,

Table 7–9

Intravenous Diuretics Used to Treat Heart Failure–Related Fluid Retention

	Onset of Action (minutes)	Duration of Action (hours)	Relative Potency	Intermittent Bolus Dosing (mg)	Continuous Infusion Dosing (bolus/infusion)
Furosemide	2–5	4–8	40	20–200+	20–40/2.5–10
Torsemide	< 10	6–24	20	10–100	20/2–5
Bumetanide	2–3	4–6	0.5	1–10	1–4/0.5–1
Ethacrynic acid	5–15	2–7	50	0.5–1 mg/kg per dose up to 100 mg/dose	

Table 7–10

Usual Hemodynamic Effects of Commonly Used Intravenous Agents for Treatment of Acute or Severe Heart Failure

Drug	CO	PCWP	SVR	BP	HR
Diuretics	↑/↓/0	↓		↓	0
Nitroglycerin	↑	↓↓	↓	↓↓	↑/0
Nitroprusside	↑	↓↓↓	↓↓↓	↓↓↓	↑
Nesiritide	↑	↓↓	↓↓	↓↓	0
Dobutamine	↑↑	↓/0	↓/0	↓/0	↑↑
Milrinone	↑↑	↓↓	↓	↓	↑

BP, blood pressure; CO, cardiac output; HR, heart rate; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; ↑, increase; ↓, decrease; 0, no or little change.

nitroglycerin causes a decrease in preload (or filling pressures) and improves coronary blood flow. At higher doses (> 100 mcg/min), additional reduction in preload is achieved, along with a decrease in afterload and subsequent increase in SV and CO. IV nitroglycerin may be used primarily for preload reduction (lower doses) in patients exhibiting mainly pulmonary congestion or in combination with inotropes for congested patients with severely reduced CO.

Continuous infusions of nitroglycerin should be initiated at a dose of 5 to 10 mcg/min and increased every 5 to 10 minutes until symptomatic or hemodynamic improvement. If the patient is profoundly hypertensive, higher starting doses may be reasonable. Effective doses range from 35 to 200 mcg/min. The most common adverse events reported are headache, dose-related hypotension, and tachycardia. Tachyphylaxis, or tolerance of effects, may occur within 12 hours of initiation, necessitating continual titration to higher doses.

Nitroprusside Nitroprusside, like nitroglycerin, leads to the formation of nitric oxide and vascular smooth muscle relaxation. In contrast to nitroglycerin, nitroprusside exerts significant venous and arterial vasodilation regardless of dosage. Nitroprusside causes a pronounced decrease in PCWP, SVR, and BP, with a modest increase in CO. Nitroprusside has been studied to a limited extent in AHF, and no studies have evaluated its effects on mortality. Nitroprusside is initiated at 0.3 mcg/kg/min, followed by dose adjustments in 0.1 to 0.2 mcg/kg/min increments if necessary to achieve desired effect. Because of its rapid onset of action and metabolism, nitroprusside administered as a continuous infusion is easy to titrate and provides predictable hemodynamic effects. Nitroprusside requires strict monitoring of BP and HR. Its use is limited in AHF due to recommended hemodynamic monitoring with an arterial line and mandatory intensive care unit admission at many institutions. Abrupt withdrawal of therapy should be avoided due to a risk of rebound neurohormonal activation. Therefore, the dose should be tapered when discontinuing therapy. Nitroprusside has the potential to cause cyanide and thiocyanate toxicity, especially in patients with hepatic and renal insufficiency, respectively. Toxicity is most common with use longer than 3 days and with higher doses. Nitroprusside should be avoided in patients with active ischemia because its powerful afterload-reducing effects within the myocardium can "steal" coronary blood flow from myocardial segments that are supplied by epicardial vessels with high-grade atherosclerotic lesions.

Nesiritide Recombinant BNP, or nesiritide, binds to guanylate cyclase receptors in vascular smooth muscle and endothelial cells, causing an increase in cGMP concentrations leading to vasodilation (venous and arterial) and natriuresis. Nesiritide also antagonizes the effects of the RAAS and endothelin. Nesiritide reduces PCWP, right atrial pressure, and SVR. Consequently, it also indirectly increases SV and CO without affecting HR. Continuous infusions result in sustained effects for 24 hours without tachyphylaxis, although experience with its use beyond 72 hours is limited.

Unlike nitroglycerin and nitroprusside, nesiritide has been studied in randomized clinical trials for AHF. Compared to

Table 7–11

Usual Doses and Monitoring of Commonly Used Hemodynamic Medications

Drug	Dose	Monitoring Variables[a]
Dopamine	0.5–20 mcg/kg/min	BP, HR, urinary output and kidney function, ECG, extremity perfusion (higher doses only)
Dobutamine	2.5–20 mcg/kg/min	BP, HR, urinary output and function, ECG
Milrinone	0.375–0.75 mcg/kg/min	BP, HR, urinary output and function, ECG, changes in ischemic symptoms (eg, chest pain), electrolytes
Nitroprusside	0.3–3 mcg/kg/min	BP, HR, liver and kidney function, blood cyanide and/or thiocyanate concentrations if toxicity suspected (nausea, vomiting, altered mental function)
Nitroglycerin	5–200+ mcg/min	BP, HR, ECG, changes in ischemic symptoms
Nesiritide[b]	Bolus: 2 mcg/kg; infusion: 0.01 mcg/kg/min	BP, HR, urinary output and kidney function, blood BNP/NT-proBNP concentrations

[a] In addition to pulmonary capillary wedge pressure and cardiac output.

[b] No longer manufactured in United States as of 2018.

BNP, B-type natriuretic peptide; BP, blood pressure; ECG, electrocardiogram; HR, heart rate; NT-proBNP, N-terminal proBNP.

standard care, it is associated with significant improvement in PCWP, but only modest improvements in dyspnea, and no significant effect on risk of death or rehospitalizations within 30 days.[44,45] Nesiritide is no longer being manufactured in the United States, although some supply may still be available.

▶ *Inotropic Agents*

Currently available positive inotropic agents act via increasing intracellular cyclic adenosine monophosphate (cAMP) concentrations through different mechanisms. β-Agonists, or catecholamine inotropes, activate adenylate cyclase through stimulation of β-adrenergic receptors, which subsequently catalyzes the conversion of ATP to cAMP. Phosphodiesterase inhibitors reduce degradation of cAMP. The resulting elevation in cAMP levels leads to enhanced phospholipase activity, which then increases the rate and extent of calcium influx during systole, thereby enhancing contractility. Additionally, cAMP promotes uptake of calcium by the sarcoplasmic reticulum during diastole, which improves cardiac relaxation. Routine use of inotropes during acute decompensations is less preferable to use of vasodilators, which should be attempted first for AHF. The 2013 ACC/AHA HF guidelines recommend the use of temporary inotropic support to maintain perfusion and preserve organ function in patients who are refractory as a bridge to definitive therapy.[1] Long-term use of inotropes may be considered in patients for the purposes of palliative care.

Dobutamine Dobutamine has historically been the inotrope of choice for AHF. As a synthetic catecholamine, it acts as an agonist mainly on β_1- and β_2-receptors and minimally on α_1-receptors. The resulting hemodynamic effects are due to both receptor- and reflex-mediated activities. These effects include increased contractility and HR through β_1- (and β_2-) receptors and vasodilation through a relatively greater effect on β_2-receptors than α_1-receptors. Dobutamine can increase, decrease, or cause little change in mean arterial pressure depending on whether the resulting increase in CO is enough to offset the modest vasodilation. Although dobutamine has a half-life of approximately 2 minutes, its positive hemodynamic effects can be observed for several days to months after administration. The use of dobutamine is supported by several small studies documenting improved hemodynamics, but large-scale clinical trials in AHF are lacking.

Dobutamine is initiated at a dose of 2.5 to 5 mcg/kg/min, which can be gradually titrated to 20 mcg/kg/min based on clinical response. There are several practical considerations to dobutamine therapy. First, owing to its vasodilatory potential, monotherapy with dobutamine is reserved for patients with systolic BP greater than 90 mm Hg. However, it may be used in combination with vasopressors in patients with lower systolic BP. Second, downregulation of β_1-receptors or uncoupling of β_2-receptors from adenylate cyclase with prolonged exposure has been reported with dobutamine and other catecholamine agents. This leads to an attenuation of hemodynamic effects as early as 48 hours after initiation of a continuous infusion, although tachyphylaxis is more evident with use longer than 72 hours. Full sensitivity to dobutamine's effects can be restored 7 to 10 days after the drug is withdrawn. Third, many patients with AHF will be taking β-blockers chronically. Because β-blockers exhibit high affinity for β-receptors, the effectiveness of β-agonists such as dobutamine will be reduced when administered concomitantly. In patients on β-blocker therapy, it is recommended that consideration be given to the use of phosphodiesterase inhibitors such as milrinone, which do not depend on β-receptors for effect.[46,47] Although commonly practiced, use of high doses of dobutamine to overcome the β-blockade should be discouraged because this negates any of the protective benefits of the β-blocker and may increase risk for arrhythmias.

Dopamine Dopamine is most commonly reserved for patients with low systolic BP and those approaching cardiogenic shock. Dopamine exerts its effects through direct stimulation of adrenergic receptors, as well as release of norepinephrine from adrenergic nerve terminals. Dopamine produces hemodynamic effects that differ based on dosing. At lower doses (< 3 mcg/kg/min), dopamine stimulates renal dopaminergic type 1 (D1) receptors, resulting in renal artery vasodilation and possible increases in renal blood flow. Positive inotropic effects are more pronounced at doses of 3 to 10 mcg/kg/min where predominantly β_1-receptors are activated. CI is increased due to increased SV and HR. At doses higher than 10 mcg/kg/min, chronotropic and α_1-mediated vasoconstriction effects predominate. This causes an increase in mean arterial pressure due to higher SVR. The ultimate effect on cardiac hemodynamics will depend largely on the dosage prescribed and must be individually tailored to the patient's clinical status. Dopamine is generally associated with an increase in CO and BP, with a concomitant increase in PCWP. Dopamine increases myocardial oxygen demand and may decrease coronary blood flow through vasoconstriction and increased wall tension. As with other inotropes, dopamine is associated with increased myocardial workload and an increased risk for arrhythmias.

Phosphodiesterase Inhibitors Milrinone and amrinone (or inamrinone) work by inhibiting phosphodiesterase III, the enzyme responsible for the breakdown of cAMP. The increase in cAMP levels leads to increased intracellular calcium concentrations and enhanced contractile force generation. Milrinone has replaced amrinone as the phosphodiesterase inhibitor of choice due to the higher frequency of thrombocytopenia seen with amrinone.

Milrinone has both positive inotropic and vasodilating properties and as such is referred to as an "inodilator." Its vasodilating activities are especially prominent on venous capacitance vessels and pulmonary vascular beds, although a reduction in arterial tone is also noted. IV administration results in an increase in SV and CO, and usually modest increases in HR. Milrinone also lowers PCWP through venodilation. Routine use of milrinone during acute decompensations in NYHA FC II to IV HF is not recommended, and milrinone use remains limited to patients who require inotropic support.[48]

Dosing recommendations for milrinone may include a loading dose of 50 mcg/kg, followed by an infusion beginning at 0.5 mcg/kg/min (range: 0.23 mcg/kg/min for patients with renal failure up to 0.75 mcg/kg/min). A loading dose is not necessary if immediate hemodynamic effects are not required or if patients have low systolic BP (< 90 mm Hg). Decreases in BP during an infusion may necessitate dose reductions as well. Doses need to be reduced in patients with renal insufficiency as milrinone is primarily renally excreted.

Milrinone is a good option for patients requiring an inotrope who are also chronically receiving β-blockers because the inotropic effects are achieved independent of β-adrenergic receptors. However, milrinone exhibits a long distribution and elimination half-life compared with β-agonists. Potential adverse effects include hypotension, arrhythmias, and less commonly, thrombocytopenia. Additionally, milrinone has been associated with increased risk for death in some studies. Milrinone should not be used in patients in whom vasodilation is contraindicated.

Mechanical, Surgical, and Device Therapies

▶ *Percutaneous Mechanical Circulatory Support Devices*

Intra-aortic balloon counterpulsation (IABC) or intra-aortic balloon pumps (IABPs) are widely used mechanical circulatory assistance devices for patients with cardiac failure who do not respond to standard therapies. An IABP is placed percutaneously into the femoral artery and advanced to the high descending thoracic aorta. Once in position, the balloon is programmed to inflate during diastole and deflate during systole. Two main beneficial mechanisms are (a) inflation during diastole increases aortic pressure and perfusion of the coronary arteries; and (b) deflation just prior to the aortic valve opening reduces afterload. As such, IABP increases myocardial oxygen supply and decreases oxygen demand. This device has many indications, including cardiogenic shock, high-risk unstable angina in conjunction with percutaneous interventions, preoperative stabilization of high-risk patients prior to surgery, and in patients who cannot be weaned from cardiopulmonary bypass. Possible complications include infection, bleeding, thrombosis, limb ischemia, and device malfunction. The device is typically useful for short-term therapy due to its invasiveness, need for limb immobilization, and requirement for anticoagulation.

Other support devices used in this setting are the Impella and TandemHeart. Both the Impella and TandemHeart are placed percutaneously with the Impella pumping blood directly from the LV into the aorta and the TandemHeart taking blood from the left atrium and returning it into the femoral artery. Unlike the IABP, the Impella and TandemHeart provide continuous blood flow and do not require timing with the cardiac cycle. Complications that occur with these devices are similar to that of the IABP. Additionally, given they are both dependent on LV preload, it is important to monitor for right ventricle failure. One potential advantage of the TandemHeart compared to the Impella is that it can be used in patients with LV thrombus.

▶ *Ventricular Assist Device*

The ventricular assist device (VAD) is a surgically implanted pump that reduces or replaces the work of the right, left, or both ventricles. VADs are indicated for short-term support in patients refractory to pharmacologic therapies, as long-term bridge therapy (a temporary transition treatment) in patients awaiting cardiac transplant, or in some instances, as destination therapy for patients who are not appropriate candidates for transplantation.[1] The most common complications are infection and thromboembolism. Other adverse effects include bleeding, right ventricle failure, air embolism, device failure, and multiorgan failure.

▶ *Heart Transplant*

Heart transplantation represents the final option for refractory end-stage HF patients who have exhausted medical and device therapies. Heart transplantation should be considered a trade between a life-threatening syndrome and the risks associated with the operation and long-term immunosuppression. Assessment of appropriate candidates includes comorbid illnesses, psychosocial behavior, available financial and social support, and patient willingness to adhere to lifelong therapy and close medical follow-up.[1] Overall, the transplant recipient's quality of life may be improved, but not all patients receive this benefit. Posttransplant survival continues to improve due to advances in immunosuppression, treatment and prevention of infection, and optimal management of patient comorbidities.

Outcome Evaluation of Acute Heart Failure

- Focus on (a) acute improvement of symptoms and hemodynamics using IV therapies and (b) optimization of oral therapies.
- Monitor for rapid relief of symptoms related to the chief complaint on admission. This includes improvement of

Patient Encounter Part 4

After 6 months, the patient presents to the emergency department complaining of extreme SOB and fatigue at rest. He sleeps sitting up due to severe orthopnea and states he has gained 22 lb (10 kg) from his baseline weight. He has had a fever, cough, and nausea for the past 2 days. He states he has been compliant with his medications but has been drinking a lot of canned soup. He is admitted to the cardiac intensive care unit.

SH: Denies smoking and illicit drug use. Has one beer a day.

Meds: Aspirin 81 mg once daily, carvedilol 6.25 mg twice daily, enalapril 5 mg twice daily, spironolactone 12.5 mg twice daily, digoxin 0.25 mg once daily, atorvastatin 20 mg once daily

VS: BP 106/54 mm Hg, pulse 112 beats/min and regular, respiratory rate 24 breaths/min, temperature 38.1°C (100.6°F), Wt 276 lb (125 kg), BMI 41.9 kg/m^2

Lungs: Decreased breath sounds and rales present bilaterally

CV: JVP is 18 cm above sternal angle. Tachycardic with regular rhythm, with normal S_1 and S_2; there is an S_3 and an S_4; a 4/6 systolic ejection murmur is present and heard best at the left lower sternal border; point of maximal impulse is displaced laterally

Abd: Tense, tender, and bowel sounds are present; 3+ pitting edema of extremities is observed

CXR: Bilateral pleural effusions and cardiomegaly

Echo: EF = 20% (0.20)

Pertinent labs: NT-proBNP 2210 pg/mL (ng/L; 261 pmol/L), K: 3.4 mEq/L (mmol/L), BUN 64 mg/dL (22.8 mmol/L), SCr 2.4 mg/dL (212 μmol/L), Mg 1.8 mEq/L (0.9 mmol/L), digoxin 1.4 ng/mL (mcg/L; 1.8 nmol/L); a pulmonary catheter is placed, revealing the following: PCWP 32 mm Hg (4.3 kPa); CI 1.9 L/min/m^2 (0.032 L/s/m^2)

What NYHA functional class, ACC/AHA stage, and hemodynamic subset is the patient currently in?

What are your initial treatment goals?

What pharmacologic interventions are appropriate at this time?

Identify a monitoring plan to assess for efficacy and toxicity of the recommended drug therapy.

Once symptoms are improved, how could the oral medication therapy for this patient's HF be further optimized?

Patient Care Process

Collect Information:

- Obtain a thorough history of prescription, nonprescription, and herbal medication use.
- Review the patient's lifestyle habits including salt and alcohol intake, tobacco product use, exercise routine.
- Gather recent history of symptoms of congestion and hypoperfusion, including weight gain, swelling in extremities, etc.

Assess the Information:

- Assess the severity and duration of the patient's symptoms of HF and hypoperfusion, including limitations in activity. Rule out potential exacerbating factors. See Clinical Presentation and Diagnosis of Chronic Heart Failure textbox and Tables 7–1, 7–3, and 7–4.
- Review available diagnostic information from the chest radiograph, ECG, and echocardiogram. Investigate the patient's underlying etiology of HF.

Develop a Care Plan:

- Determine whether additional adjustment or new therapy is needed to address patient's acute and chronic conditions.
- Develop a treatment plan to alleviate symptoms and maintain euvolemia with diuretics (Tables 7–6 and 7–7). Daily weights to assess fluid retention are recommended.
- Develop a medication regimen to slow the progression of HF with the use of neurohormonal blockers such as vasodilators (ACE inhibitors, ARBs, sacubitril/valsartan, or hydralazine/isosorbide dinitrate), β-blockers, and aldosterone receptor antagonists (Tables 7–6 and 7–7). Utilize digoxin if the patient remains symptomatic despite optimization of the therapies just described, and ivabradine in patients with HR of 70 beats/min or higher despite optimization of β-blocker.

Implement the Care Plan:

- Ensure the patient is at goal or maximally tolerated doses of vasodilator and β-blocker therapy (Table 7–6), or titrate to the next dosing level if possible.
- Educate the patient on lifestyle modifications such as salt restriction (maximum 2 g/day), fluid restriction if appropriate, limitation of alcohol, tobacco cessation, participation in a cardiac rehabilitation and exercise program, and proper immunizations such as the pneumococcal vaccine and yearly influenza vaccine.
- Stress the importance of adherence to the therapeutic regimen and lifestyle changes for maintenance of a compensated state and slowing of disease progression.

Follow-up: Monitor and Evaluate:

- Monitor patient, including appropriate hemodynamic monitoring for AHF (Table 7–8), for desired outcomes.
- Evaluate the patient for presence of adverse drug reactions, drug allergies, and drug interactions.
- Provide patient education with regard to disease state and drug therapy and reinforce medication adherence and self-monitoring for symptoms of HF (eg, daily weights). Emphasize follow-up with healthcare practitioners.
- Assess changes in echocardiographic parameters from a follow-up echocardiography, ideally performed 2 months after medication optimization. Has the LVEF risen to above 40% (0.40)?

dyspnea, oxygenation, fatigue, JVD, and other markers of congestion or distress.

- Monitor for adequate perfusion of vital organs through assessment of mental status, urine output, CrCl, liver function tests, serum lactate, a stable HR between 50 and 100 beats/min, and normal acid–base balance.
- Monitor changes in hemodynamic variables if available. PCWP should decrease in volume-overloaded patients to a goal of less than 18 mm Hg (2.4 kPa). CI should increase, with a goal to maintain above 2.2 L/min/m^2 (0.037 L/s/m^2).
- Closely monitor BP, renal function, and intravascular volume status while decreasing preload with diuretics and vasodilators.
- Ensure patients are euvolemic or nearly euvolemic prior to discharge.
- Because oral therapies can both improve symptoms and prolong survival, optimizing outpatient HF management is a priority when preparing a patient for hospital discharge. Ensure the patient's regimen includes an ACE inhibitor, ARB, or ARNI, β-blocker, a diuretic at an adequate dose to maintain euvolemia, and aldosterone antagonist if appropriate.

Abbreviations Introduced in This Chapter

ACC/AHA	American College of Cardiology/American Heart Association
ACE	Angiotensin-converting enzyme
AHF	Acute heart failure
ANP	Atrial natriuretic peptide
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
AT_1	Angiotensin type 1 receptor
AT_2	Angiotensin type 2 receptor
ATP	Adenosine triphosphate
ATTR	Transthyretin amyloidosis
BMI	Body mass index
BNP	B-type natriuretic peptide
BPM	Beats/min
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
CAD	Coronary artery disease
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CI	Cardiac index
CNS	Central nervous system

CO	Cardiac output
COX-2	Cyclooxygenase-2
CrCL	Creatinine clearance
CVP	Central venous pressure
CYP	Cytochrome P-450 isoenzyme
D1	Dopamine receptor type 1
DBP	Diastolic blood pressure
DPP-4	Dipeptidyl peptidase-4 inhibitors
ECG	Electrocardiogram
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ET-1	Endothelin-1
ET-A	Endothelin-A
ET-B	Endothelin-B
FDA	Food and Drug Administration
Gal-3	Galectin-3
GDMT	Guideline-directed medical therapies
GI	Gastrointestinal
HCN	Hyperpolarization-activated cyclic nucleotide-gated
HF	Heart failure
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFrecEF	Heart failure with recovered ejection fraction
HJR	Hepatojugular reflux
HR	Heart rate
hsTn	High-sensitivity troponin
IABC	Intra-aortic balloon counterpulsation
IABP	Intra-aortic balloon pump
IL	Interleukin
iNOS	Inducible nitric oxide synthetase
IV	Intravenous
JVD	Jugular venous distention
JVP	Jugular venous pressure
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVF	Left ventricular failure
MAP	Mean arterial pressure
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
MR-proADM	Midregional proadrenomedullin
MVO_2	Myocardial oxygen consumption
NGAL	Neutrophil gelatinase-associated lipocalin
NOAC	Non–vitamin K oral anticoagulant
NSAID	Nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal proBNP
NYHA FC	New York Heart Association Functional Classification
PAC	Pulmonary artery catheter
PAD	Pulmonary artery diastolic
PAP	Pulmonary arterial pressure
PAS	Pulmonary artery systolic
PCWP	Pulmonary capillary wedge pressure
PND	Paroxysmal nocturnal dyspnea
PVR	Pulmonary vascular resistance
RAAS	Renin-angiotensin-aldosterone system
RVF	Right ventricular failure
SBP	Systolic blood pressure
SCr	Serum creatinine
sGC	Soluble guanylate cyclase
SGLT2	Sodium glucose cotransporter-2
SNS	Sympathetic nervous system
SOB	Shortness of breath
sST2	Soluble suppression of tumorigenicity-2
SV	Stroke volume
SVR	Systemic vascular resistance
TGF-β	Transforming growth factor-β
TNF-α	Tumor necrosis factor-α
V_{1a}	Vasopressin type 1a
V_2	Vasopressin type 2
VAD	Ventricular assist device

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8

Stable Ischemic Heart Disease

Dejan Landup and Dawn Havrda

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Identify risk factors for the development of ischemic heart disease (IHD).
2. Differentiate between the pathophysiology of chronic stable angina and acute coronary syndromes (ACS).
3. Recognize symptoms and diagnostic criteria of IHD in a specific patient.
4. Compare and contrast the diagnostic criteria of IHD and ACS.
5. Identify treatment goals of stable ischemic heart disease (SIHD).
6. Identify appropriate lifestyle modifications and pharmacologic therapy to address each treatment goal.
7. Design an appropriate treatment regimen for the management of SIHD based on patient-specific information.
8. Formulate a monitoring plan to assess effectiveness and adverse effects of a SIHD drug regimen.

INTRODUCTION

Ischemic heart disease (IHD) is also called coronary heart disease (CHD) or coronary artery disease (CAD). The term *ischemic* refers to a decreased supply of oxygenated blood to the heart muscle. IHD is caused by stenosis, or narrowing, in one or more of the major coronary arteries that supply blood to the heart, most commonly by atherosclerotic plaques. Atherosclerotic plaques may impede coronary blood flow to the extent that cardiac tissue distal to the coronary artery narrowing is deprived of sufficient oxygen to meet oxygen demand. **KEY CONCEPT** IHD results from an imbalance between myocardial oxygen supply and oxygen demand (Figure 8–1). Common clinical manifestations of IHD include chronic stable angina and the acute coronary syndromes (ACS) of unstable angina (UA), non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).

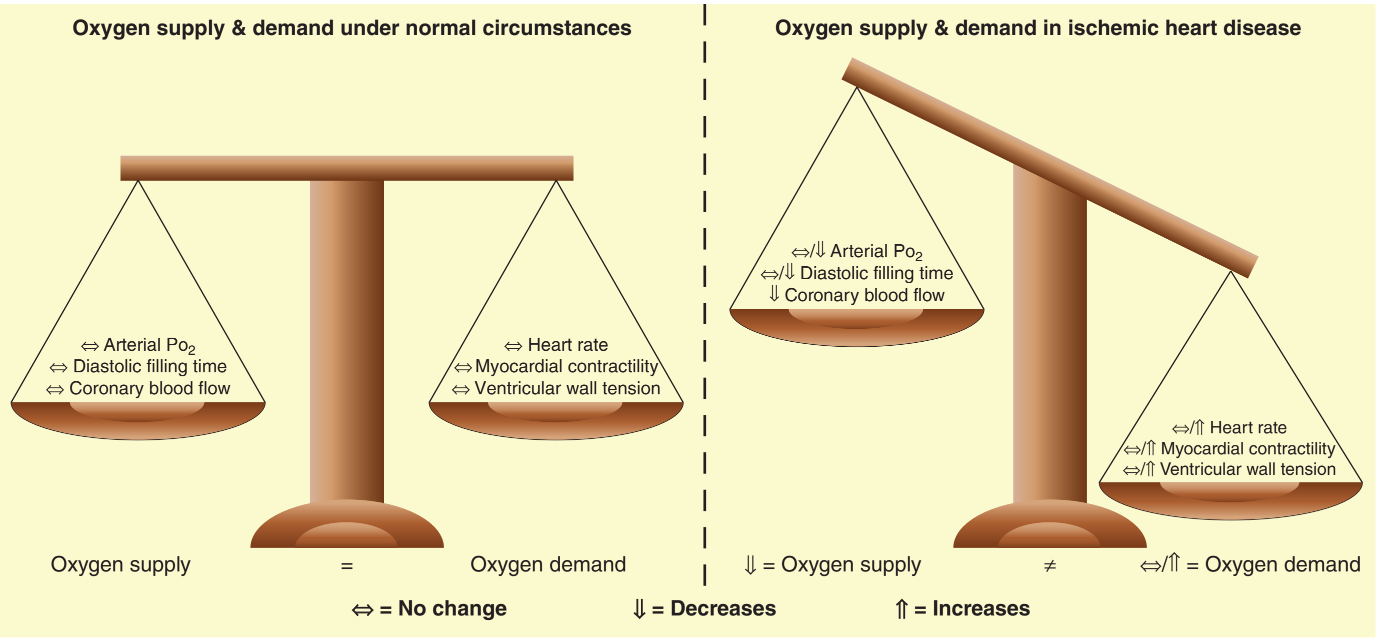
Angina pectoris, or simply angina, is the most common symptom of IHD. Angina is discomfort in the chest that occurs when the blood supply to the myocardium is compromised. Chronic stable angina is a chronic occurrence of chest discomfort due to transient myocardial ischemia with physical exertion or other conditions that increase myocardial oxygen demand. The primary focus of this chapter is management of stable ischemic heart disease (SIHD), the most common manifestation of which is chronic stable angina. However, some information is also provided related to ACS, given the overlap between the two disease states. The American College of Cardiology (ACC), the American Heart Association (AHA), and several other organizations have jointly published practice guidelines for the management of SIHD. Refer to these and related guidelines for further information.[1-3]

EPIDEMIOLOGY AND ETIOLOGY

IHD affects over 18 million Americans and is the leading cause of death for both men and women in the United States.[4] Incidence of IHD is higher in middle-aged men compared with women. However, the rate of IHD increases twofold to threefold in women after menopause. Chronic stable angina is the initial manifestation of IHD in about 50% of patients, whereas ACS is the first sign of IHD in other patients. Patients with SIHD experience considerable morbidity and frequently require hospitalization for chest pain and evaluation for potential ACS. In addition, SIHD negatively impacts health-related quality of life. Thus, in patients with SIHD, it is important to optimize pharmacotherapy to reduce symptoms, improve quality of life, slow disease progression, and prevent ACS.

Conditions Associated with Angina

Figure 8–2 shows the anatomy of the coronary arteries. The major epicardial coronary arteries are the left main, left anterior descending, left circumflex, and right coronary arteries. Atherosclerosis leading to obstructive lesions in one or more of the major coronary arteries or their principal branches is the major cause of angina. Vasospasm at the site of an atherosclerotic plaque may further constrict blood flow and contribute to angina. Less commonly, vasospasm in coronary arteries with no or minimal atherosclerotic disease can produce angina and even precipitate ACS. This uncommon form of angina is referred to as variant or Prinzmetal angina. Other nonatherosclerotic conditions that can cause angina-like symptoms are listed in Table 8–1.[1] It is important to differentiate the etiology of chest discomfort because treatment varies depending on the underlying disease process.



Oxygen supply & demand under normal circumstances
⇔ Arterial Po_2
⇔ Diastolic filling time
⇔ Coronary blood flow
⇔ Heart rate
⇔ Myocardial contractility
⇔ Ventricular wall tension
Oxygen supply
=
Oxygen demand
Oxygen supply & demand in ischemic heart disease
⇔/⇓ Arterial Po_2
⇔/⇓ Diastolic filling time
⇓ Coronary blood flow
⇔/⇑ Heart rate
⇔/⇑ Myocardial contractility
⇔/⇑ Ventricular wall tension
⇓ = Oxygen supply
≠
⇔/⇑ = Oxygen demand
⇔ = No change
⇓ = Decreases
⇑ = Increases

FIGURE 8–1. This illustration depicts the balance between myocardial oxygen supply and demand and various factors that affect each. It should be noted that diastolic filling time is not an independent predictor of myocardial oxygen supply per se but rather a determinant of coronary blood flow. On the left is myocardial oxygen supply and demand under normal circumstances. On the right is the mismatch between oxygen supply and demand in patients with IHD. In patients without IHD, coronary blood flow increases in response to increases in myocardial oxygen demand. However, in patients with IHD, coronary blood flow cannot sufficiently increase (and may decrease) in response to increased oxygen demand, resulting in angina. (IHD, ischemic heart disease; Po_2, partial pressure of oxygen.)

Risk Factors

Major risk factors that predispose an individual to IHD are listed in Table 8–2. Both modifiable and nonmodifiable risk factors may be present that increase the risk for development of IHD. Patients with multiple risk factors, particularly those with diabetes, are at greatest risk for IHD, experiencing fivefold to sevenfold higher risk compared to individuals without risk factors.[4] Optimization of modifiable risk factors can significantly reduce risk of myocardial infarction (MI).[1] Hypertension, diabetes, dyslipidemia, and cigarette smoking are associated with endothelial damage and dysfunction and contribute to development of atherosclerosis. Physical inactivity and obesity independently increase risk for IHD, in addition to predisposing individuals to hypertension, dyslipidemia, and diabetes. **KEY CONCEPT** Early detection and aggressive modification of risk factors are among the primary strategies for delaying IHD progression and preventing IHD-related events including death.

PATHOPHYSIOLOGY

Determinants of myocardial oxygen supply and demand are shown in Figure 8–1. Increases in heart rate, cardiac contractility, and left ventricular wall tension increase the rate of myocardial oxygen consumption (MVO_2). Ventricular wall tension is a function of blood pressure (BP), systemic vascular resistance, left ventricular end-diastolic volume, and ventricular wall thickness. Physical exertion increases MVO_2 and commonly precipitates symptoms of angina in patients with significant coronary atherosclerosis.

Reductions in coronary blood flow (secondary to atherosclerotic plaques, vasospasm, or thrombus formation) and arterial oxygen content (secondary to hypoxia) decrease myocardial oxygen supply. Because the coronary arteries fill during diastole, decreases in diastolic filling time (eg, tachycardia) can also reduce coronary perfusion and myocardial oxygen supply. Anemia, carbon monoxide poisoning, and cyanotic congenital heart disease are examples of conditions that can lead to diminished myocardial oxygen delivery and precipitate angina in the face of adequate coronary perfusion.

Coronary Atherosclerosis

The normal arterial wall is illustrated in panel A of Figure 8–3. The intima consists of a layer of endothelial cells that line the lumen of the artery and form a selective barrier between the vessel wall and blood contents. Vascular smooth muscle cells are found in the media. The vascular adventitia comprises the artery's outer layer. Atherosclerotic lesions form in the subendothelial space in the intimal layer.

Endothelial damage and dysfunction, commonly caused by hypertension, diabetes, and smoking, allow low-density lipoprotein (LDL) cholesterol and inflammatory cells (eg, monocytes and T lymphocytes) to migrate from the plasma to the subendothelial space, as illustrated in Figure 13–4 in Chapter 13, "Dyslipidemia." The process begins by monocyte-derived macrophages ingesting lipoproteins to form foam cells. Macrophages also secrete growth factors that promote smooth muscle cell migration from the media to the intima. The result is development of early atherosclerosis in the form of a fatty streak consisting of lipid-laden macrophages and smooth muscle cells.

The fatty streak enlarges as foam cells, smooth muscle cells, and necrotic debris accumulate in the subendothelial space. A collagen matrix forms a fibrous cap that covers the lipid core of the lesion to establish an atherosclerotic plaque. The atherosclerotic

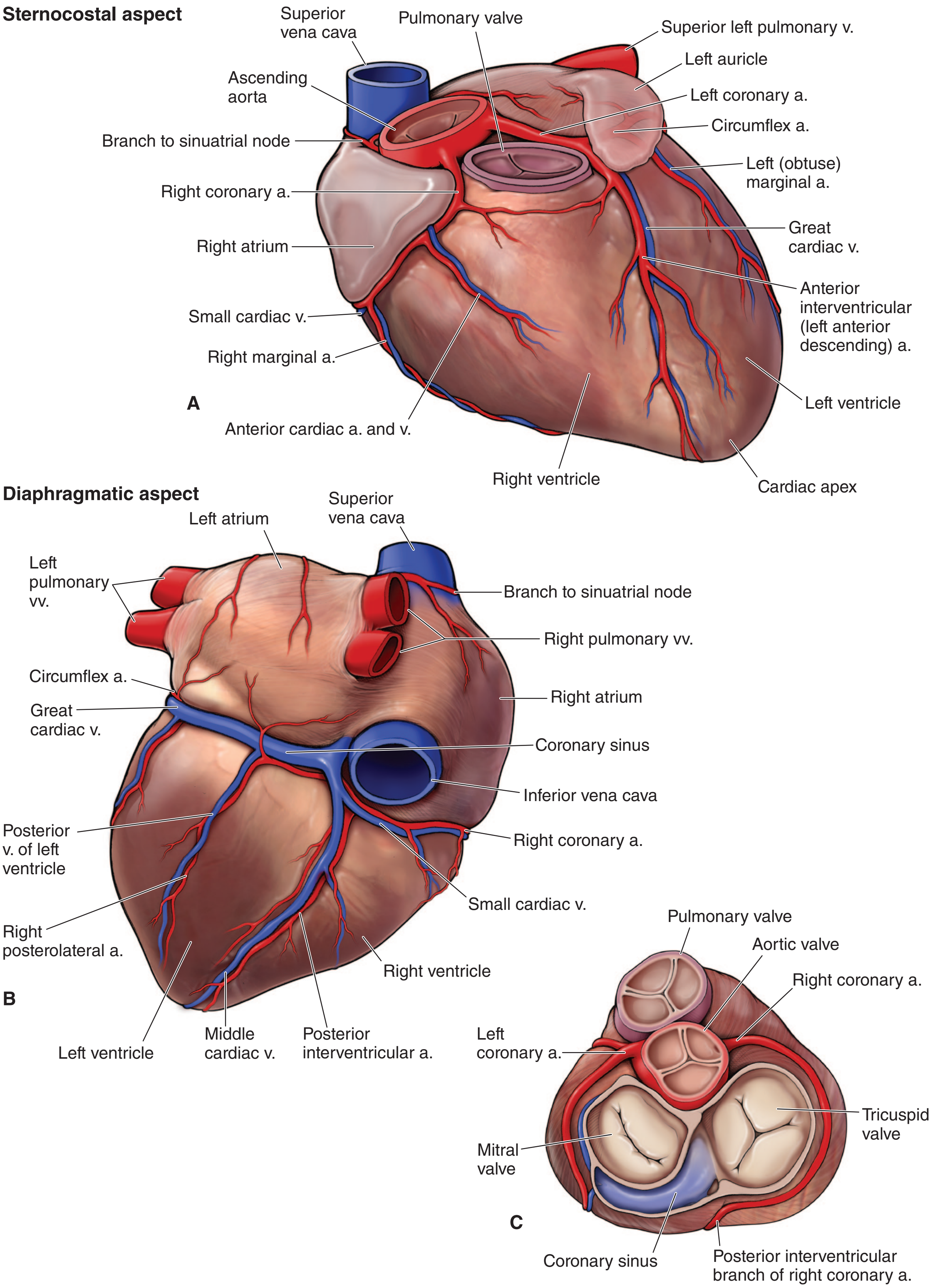

Sternocostal aspect
Superior vena cava
Pulmonary valve
Superior left pulmonary v.
Left auricle
Ascending aorta
Left coronary a.
Circumflex a.
Branch to sinuatrial node
Left (obtuse) marginal a.
Right coronary a.
Great cardiac v.
Right atrium
Anterior interventricular (left anterior descending) a.
Small cardiac v.
Right marginal a.
Left ventricle
A
Anterior cardiac a. and v.
Right ventricle
Cardiac apex
Diaphragmatic aspect
Superior vena cava
Left atrium
Left pulmonary vv.
Branch to sinuatrial node
Right pulmonary vv.
Circumflex a.
Right atrium
Great cardiac v.
Coronary sinus
Inferior vena cava
Posterior v. of left ventricle
Right coronary a.
Small cardiac v.
Pulmonary valve
Right posterolateral a.
Aortic valve
Right ventricle
Right coronary a.
B
Left ventricle
Middle cardiac v.
Posterior interventricular a.
Left coronary a.
Tricuspid valve
Mitral valve
C
Coronary sinus
Posterior interventricular branch of right coronary a.

FIGURE 8–2. Coronary artery anatomy with sternocostal and diaphragmatic views. (a., artery; v., vein.) (Reproduced from Chapter 4. Heart. In: Morton DA, Foreman K, Albertine KH, eds. The Big Picture: Gross Anatomy. New York, NY: McGraw-Hill; 2011. http://accesspharmacy.mhmedical.com/content.aspx?bookid=381&sectionid=40140010, with permission.)

Table 8–1

Nonatherosclerotic Conditions That Can Cause Angina-Like Symptoms[1]

Organ System	Condition
Cardiac	**Aortic dissection**, **aortic stenosis**, coronary artery vasospasm, **pericarditis**, **valvular heart disease**, severe uncontrolled hypertension
Noncardiac	Anemia, anxiety disorders, carbon monoxide poisoning, chest wall trauma, cocaine use, esophageal reflux or spasm, peptic ulcer disease, **pleuritis**, pneumonia, **pneumothorax**, **pulmonary embolus**, **pulmonary hypertension**, **thyrotoxicosis**

plaque may progress until it protrudes into the artery lumen and impedes blood flow. When the plaque occludes 70% or more of a major coronary artery or 50% or more of the left main coronary artery, the patient may experience angina during activities that increase myocardial oxygen demand.

Compared with men, women with angina are more likely to present with microvascular disease.[5] Microvascular angina, also called cardiac syndrome X, refers to disease of the smaller coronary vessels causing typical angina in the absence of obstructive CAD of the epicardial arteries. Endothelial dysfunction and reduced smooth muscle relaxation, resulting in reduced vasodilation and enhanced vasoconstriction, are proposed to contribute to microvascular disease.

Stable Versus Unstable Atherosclerotic Plaques

The hallmark feature in the pathophysiology of SIHD is an established atherosclerotic plaque in one or more of the major coronary arteries that impedes coronary blood flow such that myocardial oxygen supply can no longer meet myocardial oxygen demand. In contrast, the hallmark feature in the pathophysiology of ACS is atherosclerotic plaque rupture with subsequent thrombus formation. Plaque rupture refers to fissuring of the fibrous cap and exposure of the plaque contents to elements in the blood. Plaque composition, rather than the degree of coronary stenosis, determines the stability of the plaque and the likelihood of rupture and ACS. As depicted in Figure 8–3B, a stable lesion characteristic of SIHD consists of a small lipid core surrounded by a thick fibrous cap that protects the lesion from the shear stress of blood flow. In contrast, an unstable plaque consists of a thin, weak cap covering a large lipid-rich core that renders the plaque vulnerable to rupture (Figure 8–3C). Transformation of a stable plaque into an unstable plaque involves degradation of the fibrous cap by substances released from macrophages and other inflammatory cells. Following plaque rupture, platelets adhere to the site of rupture (Figure 8–3D), aggregate (Figure 8–3E), and generate thrombin leading to the development of a fibrin clot (Figure 8–3F). Coronary thrombi extend into the vessel lumen, where they partially or completely occlude blood flow, potentially resulting in UA or MI.

Unstable plaque often produces minimal occlusion of the coronary vessel, and the patient remains asymptomatic until the plaque ruptures. In fact, many ACS arise from vulnerable plaques that occlude less than 50% of the coronary lumen.[6]

Table 8–2

Major Risk Factors for Ischemic Heart Disease

Modifiable	Nonmodifiable
Cigarette smoking Dyslipidemia • Elevated LDL or total cholesterol • Reduced HDL cholesterol Diabetes mellitus Hypertension Physical inactivity Obesity (body mass index ≥ 30 kg/m^2) Low daily fruit and vegetable consumption Alcohol overconsumption	Age ≥ 45 years for men, age ≥ 55 years for women Gender (men and postmenopausal women) Family history of premature cardiovascular disease, defined as cardiovascular disease in a male first-degree relative (ie, father or brother) < 55 years or a female first-degree relative (ie, mother or sister) < 65 years

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Coronary Artery Vasospasm

Prinzmetal or variant angina results from spasm (or vasoconstriction) of a coronary artery in the absence of significant atherosclerosis. Variant angina usually occurs at rest, especially in the early morning hours. Although vasospasm is generally transient, it may persist long enough to cause myocardial ischemia and subsequent infarction. Patients with variant angina are typically younger than those with chronic stable angina and often do not possess the classic risk factors for IHD. The cause of variant angina is unclear but appears to involve vagal withdrawal, endothelial dysfunction, and paradoxical response to agents that normally cause vasodilation. Precipitants of variant angina include cigarette smoking, cocaine or amphetamine use, hyperventilation, and exposure to cold temperatures. Management of variant angina differs from that of classic angina, and it is important to distinguish between the two. However, patients with IHD may also present with vasospasm, and though the pathophysiology and management may differ, the two are not mutually exclusive.

CLINICAL PRESENTATION AND DIAGNOSIS

History

Evaluation of a patient with suspected IHD begins with a detailed history of symptoms. **KEY CONCEPT** The classic presentation of angina is described in the Clinical Presentation and Diagnosis text box. Patients may present with typical symptoms of angina, atypical symptoms of angina, or a combination of both. Identification of an atypical presentation is vital as some individuals with IHD may present without any of the classic symptoms of angina. Chronic stable angina should be distinguished from UA because the latter is associated with a greater risk for MI and death and requires hospitalization for more aggressive treatment. Because the pathophysiology of SIHD is due primarily to increases in oxygen demand rather than acute changes in oxygen supply, symptoms are typically reproducible when provoked by exertion, exercise, or stress. The exception may be a patient with coronary artery vasospasm, in whom symptoms may be more variable and unpredictable. In contrast to SIHD, ACS generally occurs in response to an acute decrease in coronary blood flow leading to inadequate oxygen supply. Consequently, ACS is marked by prolonged symptoms, often occurring at rest, or an escalation in the frequency or severity of angina over a short period of time. Presentation of UA is described in Table 8–3.[7]

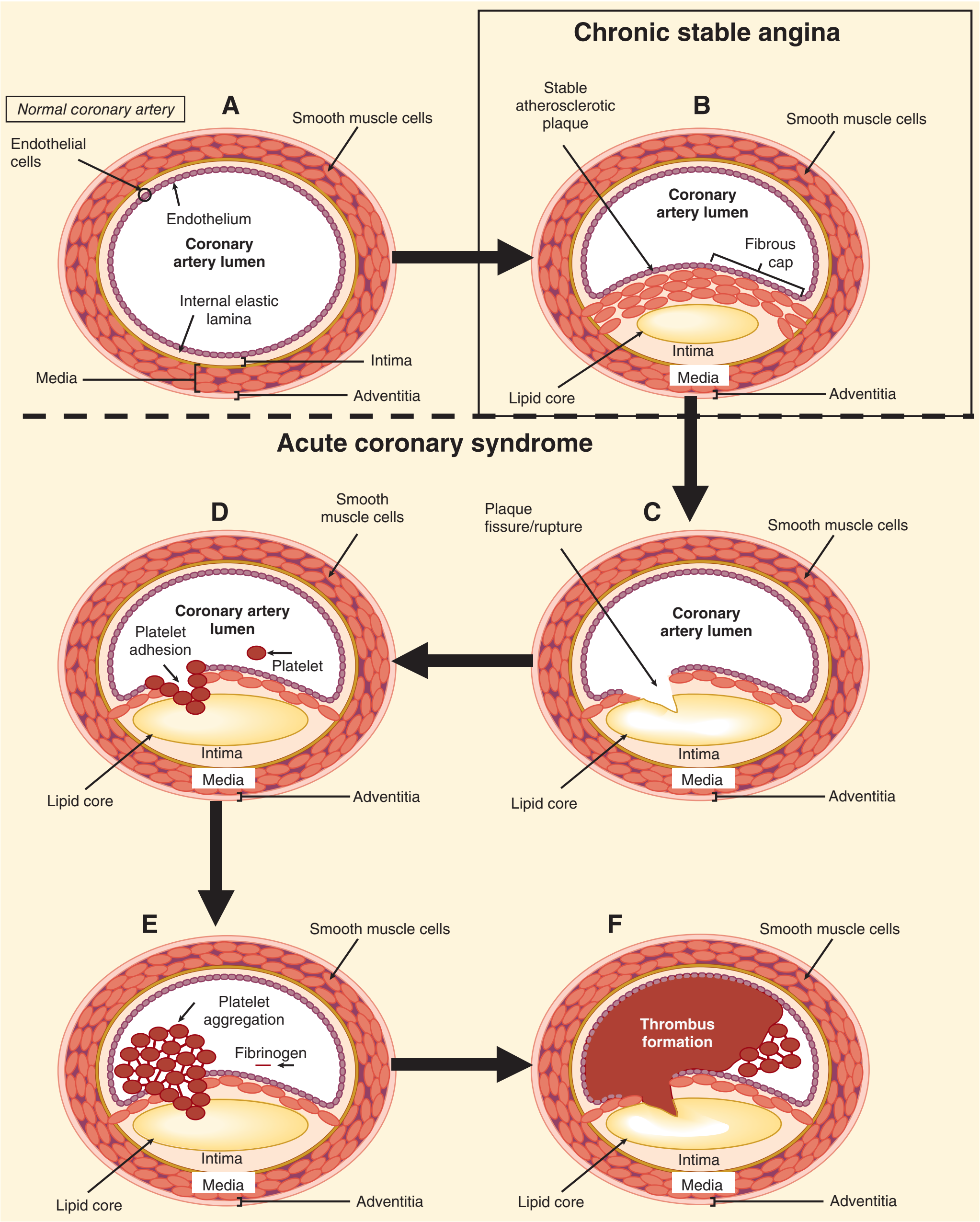

Chronic stable angina
Normal coronary artery
A
Smooth muscle cells
Endothelial cells
Endothelium
Coronary artery lumen
Internal elastic lamina
Media
Intima
Adventitia
Stable atherosclerotic plaque
B
Smooth muscle cells
Coronary artery lumen
Fibrous cap
Intima
Media
Lipid core
Adventitia
Acute coronary syndrome
D
Smooth muscle cells
Coronary artery lumen
Platelet adhesion
Platelet
Intima
Media
Lipid core
Adventitia
Plaque fissure/rupture
C
Smooth muscle cells
Coronary artery lumen
Intima
Media
Lipid core
Adventitia
E
Smooth muscle cells
Platelet aggregation
Fibrinogen
Intima
Media
Lipid core
Adventitia
F
Smooth muscle cells
Thrombus formation
Intima
Media
Lipid core
Adventitia

FIGURE 8–3. Pathophysiology of chronic stable angina versus acute coronary syndromes. **Panel A** depicts the cross-section of a normal coronary artery. **Panel B** depicts the cross-section of a coronary artery with a stable atherosclerotic plaque. Note that the lipid core is relatively small in size and the fibrous cap is made up of several layers of smooth muscle cells. **Panel C** depicts an unstable atherosclerotic plaque with a larger lipid core, and a thin fibrous cap composed of a single layer of smooth muscle cells with a fissure or rupture. **Panel D** depicts platelet adhesion in response to the fissured plaque. Platelet activation may ensue, leading to platelet aggregation as fibrinogen binds platelets to one another to form a mesh-like occlusion in the coronary lumen (**Panel E**). At this stage, patients may experience symptoms of acute coronary syndrome. If endogenous anticoagulant proteins fail to halt this process, platelet aggregation continues and fibrinogen is converted to fibrin, resulting in an occlusive thrombus (**Panel F**).

Table 8–3

Presentations of Acute Coronary Syndromes[7]

- Angina at rest that is prolonged in duration, usually lasting 10 minutes or more
- Angina of recent onset that markedly limits usual activity
- Angina that increases in severity (ie, by Canadian Cardiovascular Society Classification System Class of one level or greater [Table 8–4]), frequency, or duration, or that occurs with less provocation over a short time period (ie, within 2 months)

Clinical Presentation and Diagnosis of Ischemic Heart Disease

General

- Patients with SIHD will generally be in no acute distress. In patients presenting in acute distress, the clinician should be suspicious of ACS.

Symptoms of Angina Pectoris

- The five components used to characterize chest pain are quality, location, duration, provoking factors, and mitigating factors.
- Patients typically describe pain as a sensation of pressure, heaviness, tightness, or squeezing in the anterior chest area. Sharp pain and pain reproducible by palpation are not typical symptoms of angina.
- Pain may radiate to the neck, jaw, shoulder, back, or arm.
- Pain may be accompanied by dyspnea, nausea, vomiting, or **diaphoresis**.
- Pain typically persists for several minutes.
- Symptoms are often provoked by exertion (eg, walking, climbing stairs) or emotional stress and relieved within minutes by rest or sublingual nitroglycerin. Other precipitating factors include exposure to cold temperatures and heavy meals. Pain that occurs at rest (without provocation) or that is prolonged and unrelieved by sublingual nitroglycerin is indicative of ACS.
- Some patients, most commonly women, the elderly, and patients with diabetes, may present with atypical symptoms including indigestion, gastric fullness, back pain, and shortness of breath. Patients with diabetes and the elderly may experience associated symptoms, such as dyspnea, diaphoresis, nausea, fatigue, and dizziness, without having any of the classic angina symptoms.
- In some cases, "silent ischemia" occurs in which patients are asymptomatic.

Signs

- Findings on physical examination are often normal with SIHD. However, during episodes of ischemia, patients may present with abnormal heart sounds, such as paradoxical splitting of the second heart sound, a third heart sound, or a loud fourth heart sound.

Laboratory Tests

- Cardiac troponin (troponin I or troponin T) is the most sensitive biomarker to detect myocardial damage and is elevated in MI but typically normal in SIHD and UA.
- Hemoglobin, fasting glucose, and fasting lipid profile should be determined for assessing cardiovascular risk factors and establishing the differential diagnosis.

Other Diagnostic Tests

- A 12-lead electrocardiogram (ECG) recorded during rest is often normal in patients with SIHD in the absence of active ischemia. Significant Q waves may indicate prior MI. ST-segment changes (ST-segment depression or elevation) or T-wave inversion in two or more contiguous leads during symptoms of angina support the diagnosis of IHD. ST-segment depression or T-wave inversion may be observed in chronic stable angina, UA, and NSTEMI, whereas ST-segment elevation occurs with STEMI and Prinzmetal (variant) angina.
- Treadmill or bicycle exercise ECG, commonly referred to as a "stress test," is considered positive for IHD if the ECG shows at least a 1-mm deviation of the ST segment (depression or elevation).
- Wall motion abnormalities or left ventricular dilation with stress echocardiography or cardiac magnetic resonance (MR) (exercise or pharmacological) are indicative of IHD.
- Perfusion abnormalities can be detected by stress myocardial perfusion imaging using either radionuclides technetium-99m sestamibi or thallium-201 or cardiac MR (with or without late gadolinium enhancement).
- Coronary angiography detects the location and degree of coronary atherosclerosis and is used to evaluate the potential benefit from revascularization procedures. Stenosis of at least 70% of the diameter of at least one of the major epicardial arteries (50% or greater for the left main coronary artery) on coronary angiography is indicative of significant IHD.
- Coronary angiography may be normal with microvascular angina.

Canadian Cardiovascular Society Classification System

The Canadian Cardiovascular Society Classification System (Table 8–4) is commonly used to assess the degree of disability resulting from IHD.[8] Patients are categorized into one of four classes depending on the extent of activity that produces angina. Grouping patients according to this or a similar method is commonly used to assess changes in IHD severity over time and the effectiveness of pharmacologic therapy.

Table 8–4

Canadian Cardiovascular Society Classification System of Angina[8]

Class	Description
I	Able to perform ordinary physical activity (eg, walking, climbing stairs) without symptoms. Strenuous, rapid, or prolonged exertion causes symptoms.
II	Symptoms slightly limit ordinary physical activity. Walking rapidly or for more than two blocks, climbing stairs rapidly, or climbing more than one flight of stairs causes symptoms.
III	Symptoms markedly limit ordinary physical activity. Walking less than two blocks or climbing one flight of stairs causes symptoms.
IV	Angina may occur at rest. Any physical activity causes symptoms.

Physical Findings and Laboratory Analysis

A thorough medical history, physical examination, and laboratory analysis are necessary to ascertain cardiovascular risk factors and to exclude nonischemic and noncardiac conditions that could mimic angina-like symptoms. Laboratory analyses should assess for glycemic control (ie, fasting glucose, hemoglobin A_{1c}), fasting lipids, hemoglobin, and organ function (ie, blood urea nitrogen, creatinine, liver function tests, thyroid function tests). For patients with ACS, serial measurements of cardiac troponin (usually 2–3 measurements over a period of 3–12 hours) are performed to exclude the diagnosis of an acute MI. Cardiac findings on the physical examination are often normal in patients with SIHD. However, findings such as carotid bruits, abdominal and/or renal bruits, or abnormal peripheral pulses would indicate atherosclerosis in other vessel systems and raise the suspicion for IHD.

Diagnostic Tests

A resting 12-lead ECG is indicated in all patients with new or worsening symptoms of ischemia. Patients with characteristic chest discomfort, accompanied by ST-segment elevation in two or more contiguous leads, or a new left bundle branch block are often diagnosed with MI (STEMI) and are at the highest risk of death. Consequently, STEMI is treated as a medical emergency. For patients with ACS, cardiac troponin is measured serially to distinguish between MI (elevated cardiac troponin) and either UA or noncardiac causes of chest discomfort (normal cardiac troponin).

"Stress" testing with either exercise or pharmacologic agents increases myocardial oxygen demand and is commonly used to evaluate the patient with suspected IHD. Approximately 50% of patients with IHD who have a normal ECG at rest will develop ECG changes with exercise on a treadmill or bicycle ergometer. Dobutamine is a common pharmacologic agent administered as an intravenous (IV) infusion to patients who are unable to exercise. Dobutamine increases oxygen demand by stimulating the β_1-receptor, increasing heart rate and contractility. Echocardiography is commonly performed along with exercise or dobutamine to identify stress-induced wall motion abnormalities of the left ventricle indicative of IHD.

Exercise or pharmacologic agents are also commonly combined with radionuclide myocardial perfusion imaging (nuclear imaging studies) or cardiac MR to detect IHD. An IV radioactive tracer is administered and accumulates in normal myocytes in proportion to coronary blood flow. Adenosine, dipyridamole, and regadenoson are coronary vasodilators that increase coronary blood flow in healthy arteries but not in atherosclerotic vessels. Radionuclide myocardial perfusion imaging is performed at rest and following exercise or pharmacologic stressor to detect perfusion defects indicative of IHD. Similar to other myocardial perfusion imaging, stress cardiac MR can detect wall motion abnormalities as well as perfusion defects, the latter often performed using late gadolinium enhancement, to determine the extent and severity of myocardial scarring that may be present.

Coronary artery calcium scoring via computed tomography (CT) may be performed as a noninvasive means to assess for IHD. Calcium deposits within the atherosclerotic coronary arteries are detected on CT, a calcium score is calculated, and risk for IHD-related events is estimated.

Coronary angiography (also referred to as a cardiac catheterization or "cardiac cath") is indicated when stress testing results are either abnormal or inconclusive, symptoms of angina are poorly controlled, or in patients for whom the clinical suspicion of IHD remains high despite a normal stress test result. Angiography involves catheter insertion into either the femoral or radial artery with advancement of the catheter into the ascending aorta near the coronary ostia. Contrast medium is injected through the catheter into the coronary arteries, and fluoroscopy is performed to visualize the coronary anatomy and detect IHD. The decision to establish the diagnosis of IHD via stress testing, coronary angiography, or both is often individualized for each patient based on several factors including baseline assessment of IHD risk (eg, pretest probability), sensitivity and specificity of the diagnostic test, results of previous diagnostic tests, and risk for complications (eg, contrast nephropathy).

TREATMENT

Desired Outcomes

Once a patient is diagnosed with IHD, the clinician should provide counseling on lifestyle modifications, institute appropriate pharmacologic therapy, and evaluate the need for revascularization. Optimal medical therapy is essential for managing patients with SIHD. **KEY CONCEPT** The major goals for the treatment of SIHD are to:

- Prevent ACS and death
- Alleviate acute symptoms of angina
- Prevent recurrent symptoms of angina
- Prevent progression of the disease
- Reduce complications of IHD
- Avoid or minimize adverse treatment effects

The treatment approach to address these goals is illustrated in Figure 8–4.

General Approach to Treatment

Primary strategies for preventing ACS and death (eg, primary or secondary prevention) are to:

- Aggressively modify cardiovascular risk factors
- Slow the progression of coronary atherosclerosis
- Stabilize existing atherosclerotic plaques

The treatment algorithm in Figure 8–5 summarizes the appropriate management of IHD. Risk factor modification is accomplished through lifestyle changes and pharmacologic therapy. **KEY CONCEPT** Both 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG-CoA reductase inhibitors or statins) and angiotensin-converting enzyme (ACE) inhibitors possess vasculoprotective effects (eg, anti-inflammatory effects, antiplatelet effects, improvement in endothelial function, and/or improvement in arterial compliance and tone). Together with aspirin,

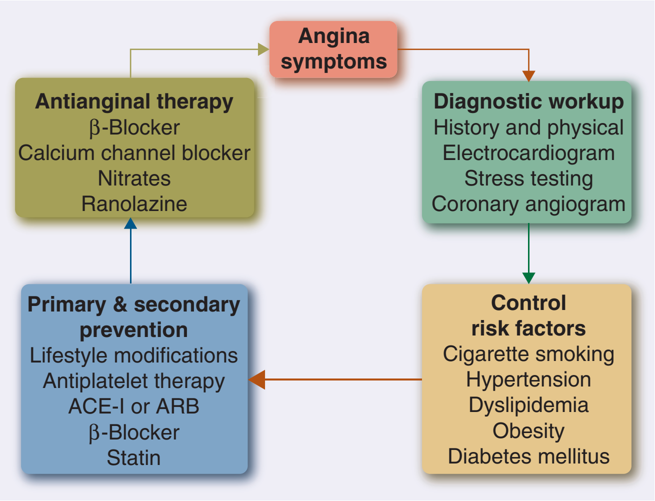


FIGURE 8–4. General treatment strategies for angina follow in clockwise fashion from the top center. (ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.)

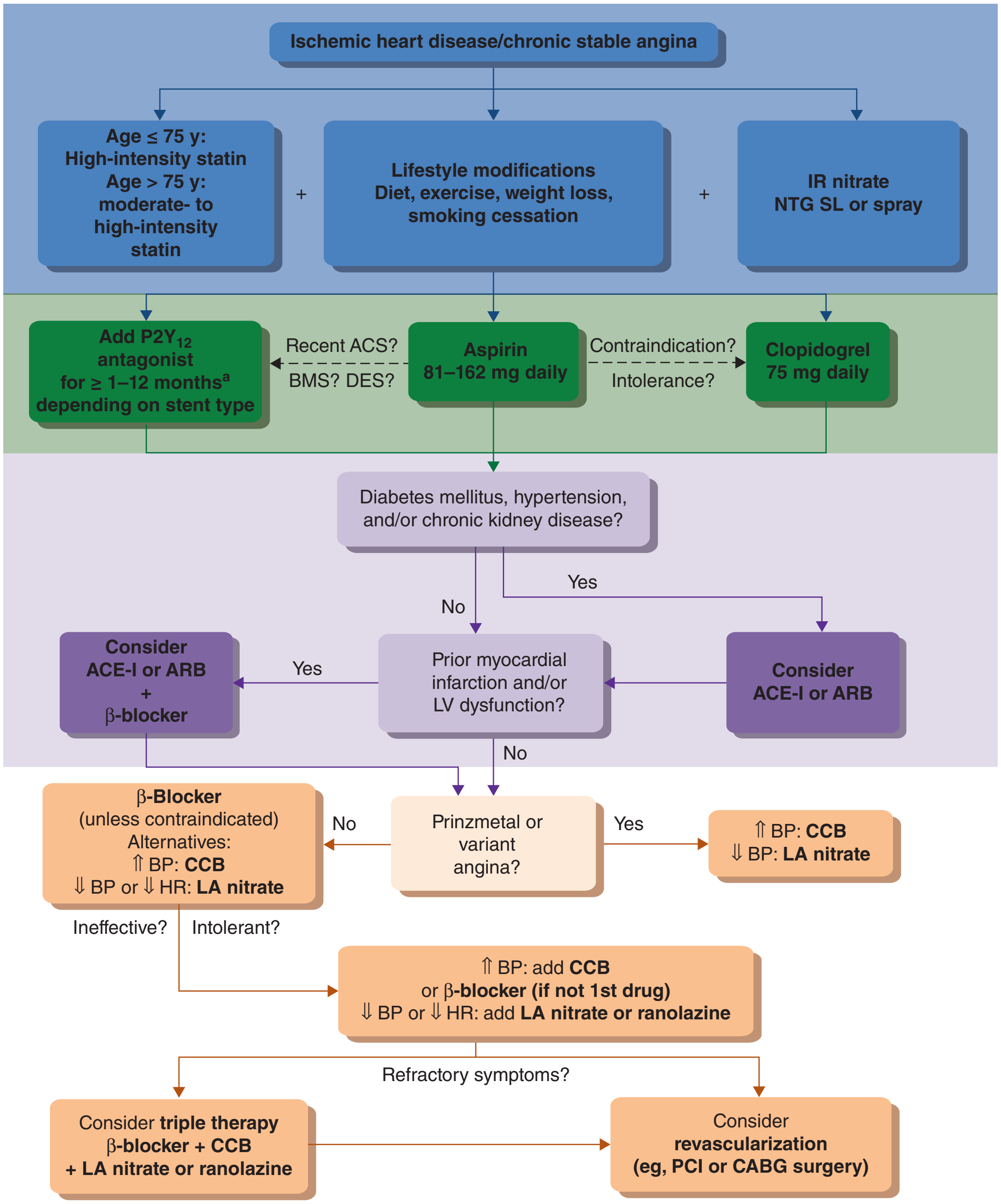

Ischemic heart disease/chronic stable angina
Age ≤ 75 y: High-intensity statin Age > 75 y: moderate- to high-intensity statin
+
Lifestyle modifications Diet, exercise, weight loss, smoking cessation
+
IR nitrate NTG SL or spray
Add P2Y12 antagonist for ≥ 1–12 months^a depending on stent type
Recent ACS? BMS? DES?
Aspirin 81–162 mg daily
Contraindication? Intolerance?
Clopidogrel 75 mg daily
Diabetes mellitus, hypertension, and/or chronic kidney disease?
Yes
No
Consider ACE-I or ARB + β-blocker
Yes
Prior myocardial infarction and/or LV dysfunction?
Consider ACE-I or ARB
No
β-Blocker (unless contraindicated) Alternatives: ⇑ BP: CCB ⇓ BP or ⇓ HR: LA nitrate
No
Prinzmetal or variant angina?
Yes
⇑ BP: CCB ⇓ BP: LA nitrate
Ineffective?
Intolerant?
⇑ BP: add CCB or β-blocker (if not 1st drug) ⇓ BP or ⇓ HR: add LA nitrate or ranolazine
Refractory symptoms?
Consider triple therapy β-blocker + CCB + LA nitrate or ranolazine
Consider revascularization (eg, PCI or CABG surgery)

FIGURE 8–5. Treatment algorithm for ischemic heart disease. It begins at the top (blue section), which suggests risk factor modifications as the first treatment modality. Moving down to the green section, appropriate antiplatelet therapy is selected. The purple section identifies patients at high risk for major adverse cardiac events (MACE) and suggests appropriate drug therapy to decrease cardiovascular risk. The orange section at the bottom recommends appropriate antianginal therapy. [a]The minimum duration of $P2Y_{12}$ inhibitors in combination with aspirin (dual antiplatelet therapy) following intracoronary stent placement is as follows: at least 1 month for BMSs and at least 6 months for DESs for patients with stable ischemic heart disease, and at least 12 months in patients with stents placed for ACS regardless of stent type. (ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMS, bare metal stent; BP, blood pressure; CABG, coronary artery bypass graft; CCB, calcium channel blocker; DES, drug-eluting stent; HR, heart rate; IR, immediate release; LA, long acting; LV, left ventricular; NTG, nitroglycerin; PCI, percutaneous coronary intervention; SL, sublingual.)

these drugs reduce the risk of acute coronary events and death in patients with SIHD. In select patients with IHD (following hospitalization for ACS ± percutaneous coronary intervention [PCI] and/or following intracoronary stent placement), dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ antagonist has also been shown to reduce ischemic events. Angiotensin receptor blockers (ARBs) may be used in patients who cannot tolerate ACE inhibitors because of side effects (eg, chronic cough). β-Blockers decrease morbidity and improve survival in patients who have suffered an MI, particularly in patients with concomitant heart failure with reduced ejection fraction (HFrEF).

The goal of therapies that alleviate and prevent angina is improving the balance between myocardial oxygen demand and supply. Drug treatment is primarily used to reduce oxygen

Patient Encounter Part 1

A 62-year-old woman with a history of hypertension, diabetes, and dyslipidemia presents to your clinic complaining of chest pain occurring several times in the past month. The pain is described as tightness in the anterior chest area and is accompanied by back pain, nausea, and shortness of breath. Occasionally, the pain extends down to her left arm. She first noticed the discomfort while walking up two flights of stairs. Since then, she experienced the same symptoms while exercising and carrying groceries from the store. In each instance, the pain resolved after 5 minutes of rest.

What information is suggestive of angina?

What tests would be beneficial in establishing a diagnosis?

What additional information do you need to create a treatment plan for this patient?

demand, whereas revascularization by PCI and coronary artery bypass graft (CABG) surgery effectively restore coronary blood flow, improving myocardial oxygen supply.

Adverse treatment effects can be averted by avoiding drug interactions and the use of drugs that may have unfavorable effects on comorbid diseases. Appropriate drug dosing and monitoring reduces the risk for adverse treatment effects. Drugs should be initiated in low doses, with careful uptitration as necessary to control symptoms of angina and cardiovascular risk factors.

Lifestyle Modifications

Lifestyle modifications (smoking cessation, dietary modifications, increased physical activity, and weight loss) reduce cardiovascular risk factors, slow the progression of IHD, and decrease the risk for SIHD-related complications. Cigarette smoking is one of the most preventable causes of SIHD and SIHD-related death. Smoking may also attenuate the antianginal effects of drug therapy. Clinicians should counsel patients and/or family members who smoke on the importance of smoking cessation at each encounter and offer referral to smoking cessation programs. There are several pharmacologic aids (transdermal nicotine replacement therapy, bupropion, and varenicline) for smoking cessation that are efficacious and safe in patients at risk for or with IHD.[9] Varenicline, a partial nicotine receptor agonist, and bupropion have been associated with worsening of preexisting depression and suicidal ideation. The drugs have been studied in smokers with and without psychiatric disorders, and no increase in neuropsychiatric adverse effects were found.[10] Weight loss, through lifestyle interventions of caloric restriction and increased physical activity, should be encouraged in patients who have a body mass index greater than 25 kg/m^2. Dietary counseling should be provided to all patients with newly diagnosed angina regardless of weight. The AHA recommends a diet that includes a variety of fruits, vegetables, whole grains, fish, nuts, and legumes. Processed meats, refined carbohydrates, and sweetened beverages should be minimized and *trans* fats should be avoided.[11] The addition of phytosterols (1–3 g/day) and/or soluble/viscous fiber (3.0–12.4 g/day) are effective in lowering LDL cholesterol.[12] Specific dietary recommendations for patients with IHD should include the following[1,11]:

- Limit cholesterol intake to less than 200 mg/day.
- Limit consumption of saturated fat to less than 7% and *trans* fatty acids to less than 1% of total calories.
- Limit daily sodium intake to less than 1500 mg for BP control.
- Limit alcohol consumption to one drink/day for women and one to two drinks/day for men unless otherwise contraindicated.

Exercise facilitates weight loss, BP reduction, and glycemic control. In addition, regular exercise in patients with SIHD improves functional capacity, reduces symptoms of angina, and reduces mortality.[1,13] Guidelines recommend moderate-intensity aerobic

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Hypertension, diagnosed 12 years ago; diabetes, diagnosed 6 years ago; dyslipidemia, diagnosed 6 years ago; osteoarthritis, diagnosed last year

FH: Father with CAD, died of MI at age 52 years; mother with CAD and heart failure diagnosed at age 60 years

SH: Active smoker, 30-year pack history; denies alcohol or illicit drug use; no regular exercise program

Meds: Aspirin 81 mg PO daily, chlorthalidone 25 mg PO daily, metoprolol extended-release 25 mg PO daily, metformin 1000 mg PO twice daily, simvastatin 20 mg PO daily, ibuprofen 600 mg PO twice daily

Allergies/intolerances (reaction): No known drug allergies nor intolerances

PE:

VS: BP 146/88 mm Hg, HR 80 beats/min, RR 18 breaths/min, T 37°C (98.6°F), Ht 5 ft 7 in (170 cm), Wt 230 lb (104.3 kg)

Cardiovascular: Regular rate and rhythm, normal S_1 and S_2, no S_3 or S_4; no murmurs, rubs, gallops; + carotid bruit

Lungs: Clear to auscultation and percussion

Abd: Nontender, nondistended, + bowel sounds

Ext: No clubbing, cyanosis, or edema

Labs: Fasting lipid profile: total cholesterol 200 mg/dL (5.17 mmol/L), HDL cholesterol 40 mg/dL (1.03 mmol/L), LDL cholesterol 134 mg/dL (3.47 mmol/L), triglycerides 130 mg/dL (1.47 mmol/L); fasting glucose 190 mg/dL (10.5 mmol/L); hemoglobin A_{1c} 8.4% (0.084; 68 mmol/mol Hb); other laboratory values within normal limits

Dobutamine stress echocardiography: Concentric left ventricular hypertrophy, left ventricular ejection fraction at rest 40% (0.4), regional wall motion abnormalities during peak exercise suggestive of ischemia

Identify the patient's risk factors for SIHD.

How might her current drug regimen adversely affect the patient's SIHD?

Does she appear to have any SIHD-related complications?

What therapeutic alternatives are available to manage her SIHD?

activity, such as brisk walking, ideally for at least 150 minutes per week (eg, 30–60 minutes at least 5 and preferably 7 days weekly) and reducing sedentary behaviors (low energy expenditure in a sitting or reclining posture).[1,11] Medically supervised cardiac rehabilitation programs are recommended for high-risk patients.

Interventional Approaches to Revascularization

▶ *Percutaneous Coronary Intervention*

For patients with SIHD, optimal medical therapy is equivalent to PCI in reducing major adverse cardiac events (MACE), which include death, nonfatal MI, and revascularization.[14] Therefore, medical therapy is preferred as the initial treatment strategy. However, when optimal medical therapy fails, symptoms are unstable, or extensive coronary atherosclerosis is present (eg, > 70% occlusion of coronary lumen), PCI is often performed to restore coronary blood flow and relieve symptoms. Several catheter-based interventions may be used during PCI, including:

- Percutaneous transluminal coronary angioplasty (PTCA)
- Intracoronary bare metal stent (BMS) placement
- Intracoronary drug-eluting stent (DES) placement
- Rotational atherectomy

During PCI, a catheter is advanced into the diseased coronary artery, as described for cardiac catheterization. If PTCA is performed, a balloon at the end of the catheter is inflated inside the artery at the site of the critical stenosis, compressing the atherosclerotic plaque from the coronary lumen and restoring normal myocardial blood flow. Most PCI procedures involve the placement of a stent, a small metal scaffold-like device similar in size and shape to the spring at the tip of a ballpoint pen, at the site of angioplasty. Either a BMS or a DES may be used. Drug-eluting stents are impregnated with low concentrations of an antiproliferative drug (paclitaxel, everolimus, sirolimus, or zotarolimus), which is released locally over a period of weeks to inhibit in-stent restenosis of the coronary artery after PCI. Compared to BMS, DESs have been associated with a significant reduction in all-cause mortality for patients with IHD.[15] Stents are thrombogenic, especially until they become endothelialized (covered in endothelial cells like a normal coronary artery). To reduce risk for in-stent thrombosis, MI, or death, DAPT (discussed later) is required until the stent becomes endothelialized. Lastly, rotational atherectomy may be performed wherein a special catheter is used to essentially cut away the atherosclerotic plaque, restoring coronary blood flow.

▶ *Coronary Artery Bypass Graft Surgery*

As an alternative to PCI, CABG surgery, or open-heart surgery, may be performed if the patient is found to have extensive coronary atherosclerosis (generally > 70% occlusion of three or more coronary arteries) or is refractory to optimal medical treatment. In the former case, evidence suggests that CABG surgery is associated with a reduction in both the need for revascularization and mortality compared with PCI, particularly in patients with diabetes.[16] During CABG surgery, veins from the leg (ie, saphenous veins) and/or arteries from the chest wall (ie, internal mammary arteries) or less commonly from the arm (ie, radial artery) or stomach (gastroepiploic artery) are harvested and used as conduits to restore coronary blood flow. A median sternotomy, in which an incision is made the length of the sternum followed by surgical division of the sternum with an oscillating saw, is commonly required to gain access to the thoracic cavity and expose the heart. As the "new" blood vessels are being engrafted, the patient is typically placed on cardiopulmonary bypass (ie, heart-lung machine) to maintain appropriate myocardial and systemic perfusion. Because of its extremely invasive nature, CABG surgery is generally reserved for patients with extensive IHD or as a treatment of last resort in patients with symptoms refractory to medical therapy.

Pharmacologic Therapy

▶ *Pharmacotherapy to Prevent Acute Coronary Syndromes and Death*

Control of Risk Factors

A major component of any SIHD treatment plan is control of modifiable risk factors, including dyslipidemia, hypertension, and diabetes. Treatment strategies for dyslipidemia, hypertension, and diabetes in the patient with IHD are summarized in the following paragraphs. Visit chapters in this textbook on the management of hypertension (see Chapter 6), dyslipidemia (see Chapter 13), and diabetes mellitus (see Chapter 44) for further information.

Because lipoprotein metabolism and the pathophysiology of atherosclerosis are closely linked, treatment of dyslipidemias is critical for both primary and secondary prevention of IHD-related cardiac events. In 2018, the ACC/AHA revised guidelines for the management of patients with dyslipidemia.[17] In addition to lifestyle modifications with diet and exercise, statins remain the foundation of pharmacologic therapy in patients with atherosclerotic cardiovascular disease (ASCVD). Ezetimibe, bile acid sequestrants, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors can be added to statin therapy in select cases. Recommendations for treatment of dyslipidemia in patients with IHD include:

- High-intensity or maximally tolerated statin in very high-risk patients with ASCVD, as defined by a history of multiple major ASCVD events or one major event and multiple high-risk conditions (see the 2018 ACC/AHA blood cholesterol guidelines for definitions of major ASCVD events and high-risk conditions).
- High-intensity statin in patients less than or equal to 75 years of age with ASCVD who are not considered very high risk. If high-intensity statin is not tolerated, a moderate-intensity statin can be used.
- Moderate- to high-intensity statin therapy for patients greater than 75 years of age with ASCVD who are not considered very high risk.
- Consideration for ezetimibe in individuals with clinical ASCVD on maximally tolerated statin therapy with LDL cholesterol greater than or equal to 70 mg/dL (1.81 mmol/L).
- Consideration for PCSK9 inhibitors in patients on maximally tolerated LDL-lowering therapy (maximally tolerated statin and ezetimibe) with LDL cholesterol greater than or equal to 70 mg/dL (1.81 mmol/L) or non-high-density lipoprotein (non-HDL) cholesterol greater than or equal to 100 mg/dL (2.59 mmol/L).

Hypertension is another major, modifiable risk factor for the development of IHD and related complications. Aggressive identification and management of hypertension are warranted in patients with SIHD to minimize the risk of MACE. In 2017, the ACC/AHA released updated guidelines for the management of hypertension in adults, with specific recommendations for patients with SIHD.[18] Patients with SIHD and a BP of 130/80 mm Hg or higher should be started on antihypertensive therapy to reduce BP to a target of less than 130/80 mm Hg. Selection of initial agent is guided by the presence of compelling indications (eg, chronic stable angina, HFrEF, previous MI). β-Blockers (except atenolol and β-blockers with intrinsic sympathomimetic activity), ACE inhibitors, or ARBs are all recommended as first-line therapy in these patients. For patients who remain hypertensive (BP > 130/80 mm Hg) despite treatment with a β-blocker, ACE inhibitor, or ARB, additional medications should be added to further reduce BP to target. Choice of agent is dependent on the presence of angina symptoms. For patients with uncontrolled hypertension with angina, addition of a dihydropyridine calcium channel blocker (CCB) is recommended. For patients with SIHD whose angina symptoms are controlled, addition of dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists (MRAs) may all be considered.

As with dyslipidemia and hypertension, diabetes is a significant, modifiable risk factor for IHD.[4] Cardiovascular disease remains the predominant cause of morbidity and mortality in patients with diabetes. Treatment guidelines now provide specific recommendations for patients with diabetes and cardiovascular disease with a focus on medications with a proven cardiovascular benefit.[19] Two classes of medications, sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, have shown to improve cardiovascular outcomes in patients with clinical ASCVD or at high risk for IHD. The SGLT2 inhibitors empagliflozin and canagliflozin have both shown to decrease MACE in patients with diabetes and ASCVD. GLP-1 receptor agonists, specifically liraglutide, semaglutide, and dulaglutide, have demonstrated a reduction in MACE in patients with diabetes and IHD. Given the cardiovascular endpoints seen in trials with SGLT2 inhibitors and GLP-1 receptor agonists, treatment guidelines were updated to include specific recommendations based on the presence or absence of ASCVD. For patients with diabetes in whom ASCVD predominates, consideration for GLP-1 receptor agonists with a proven cardiovascular benefit is recommended, independent of hemoglobin A_{1c}, either as an addition to metformin or single therapy in patients intolerant to or unable to take metformin. For patients who cannot tolerate GLP-1 receptor agonists or if GLP-1 receptor agonists cannot be used, substitution with an SGLT2 inhibitor with a proven cardiovascular benefit is recommended, provided there are no contraindications. Lastly, in select patients requiring further glycemic control, a combination of SGLT2 inhibitors and GLP-1 receptor agonists may be utilized.

Antiplatelet Agents Platelets play a major role in the pathophysiology of ACS. Thromboxane A_2 (TXA_2) is a potent platelet activator. Aspirin inhibits cyclooxygenase, an enzyme responsible for the production of TXA_2, thereby inhibiting platelet activation and aggregation. In patients with IHD, aspirin has been consistently shown to reduce risk of MACE, particularly MI.[20] **KEY CONCEPT** Antiplatelet therapy with aspirin should be considered for all patients with SIHD, particularly in patients with a history of MI, in the absence of contraindications. Aspirin doses of 75 to 162 mg daily are recommended in patients with or at risk for SIHD.[1,3,21] Daily doses of aspirin above 162 mg offer no additional benefit but increase bleeding risk. If aspirin is contraindicated (eg, aspirin allergy) or is not tolerated by the patient, an alternative antiplatelet agent such as clopidogrel should be considered.[1]

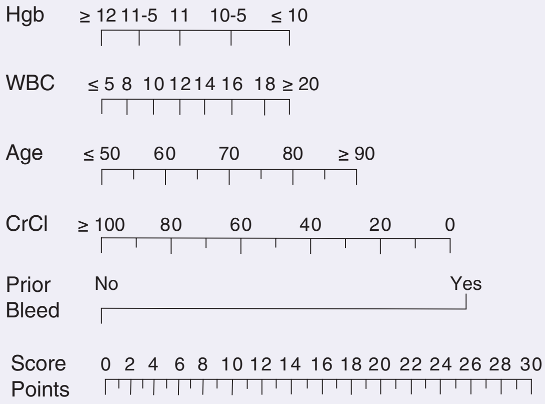
Binding of adenosine diphosphate to the $P2Y_{12}$ receptors on platelets activates glycoprotein IIb/IIIa receptors leading to platelet aggregation and thrombus formation. **KEY CONCEPT** Inhibition of the $P2Y_{12}$ receptor with either a thienopyridine (clopidogrel, prasugrel) or ticagrelor prevents platelet aggregation and is indicated in combination with aspirin in select patients with IHD. DAPT with aspirin and a $P2Y_{12}$ inhibitor is recommended following hospitalization for ACS and/or following PCI with stent placement to prevent ischemic events, although indications for specific drugs differ slightly.[3,7,22] Clopidogrel is a prodrug that is converted via a two-step process to its active thiol metabolite. The cytochrome P450 (CYP) 2C19 enzyme is involved in both steps of the biotransformation. Individuals with reduced CYP2C19 activity, either from inherited deficiencies of CYP2C19 or use of CYP2C19 inhibitors (eg, proton pump inhibitors), may produce less of the active thiol metabolite. These individuals are at increased risk for stent thrombosis and MACE during clopidogrel treatment compared to those with "normal" CYP2C19 activity.[23] Clopidogrel labeling now warns of reduced effectiveness in CYP2C19 poor metabolizers, who carry two dysfunctional *CYP2C19* gene alleles. The *CYP2C19*2* and *CYP2C19*3* alleles are the most common alleles leading to reduced CYP2C19 activity.

Prasugrel is a thienopyridine that also requires biotransformation to its active metabolite. However, unlike clopidogrel, CYP2C19 deficiency does not alter its effectiveness. Ticagrelor is a direct-acting $P2Y_{12}$ inhibitor that does not require biotransformation to exert its antiplatelet effects and is unaffected by CYP2C19 activity. Thus, prasugrel or ticagrelor may be suitable alternatives to clopidogrel when reduced CYP2C19 activity is suspected.

Antiproliferative drugs in DES reduce the risk of in-stent restenosis but delay endothelialization. Until endothelialization occurs, platelets are exposed to the foreign surface of the stent and can stimulate platelet adhesion, activation, aggregation, and eventual thrombus formation within the implanted stent resulting in acute ischemia. Thus, a longer period of DAPT is recommended in patients with SIHD treated with DES compared with BMS to prevent in-stent thrombosis. Following BMS implantation, patients with SIHD should be treated with DAPT for a minimum of 1 month compared to a minimum of 6 months following DES implantation.[3] In contrast to patients with SIHD, a longer duration of DAPT (minimum of 12 months) is recommended for patients who have had stent implantation in the setting of ACS, regardless of the type of stent implanted. Select patients with IHD who have not experienced a bleeding complication on DAPT and are not at high risk for bleeding (eg, prior bleeding on DAPT, coagulopathy, oral anticoagulant use) may be considered for "prolonged" or "extended" duration of DAPT (> 1 month in SIHD with BMS, > 6 months in SIHD with DES, > 12 months in ACS with either BMS or DES) to further reduce the risk of ischemic complications, including late in-stent thrombosis and spontaneous MI, but at the expense of an increased risk of bleeding. Conversely, patients who experience a significant bleeding complication are at high risk for bleeding or have a high risk of severe bleeding complications (eg, major intracranial surgery) may be considered for a shorter duration of DAPT (3 months for SIHD with DES, 6 months after ACS with stent implantation). Given the delicate balance between benefit and harm associated with prolonged DAPT following stent implantation, risk stratification tools may be useful to individualize the decision on DAPT duration by predicting patients who will derive benefit.[3,24] Several scoring tools were developed to guide clinicians in the decision-making process regarding the ideal DAPT duration in an individual patient. The "PRECISE-DAPT score" and the "DAPT score" (Table 8–5) can be used to complement clinical decision making, with the former calculated at the time of PCI with coronary stenting and the latter after completing 12 months of DAPT.[3,25] Utilization of these risk scores can help individualize therapy, determine the net clinical benefit of a specific DAPT duration, and minimize ischemic and bleeding complications.

Table 8–5

"PRECISE-DAPT" and "DAPT" Score Calculation to Guide Dual Antiplatelet Therapy (DAPT) Duration Following Stent Implantation[3,24,25]

<table>
<tr><th></th><th>PRECISE-DAPT Score</th><th>DAPT Score</th></tr>
<tr><td>When to use</td><td>During PCI with stent implantation</td><td>After 12 months of event-free DAPT</td></tr>
<tr><td>Calculation</td><td> </td><td><table>
<tr><th>Variable</th><th>Points</th></tr>
<tr><td>Age ≥ 75 years</td><td>−2</td></tr>
<tr><td>Age 65 to < 75 years</td><td>−1</td></tr>
<tr><td>Age < 65 years</td><td>0</td></tr>
<tr><td>Current cigarette smoker</td><td>1</td></tr>
<tr><td>Diabetes mellitus</td><td>1</td></tr>
<tr><td>MI at presentation</td><td>1</td></tr>
<tr><td>Prior PCI or MI</td><td>1</td></tr>
<tr><td>Stent diameter < 3 mm</td><td>1</td></tr>
<tr><td>Paclitaxel-eluting stent</td><td>1</td></tr>
<tr><td>Heart failure or LVEF < 30% (0.30)</td><td>2</td></tr>
<tr><td>PCI of saphenous vein graft</td><td>2</td></tr>
</table></td></tr>
<tr><td>Score range</td><td>0 to 100 points</td><td>−2 to 10 points</td></tr>
<tr><td>Clinical application</td><td>Score < 25 is associated with favorable benefit–risk ratio; consider standard/prolonged DAPT duration (12–24 months)
Score ≥ 25 is associated with unfavorable benefit–risk ratio; consider shorter DAPT duration (3–6 months)</td><td>Score ≥ 2 is associated with favorable benefit–risk ratio; consider prolonged DAPT duration
Score < 2 is associated with unfavorable benefit–risk ratio; prolonged DAPT generally not recommended</td></tr>
</table>

For the PRECISE-DAPT score calculation, use the nomogram by drawing a vertical line from the variable value down to the corresponding number of points for the given variable and add all the points together.

For the DAPT score calculation, add all of the positive values present and subtract value for age to obtain the total number of points.

CrCl, creatinine clearance (in mL/min; multiply by 60 if in units of mL/s); Hgb, hemoglobin (in g/dL; multiply values by 0.1 if in units of g/L or by 1.611 if in units of mmol/L); LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; WBC, white blood cell count.

Adapted with permission from Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force of dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39(3):213–260.

Clopidogrel, prasugrel, and ticagrelor are all indicated in combination with aspirin for at least 1 year in patients with ACS who undergo PCI.[3,7,22] Both clopidogrel and ticagrelor are also indicated in combination with aspirin in patients with NSTEMI who do not undergo PCI.[7] In patients with ACS, DAPT more effectively reduces the risk of death, MI, and stroke compared with aspirin alone even in patients who are managed medically (eg, in the absence of PCI).[26-28] Compared to clopidogrel, prasugrel and ticagrelor provide greater protection against cardiovascular events in ACS but increase risk for bleeding.[27,28] For more information regarding the use of DAPT in the setting of ACS, see Chapter 9.

Statins Statins are the preferred drugs to lower LDL cholesterol based on their potency and efficacy in preventing cardiac events. Studies in hundreds of thousands of patients with or at high risk for IHD demonstrate that lowering cholesterol with statins reduces the risk of MACE by 22% for each 39 mg/dL (1.01 mmol/L) of LDL cholesterol reduction.[29]

In addition to their LDL cholesterol-lowering effect, statins likely confer additional benefits in patients with SIHD.[30] Prompted by evidence that patients with "normal" LDL cholesterol derive benefit from statins, studies suggest statins modulate the following characteristics thought to contribute to the cardiovascular risk reduction seen with these drugs:

- Improve endothelial function and vascular tone by reducing smooth muscle cell proliferation and enhancing vasoactive response of the coronary arteries.
- Inhibit inflammation and oxidative stress by lowering C-reactive protein and other inflammatory mediators implicated in atherosclerosis.
- Improve atherosclerotic plaque stability via macrocalcification and increased fibrous cap thickness.
- Reduce platelet aggregation by decreasing platelet reactivity and TXA_2 synthesis.

KEY CONCEPT In summary, to control risk factors and prevent MACE, statin therapy should be considered in all patients with SIHD, particularly in those with elevated LDL cholesterol or diabetes. Statins are potent lipid-lowering agents, possess non–lipid-lowering effects that may provide additional benefit to patients with SIHD, and have been shown to reduce morbidity and mortality in patients with and at high risk for SIHD. Moreover, because statins improve outcomes in patients with SIHD and "normal"

LDL cholesterol, statins should be considered in all patients with SIHD, regardless of baseline LDL cholesterol.

ACE Inhibitors and Angiotensin Receptor Blockers Angiotensin II, a neurohormone produced primarily in the kidney, is a potent vasoconstrictor and stimulates the production of aldosterone. Together, angiotensin II and aldosterone increase BP and sodium and water retention (increasing ventricular wall tension), cause endothelial dysfunction, promote thrombus formation, and cause myocardial fibrosis.

ACE inhibitors decrease angiotensin II production and have consistently been shown to decrease morbidity and mortality in patients with HFrEF or history of MI.[31,32] In addition, there is evidence that ACE inhibitors reduce the risk of vascular events in patients with chronic stable angina or risk factors for SIHD.[33,34] In patients with vascular disease (including SIHD) or risk factors for vascular disease, both ramipril and perindopril reduced the risk of MACE by 20% or more in separate studies.

KEY CONCEPT In the absence of contraindications, ACE inhibitors should be considered in all patients with SIHD, particularly those individuals who also have hypertension, diabetes mellitus, chronic kidney disease, left ventricular dysfunction, history of MI, or any combination of these.[1] Additionally, ACE inhibitors should also be considered in patients at high risk for developing SIHD based on findings from the studies summarized above. ARBs may be used in patients with indications for ACE inhibitors but who cannot tolerate them due to side effects (eg, chronic cough). ARBs also antagonize the effects of angiotensin II. In one large trial, valsartan was as effective as captopril at reducing morbidity and mortality in post-MI patients.[31] However, there are far more data supporting the use of ACE inhibitors in SIHD. Therefore, ACE inhibitors are preferred over ARBs in patients with a history of MI, diabetes, chronic kidney disease, or left ventricular dysfunction. The ACE inhibitors and ARBs with indications for patients with or at risk for SIHD or IHD-related complications are listed in Table 8–6.

Table 8–6

Doses of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers Indicated in Ischemic Heart Disease (IHD)

Drug	Indications	Usual Dosage in IHD[a]
Angiotensin-Converting Enzyme Inhibitors		
Captopril	HTN, HF, post-MI, diabetic nephropathy	6.25–50 mg three times daily
Enalapril	HTN, HF	2.5–40 mg daily in one to two divided doses
Fosinopril	HTN, HF	10–80 mg daily in one to two divided doses
Lisinopril	HTN, HF, post-MI	2.5–40 mg daily
Perindopril	HTN, IHD	4–8 mg daily
Quinapril	HTN, HF, post-MI	5–20 mg twice daily
Ramipril	HTN, high risk for IHD, HF, post-MI	2.5–10 mg daily in one to two divided doses
Trandolapril	HTN, HF, post-MI	1–4 mg daily
Angiotensin Receptor Blockers		
Candesartan	HTN, HF	4–32 mg daily
Valsartan	HTN, HF, post-MI	40–320 mg daily in one to two divided doses
Telmisartan	HTN, high risk for IHD	20–80 mg daily

[a] Reduce initial dose and gradually titrate upward as tolerated in renal impairment.

HF, heart failure; HTN, hypertension; MI, myocardial infarction.

Side effects with ACE inhibitors and ARBs include hyperkalemia, deterioration in renal function, and angioedema. Serum potassium increases are secondary to aldosterone inhibition and are more likely in the presence of preexisting renal impairment, diabetes, or concomitant therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), potassium supplements, or potassium-sparing diuretics. Reductions in glomerular filtration may occur during ACE inhibitor or ARB initiation or uptitration due to inhibition of angiotensin II-mediated vasoconstriction of the efferent arteriole. This type of renal impairment is usually temporary and more common in patients with preexisting renal dysfunction or unilateral renal artery stenosis. Bilateral renal artery stenosis is a contraindication for ACE inhibitors and ARBs because of the risk for overt renal failure. Angioedema is a potentially life-threatening adverse effect that occurs in less than 1% of White patients but up to 8% of African Americans treated with ACE inhibitors. Angioedema may also occur with the administration of ARBs. Patients treated with ACE inhibitors may develop a chronic cough secondary to bradykinin accumulation. For patients who develop a persistent ACE inhibitor–induced cough or mild angioedema, substitution of an ARB for an ACE inhibitor may be appropriate. Both ACE inhibitors and ARBs can cause fetal injury and death and are contraindicated in pregnancy.

▶ *Nitroglycerin to Relieve Acute Symptoms*

Short-acting nitrates are first-line treatment to terminate acute episodes of angina. **KEY CONCEPT** Patients with SIHD should have sublingual nitroglycerin tablets or spray to relieve acute ischemic symptoms. Nitrates undergo biotransformation to nitric oxide. Nitric oxide activates smooth muscle guanylate cyclase, leading to increased intracellular concentrations of cyclic guanosine monophosphate (cGMP), release of calcium from the muscle cell, and ultimately, to smooth muscle relaxation. Nitrates primarily cause venodilation, leading to reductions in preload. The resultant decrease in ventricular volume and wall tension leads to a reduction in myocardial oxygen demand. In higher doses, nitrates cause arterial dilation and reduce afterload and BP. In addition to reducing oxygen demand, nitrates increase myocardial oxygen supply by dilating the epicardial coronary arteries and collateral vessels, as well as relieving vasospasm.

Short-acting nitrates are available in tablet and spray formulations for sublingual administration. Sublingual nitroglycerin tablets are well absorbed across the oral mucosa, produce an antianginal effect within 1 to 3 minutes, and are less expensive than the spray. However, the spray is preferred for patients who have difficulty opening the tablet container or produce insufficient saliva for rapid dissolution of sublingual tablets. At the onset of an angina attack, a 0.3 to 0.4 mg dose of nitroglycerin (tablet or spray) should be administered sublingually and repeated every 5 minutes up to three times or until symptoms resolve. Standing enhances venous pooling and may contribute to hypotension, dizziness, or light-headedness. Sublingual nitroglycerin may be used to prevent effort- or exertion-induced angina. In this case, the patient should use sublingual nitroglycerin 2 to 5 minutes prior to an activity known to cause angina, with the effects persisting for approximately 30 minutes. Isosorbide dinitrate, also available in sublingual form, has a longer half-life with antianginal effects lasting up to 2 hours. The use of short-acting nitrates alone, without concomitant long-acting antianginal therapy, may be acceptable for patients who experience angina symptoms once every few days. However, for patients with more frequent attacks, other antianginal therapies are recommended.

The use of nitrates within 24 to 48 hours of a phosphodiesterase type 5 inhibitor (eg, sildenafil, vardenafil, and tadalafil) is contraindicated. Phosphodiesterase degrades cGMP, which is responsible for the vasodilatory effects of nitrates. Concomitant use of nitrates and phosphodiesterase type 5 inhibitors enhances cGMP-mediated vasodilation and can result in serious hypotension, decreased coronary perfusion, and even death. All patients with SIHD should be prescribed sublingual nitroglycerin and educated regarding its use. Points to emphasize when counseling a patient on sublingual nitroglycerin use include:

- The seated position is generally preferred when using nitroglycerin because the drug may cause dizziness.
- Call 911 if symptoms are unimproved or worsen 5 minutes after the first dose.
- Keep nitroglycerin tablets in the original glass container and close the cap tightly after use.
- Nitroglycerin should not be stored in the same container as other medications because this may reduce nitroglycerin's effectiveness.
- Repeated use of nitroglycerin is not harmful or addictive and does not result in any long-term side effects. Patients should not hesitate to use nitroglycerin whenever needed.
- Nitroglycerin should not be used within 24 hours of taking sildenafil or vardenafil or within 48 hours of taking tadalafil because of the potential for life-threatening hypotension.

▶ *Pharmacotherapy to Prevent Recurrent Ischemic Symptoms*

The overall goal of antianginal therapy is to allow patients with IHD to resume normal activities without symptoms of angina and to experience minimal to no adverse drug effects. The drugs used to prevent ischemic symptoms are β-blockers, CCBs, nitrates, and ranolazine. These drugs exert their antianginal effects by improving the balance between myocardial oxygen supply and demand, with specific effects listed in Table 8–7. β-Blockers, CCBs, nitrates, and ranolazine decrease the frequency of angina and delay the onset of angina during exercise. However, there is no evidence that any of these agents prevent ACS or improve survival in patients with SIHD. Combination therapy with two or three antianginal drugs is often needed.

β-Blockers β-Blockers antagonize β_1- and β_2-adrenergic receptors in the heart, reducing heart rate and cardiac contractility, and decreasing myocardial oxygen demand. β-Blockers may also reduce oxygen demand by lowering BP and ventricular wall tension through inhibition of renin release from juxtaglomerular cells. By slowing heart rate, β-blockers prolong diastole, thus increasing coronary blood flow. However, β-blockers do not improve myocardial oxygen supply.

β-Blockers with intrinsic sympathomimetic activity (eg, acebutolol, pindolol, and penbutolol) have partial β-agonist effects and cause lesser reductions in heart rate at rest. As a result, β-blockers with intrinsic sympathomimetic activity may produce lesser reductions in myocardial oxygen demand and should be avoided in patients with SIHD. Other β-blockers appear equally effective at controlling symptoms of angina. The properties and recommended doses of various β-blockers used to prevent angina are summarized in Table 8–8. Frequency of dosing and drug cost should be taken into consideration when choosing a particular drug. Most β-blockers are available in inexpensive generic versions. β-Blockers should be initiated in doses at the lower end of the usual dosing range, with titration according to symptom and hemodynamic response. β-Blocker dose is commonly titrated to achieve the following:

- Resting heart rate between 55 and 60 beats/min.
- Maximum heart rate with exercise of 100 beats/min or less or 20 beats/min above the resting heart rate.

KEY CONCEPT In the absence of contraindications, β-blockers are the preferred initial therapy to prevent symptoms of angina in patients with SIHD because of their potential cardioprotective effects (eg, after MI and/or in patients with HFrEF). Long-term effects of β-blockers on morbidity and mortality in patients with SIHD are largely unknown. Yet, β-blockers decrease risk of reinfarction and death by 23% in patients who have suffered an MI.[35] However, controversy exists regarding the role of β-blockers as first-line therapy for all patients with SIHD. In an observational study, β-blockers did not lower risk of MACE in patients with SIHD or IHD risk factors, and in 2011, recommendations for using β-blockers for risk reduction in patients with SIHD or other vascular disease, in the absence of MI or heart failure, were downgraded.[36,37]

β-Blockers are contraindicated in patients with severe bradycardia (heart rate < 50 beats/min) or atrioventricular (AV) conduction defects in the absence of a pacemaker. β-Blockers should be used with particular caution in combination with other agents

Table 8–7

Effects of Antianginal Medications on Myocardial Oxygen Demand and Supply

	Oxygen Demand			
Antianginal Agent	Heart Rate	Wall Tension	Cardiac Contractility	Oxygen Supply
β-Blockers	↓	↔ or ↓	↓	↔
Calcium channel blockers				
Verapamil, diltiazem	↓	↓	↓	↑
Dihydropyridines	↔ or ↑	↓	↓	↑
Nitrates	↑	↓	↔	↑
Ranolazine[a]	↔	↓	↔	↔

[a]The exact mechanism of the anti-ischemic effects of ranolazine is not known.

↓ decreases; ↔, no change; ↑, increases.

Table 8–8

Properties and Dosing of β-Blockers in Ischemic Heart Disease

Drug	Receptor Affinity	Usual Dose Range	Dose Adjust in Hepatic Impairment	Dose Adjust in Renal Impairment
Atenolol	β_1-Selective	25–200 mg once daily	No	Yes
Betaxolol	β_1-Selective	5–20 mg once daily	No	Yes
Bisoprolol	β_1-Selective	2.5–10 mg once daily	Yes	Yes
Carvedilol	α_1, β_1, and β_2	3.125–25 mg twice daily	Avoid in severe impairment	No
Carvedilol phosphate	α_1, β_1, and β_2	10–80 mg once daily	Avoid in severe impairment	No
Labetalol	α_1, β_1, and β_2	100–400 mg twice daily	Yes	No
Metoprolol	β_1-Selective	50–200 mg twice daily (once daily for extended release)	Yes	No
Nadolol	β_1 and β_2	40–120 mg once daily	No	Yes
Nebivolol	β_1-Selective	5–10 mg once daily	Yes, avoid in severe impairment	Yes
Propranolol	β_1 and β_2	20–120 mg twice daily (60–240 mg once daily for long-acting formulation)	Yes	No
Timolol	β_1 and β_2	10–20 mg twice daily	Yes	Yes

that depress AV conduction (eg, digoxin, verapamil, and diltiazem) because of increased risk for bradycardia and heart block. Relative contraindications include asthma, bronchospastic disease, and severe depression. β_1-selective blockers are preferred in patients with asthma or chronic obstructive pulmonary disease. However, selectivity is dose dependent, and β_1-selective agents may induce bronchospasm in higher doses.

There are several precautions to consider with use of β-blockers in patients with diabetes or heart failure. All β-blockers may mask tachycardia and tremor (but not sweating) that commonly accompany episodes of hypoglycemia in diabetes. In addition, nonselective β-blockers may alter glucose metabolism and slow recovery from hypoglycemia in insulin-dependent diabetes. β_1-selective agents are preferred because they are less likely to prolong recovery from hypoglycemia. Importantly, β-blockers should not be avoided in patients with SIHD and diabetes, particularly in patients with a history of MI who are at high risk for recurrent cardiovascular events. β-blockers are indicated in patients with chronic HFrEF who are euvolemic due to their mortality benefit in this population. However, β-blockers are negative inotropes (ie, they decrease cardiac contractility), and may worsen symptoms of heart failure in patients with left ventricular dysfunction (ie, ejection fraction < 40% [0.40]). Initiation or titration should be delayed in patients with acute heart failure until symptoms have resolved. In particular, when used for the management of SIHD in a patient with heart failure, β-blockers should be initiated in very low doses with slow uptitration to avoid worsening heart failure symptoms.

Other potential adverse effects from β-blockers include fatigue, sleep disturbances, malaise, depression, and sexual dysfunction. Abrupt β-blocker withdrawal may increase the frequency and severity of angina, possibly because of increased receptor sensitivity to catecholamines after long-term β-blockade. If the decision is made to stop β-blocker therapy, the dose should be tapered over several days to weeks to avoid exacerbating angina.

Calcium Channel Blockers CCBs inhibit calcium entry into vascular smooth muscle and cardiac cells, resulting in the inhibition of the actin-myosin complex and contraction of the cell. Inhibition of calcium entry into the vascular smooth muscle cells leads to systemic vasodilation and reductions in afterload. Inhibition of calcium entry into the cardiac cells leads to reductions in cardiac contractility. Thus, CCBs reduce myocardial oxygen demand by lowering both wall tension (through reductions in afterload) and cardiac contractility. The nondihydropyridine CCBs, verapamil and diltiazem, slow sinoatrial and AV nodal conduction, decrease heart rate, and further decrease myocardial oxygen demand. Because of their negative chronotropic effects, verapamil and diltiazem are generally more effective antianginal agents than the dihydropyridine CCBs. In contrast, dihydropyridine CCBs, nifedipine in particular, inhibit calcium in the vasculature and are potent vasodilators that can cause baroreflex-mediated increases in sympathetic tone and heart rate. In addition to decreasing myocardial oxygen demand, all CCBs increase myocardial oxygen supply by dilating coronary arteries, thus increasing coronary blood flow and relieving vasospasm.

CCBs are as effective as β-blockers at preventing ischemic symptoms. **KEY CONCEPT** CCBs are recommended as alternative treatment in SIHD when β-blockers are contraindicated or not tolerated. In addition, CCBs may be used in combination with β-blockers when initial treatment is unsuccessful. The combination of a β-blocker and a dihydropyridine CCB may improve symptoms better than either drug used alone.[38] However, the combination should be used with caution because both drugs decrease AV nodal conduction, increasing the risk for severe bradycardia or AV block when used together. If combination therapy is warranted, a long-acting dihydropyridine CCB is preferred. β-Blockers will prevent reflex increases in sympathetic tone and heart rate with the use of CCBs with potent vasodilatory effects. For patients with variable and unpredictable occurrences of angina, indicating possible coronary vasospasm, CCBs may be more effective than β-blockers in preventing angina episodes. The dosing of CCBs in IHD is described in Table 8–9.

Verapamil and diltiazem are contraindicated in patients with bradycardia and preexisting conduction disease in the absence of a pacemaker. As previously noted, verapamil and diltiazem should be used with particular caution in combination with other drugs that depress AV nodal conduction (eg, β-blockers and digoxin). Because of their negative inotropic effects, CCBs may cause or exacerbate heart failure in patients with HFrEF and should be avoided in this population. The exceptions are amlodipine and felodipine that have less negative inotropic effects compared with other CCBs and appear to be safe in patients with left ventricular systolic dysfunction.[39,40] Finally, there is some evidence that short-acting CCBs (particularly short-acting nifedipine and

Table 8–9

Dosing of Calcium Channel Blockers in Ischemic Heart Disease

Drug	Usual Dose Range
Nondihydropyridines	
Diltiazem, extended release	120–360 mg once daily; consider dose adjustment in hepatic dysfunction
Verapamil, extended release	180–480 mg once daily; use initial dose of 120 mg in hepatic dysfunction
Dihydropyridines	
Amlodipine	5–10 mg once daily
Felodipine	5–10 mg once daily; use initial dose of 2.5 mg once daily in hepatic dysfunction
Nifedipine, extended release	30–90 mg once daily; dose adjust and monitor closely in hepatic dysfunction
Nicardipine	20–40 mg thrice daily; dose twice daily in hepatic dysfunction and up-titrate slowly in both hepatic and renal dysfunction

nicardipine) may increase the risk of cardiovascular events.[41] Therefore, short-acting agents should be avoided in the management of SIHD.

Long-Acting Nitrates Nitrate products are available in both oral and transdermal formulations for chronic use. Commonly used products are listed in Table 8–10. All long-acting nitrate products produce effects within 30 to 60 minutes and are equally effective at preventing the recurrence of angina when used appropriately.

Table 8–10

Nitrate Formulations and Dosing for Chronic Use

Formulation	Dose
Oral	
Nitroglycerin extended-release capsules	2.5 mg thrice daily initially, with up-titration according to symptoms and tolerance; allow a 10- to 12-hour nitrate-free interval
Isosorbide dinitrate tablets	5–20 mg two to three times daily, with a daily nitrate-free interval of at least 14 hours (eg, dose at 7 AM, noon, and 5 PM)
Isosorbide dinitrate slow-release capsules	40 mg one to two times daily, with a daily nitrate-free interval of at least 18 hours (eg, dose at 8 AM and 2 PM)
Isosorbide mononitrate tablets	5–20 mg twice daily initially, with up-titration according to symptoms and tolerance; doses should be taken 7 hours apart (eg, 8 AM and 3 PM)
Isosorbide mononitrate extended-release tablets	30–120 mg once daily
Transdermal	
Nitroglycerin extended-release film	0.2–0.8 mg/hour, on for 12–14 hours, off for 10–12 hours

The major limitation of nitrate therapy is the development of tolerance with continuous use. Loss of antianginal effects may occur within the first 24 hours of continuous nitrate therapy. Although the cause of tolerance is unclear, several mechanisms have been proposed, including the generation of free radicals that degrade nitric oxide. The most effective method to avoid tolerance and maintain the antianginal efficacy of nitrates is to allow a daily nitrate-free interval of at least 8 to 12 hours. Nitrates do not provide protection from ischemia during the nitrate-free period. Therefore, the nitrate-free interval should occur when the patient is least likely to experience angina, which is generally during the nighttime hours when the patient is sleeping, and myocardial oxygen demand is reduced. Thus, it is common to dose long-acting nitrates so that the nitrate-free interval begins in the evening. For example, isosorbide dinitrate is typically dosed on awakening and again 6 to 7 hours later.

Monotherapy with nitrates for the prevention of ischemia should generally be avoided. Reflex increases in sympathetic activity and heart rate, with resultant increases in myocardial oxygen demand, may occur secondary to nitrate-induced venodilation. In addition, patients are unprotected from ischemia during the nitrate-free interval. KEY CONCEPT Treatment with long-acting nitrates should be added to baseline therapy with either a β-blocker or CCB, or a combination of the two. β-Blockers attenuate the increase in sympathetic tone and heart rate that occurs during nitrate therapy. As a result, the combination of β-blockers and nitrates is particularly effective at preventing angina and provides greater protection from ischemia than therapy with either agent alone. Monotherapy with nitrates may be appropriate in patients who have low BP at baseline or who experience symptomatic hypotension with low doses of β-blockers or CCBs.

Common adverse effects of nitrates include postural hypotension, dizziness, flushing, and headache secondary to venodilation. Headache often resolves with continued therapy and may be treated with acetaminophen. Hypotension is generally of no serious consequence. However, in patients with hypertrophic obstructive cardiomyopathy or severe aortic valve stenosis, nitroglycerin may cause serious hypotension and syncope. Therefore, long-acting nitrates are relatively contraindicated in these conditions. Because life-threatening hypotension may occur with concomitant use of nitrates and phosphodiesterase type 5 inhibitors, nitrates should not be used within 24 hours of taking sildenafil or vardenafil, or within 48 hours of taking tadalafil. Skin erythema and inflammation may occur with transdermal nitroglycerin administration and may be minimized by rotating the application site.

Ranolazine Ranolazine is an anti-ischemic agent indicated for the management of chronic angina. The mechanism of action is unclear, but it is believed to inhibit the late inward sodium current during the plateau phase of the cardiac action potential. Under ischemic conditions, excess sodium may enter the myocardial cell during systole. The resultant intracellular sodium overload leads to intracellular calcium accumulation (calcium overload) through a sodium-calcium exchange mechanism. Calcium overload results in increases in left ventricular wall tension and MVO_2. By reducing intracellular sodium concentrations in ischemic myocytes, ranolazine decreases intracellular calcium overload, left ventricular wall tension, and MVO_2.

Similar to other antianginal drugs, ranolazine reduces angina and increases exercise capacity but does not reduce incidence of MACE. Ranolazine has minimal effects on heart rate or BP; thus, it may be an option in SIHD patients with low baseline BP or heart rate. Ranolazine is often reserved for patients with angina refractory to other antianginal medications due to its excessive cost. Ranolazine can prolong the QT interval. However, when used at recommended doses, the mean prolongation of QT interval is minimal (2.4 ms).[42] The risk for QT interval prolongation is elevated in patients with hepatic impairment or taking other medications known to interact with ranolazine or prolong QT interval. Ranolazine should be started at a dose of 500 mg twice daily and increased to 1000 mg twice daily if needed for symptom relief. Higher doses are poorly tolerated and should be avoided. Contraindications to ranolazine are shown in Table 8–11. Common adverse effects with ranolazine include dizziness, constipation, headache, and nausea. Syncope may occur infrequently. Ranolazine is a CYP3A4 substrate, weak CYP2D6 substrate, CYP2D6 inhibitor, organic cation transporter 2 (OCT2) inhibitor, and both an inhibitor and substrate of P-glycoprotein (P-gp). Concomitant use of ranolazine with potent CYP3A4 inhibitors (eg, ketoconazole, clarithromycin, and nelfinavir) or inducers (eg, rifampin) is contraindicated. The use of ranolazine is contraindicated in patients with significant hepatic disease. The ranolazine dose should be limited to 500 mg twice daily when combined with moderate CYP3A4 inhibitors including diltiazem and verapamil. Ranolazine should be used cautiously with P-gp inhibitors (eg, cyclosporine) and substrates (eg, digoxin). The maximum doses of simvastatin (20 mg daily) and metformin (1700 mg daily) are lower during concomitant treatment with ranolazine.

Table 8–11

Contraindications and Precautions with Ranolazine

Contraindications	Precautions
Liver cirrhosis increases ranolazine plasma concentrations by 30%–80%, resulting in increased risk for QT interval prolongation Treatment with potent CYP3A4 inhibitors (including ketoconazole, clarithromycin, and nelfinavir) increases ranolazine concentrations (3.2-fold with ketoconazole) Treatment with CYP3A4 inducers (including rifampin, phenobarbital, phenytoin, carbamazepine, and St. John's wort) may significantly decrease the efficacy of ranolazine (by 95% with rifampin)	Treatment with moderate CYP3A4 inhibitors including diltiazem, verapamil, grapefruit juice, erythromycin, and fluconazole increases ranolazine plasma concentrations (twofold with diltiazem and verapamil) Preexisting QT prolongation, history of torsades de pointes, or treatment with other QT-prolonging drugs as QT interval prolongation may occur with ranolazine Treatment with a P-gp inhibitor, such as cyclosporine, may increase ranolazine absorption Up to a 50% increase in ranolazine plasma concentration has been observed in renal impairment Ranolazine may increase bioavailability of P-gp substrates (increases digoxin plasma concentrations by 1.5-fold) Ranolazine may cause reduced metabolism of CYP2D6 substrates Ranolazine may increase exposure to drugs transported by OCT2; metformin doses should not exceed 1700 mg/day in patients treated with ranolazine 1000 mg twice daily Ranolazine may reduce the metabolism of CYP3A4 substrates; the dose of simvastatin should not exceed 20 mg in patients treated with ranolazine

CYP, cytochrome P450; OCT2, organic cation transporter 2; P-gp, P-glycoprotein.

▶ *Pharmacotherapy with No Benefit or Potentially Harmful Effects*

Hormone Replacement Therapy, Folic Acid, and Antioxidants Current guidelines recommend against the use of hormone replacement therapy (HRT), folic acid, or antioxidants for reducing cardiovascular risk.[1] Early evidence from observational studies with each of these suggested potential benefit in SIHD. However, no benefit was observed in randomized controlled clinical trials.[43,44] In the case of HRT, there was evidence of harm, with an increased risk of thromboembolic events and breast cancer with HRT in postmenopausal women.[44] Clinicians should consider discontinuing HRT therapy in women who suffer an acute coronary event while receiving such therapy.

Herbal Supplements Herbal products are widely used for their purported cardiovascular benefits. Strong evidence supporting their benefits in cardiovascular disease is generally lacking and the potential for drug interactions and the lack of standardization limits the products' usefulness in clinical practice. Safety with herbal supplements in patients with SIHD is a major concern. Numerous case reports of adverse cardiovascular events led the Food and Drug Administration (FDA) to ban ephedra-containing products (eg, ma huang) in 2004. Some herbal supplements, such as feverfew and garlic, may interact with antiplatelet and antithrombotic therapy and increase bleeding risk. Dietary supplements purported to enhance sexual performance may contain phosphodiesterase-like chemicals and increase risk for serious hypotension with nitroglycerin. Other agents may reduce the effectiveness of antianginal medications, such as St. John's wort with ranolazine. Thus, it is important to assess the use of herbal products in patients with SIHD and to counsel patients about the potential for drug interactions and adverse events with herbal therapies.

Cyclooxygenase-2 Inhibitors and Nonsteroidal Anti-inflammatory Drugs Data suggest that cyclooxygenase-2 (COX-2) inhibitors and nonselective NSAIDs may increase the risk for MI and stroke.[45] The cardiovascular risk with COX-2 inhibitors and NSAIDs may be greatest in patients with a history of, or with risk factors for, cardiovascular disease. The COX-2 inhibitors rofecoxib and valdecoxib were withdrawn from the market because of safety concerns. Product labeling for other COX-2 and nonselective NSAIDs (prescription and over-the-counter) now includes boxed warning about potential adverse cardiovascular effects. The AHA recommends the use of COX-2

Patient Encounter Part 3: Creating a Care Plan

Based on the information presented, create a specific plan for the management of the patient's SIHD. Your plan should include (a) the goals of therapy, (b) patient-specific nonpharmacologic and pharmacologic interventions to address these goals, and (c) a plan for follow-up to assess drug tolerance and whether the therapeutic goals have been achieved.

inhibitors be limited to low-dose, short-term therapy in patients for whom there is no appropriate alternative. Patients with cardiovascular disease should consult a clinician before using over-the-counter NSAIDs.

Special Populations

▶ *Variant Angina*

Vasospasm as sole etiology of angina (Prinzmetal or variant angina) is relatively uncommon. As a result, treatment options are not well studied. Nevertheless, based on the pharmacology of available drugs, several recommendations can be made. First, β-blockers should be avoided in patients with variant angina because of their potential to worsen vasospasm due to unopposed α-adrenergic receptor stimulation. In contrast, both CCBs and nitrates are effective in relieving vasospasm and are preferred in the management of variant angina. Because nitrates require an 8- to 12-hour nitrate-free interval, their role as monotherapy for prophylaxis of anginal attacks due to vasospasm is limited. However, immediate-release nitroglycerin is effective at terminating acute anginal attacks due to vasospasm. Therefore, all patients diagnosed with variant angina should be prescribed immediate-release nitroglycerin. CCBs are effective for monotherapy of variant angina. Because short-acting CCBs have been associated with increased risk of adverse cardiac events, they should be avoided.[41] Long-acting nitrates may be added to CCB therapy if needed.

▶ *Microvascular Angina*

There are limited data on optimal therapy in patients with microvascular disease. Both ACE inhibitors and statins may produce beneficial effects on endothelial function and improve microvascular angina.[5] Short-acting nitrates remain the treatment of choice for relieving acute symptoms, although they may be less effective in microvascular disease. Similar to obstructive CAD, β-blockers are first line to control symptoms of angina in patients with microvascular disease and may be more effective than CCBs and long-acting nitrates in this setting. Ranolazine may also produce favorable antianginal effects for patients with continued symptoms.

▶ *Elderly Patients with IHD*

Elderly patients are more likely to have other comorbidities that may influence drug selection for the treatment of angina than younger patients. As a result, polypharmacy is more common in elderly patients, increasing the risk of drug–drug interactions, and perhaps decreasing medication adherence. Additionally, elderly patients are often more susceptible to adverse effects of antianginal therapies, particularly the negative chronotropic and inotropic effects of β-blockers and CCBs. Therefore, drugs should be initiated in low doses with close monitoring of elderly patients with IHD.

▶ *Acute Coronary Syndromes*

Management of ACS is discussed in further detail in Chapter 9. It is important to educate patients with SIHD on the signs of ACS and steps to take if signs or symptoms occur. Importantly, patients should be instructed to seek emergent care if symptoms of angina last longer than 20 to 30 minutes, do not improve after 5 minutes of using sublingual nitroglycerin, or worsen after 5 minutes of using sublingual nitroglycerin. In patients with a history of ACS, it is crucial to select appropriate pharmacotherapy to prevent recurrent ACS and death. Appropriate pharmacotherapy for patients with a history of ACS includes aspirin (often in combination with a $P2Y_{12}$ inhibitor), ACE inhibitors or ARBs, β-blockers, statins, and sublingual nitroglycerin. In addition, control of cardiovascular risk factors (eg, dyslipidemia, hypertension, and diabetes) with lifestyle modifications and pharmacotherapy is critical.

OUTCOME EVALUATION

Assessing for Drug Effectiveness and Safety

- In general, patients with SIHD should have follow-up evaluations every 4 to 12 months.[1] Early in the treatment course (eg, first year), more frequent evaluations (every 4–6 months) are recommended. Length of the follow-up period may differ based on frequency and severity of symptoms, care coordination with other providers, regional practice patterns, patient preference, and physician availability.
- **KEY CONCEPT** Monitor symptoms of angina at baseline and at each clinic visit to assess frequency and intensity of anginal symptoms and effectiveness of antianginal therapy.[1] Determining frequency of sublingual nitroglycerin use is helpful in making this assessment. If angina is occurring with increasing frequency or intensity, adjust antianginal therapy and refer the patient for additional diagnostic testing and possibly coronary intervention (eg, PCI or CABG surgery), if indicated.
- Assess the patient for IHD-related complications, such as heart failure and arrhythmias.[1]
- Routinely monitor hemodynamic parameters to assess drug tolerance. Assess BP at baseline, after drug initiation, and after dose titration. BP should be monitored periodically in patients treated with β-blockers, CCBs, nitrates, ACE inhibitors, and/or ARBs.
- Routinely assess adherence to medical therapy and recommended lifestyle changes.
- Because of the potential for postural hypotension, warn patients that dizziness, presyncope, and even syncope may result from abrupt changes in body position during initiation or uptitration of drugs with α-blocking effects.
- Closely monitor heart rate in patients treated with drugs that have negative chronotropic effects (eg, β-blockers, verapamil, or diltiazem) or drugs that may cause reflex tachycardia (eg, nitrates or dihydropyridine CCBs). Treatment with β-blockers, verapamil, or diltiazem can usually be continued in patients with asymptomatic bradycardia. However, reduce or discontinue treatment with these agents in patients who develop symptomatic bradycardia or serious conduction abnormalities.
- Regularly assess control of existing risk factors and the presence of new risk factors for SIHD.[1] Modify the pharmacotherapy regimen to control these risk factors and lower the risk of IHD-related adverse events.
- In patients treated with ACE inhibitors and/or ARBs, routinely monitor renal function and potassium levels at baseline, after drug initiation and dose titration, and periodically thereafter. This is particularly important in patients with preexisting renal impairment or diabetes because they may be more susceptible to these adverse events.

Duration of Therapy

- Because these therapies reduce the risk for coronary events and death, treatment with antiplatelet (aspirin or clopidogrel), lipid-lowering, and neurohormonal-modifying medications for SIHD is generally lifelong.
- Antianginal therapy with a β-blocker, CCB, and/or nitrate is usually long term.
- A patient with severe symptoms managed with combination antianginal drugs who undergoes successful coronary revascularization may be able to reduce antianginal therapy. However, treatment with at least one agent is usually warranted.

Patient Care Process

Collect Information:

- Identify any patient complaints/symptoms, including recent chest pain. (See Tables 8–3 and 8–4.)
- Elicit information on the quality, location, and duration of chest pain; determine factors that provoke or relieve the pain.
- Perform a thorough medication history.
- Identify allergies and intolerances.
- Identify barriers that may affect adherence to care plan.
- Identify SIHD risk factors. (See Table 8–2.)
- Obtain vital signs and perform a physical examination.
- Collect laboratory and diagnostic information. (See Clinical Presentation and Diagnosis of Ischemic Heart Disease, and Figure 8–4.)

Assess the Information:

- Evaluate available information about chest pain and create a differential diagnosis.
- Consider potential noncardiac conditions that can explain the patient's symptoms. (See Table 8–1.)
- Evaluate available laboratory and diagnostic information for SIHD. Do they suggest or confirm SIHD? Was PCI performed? Were there any stents placed and in what setting (ACS or SIHD)?
- Assess the appropriateness, efficacy, and safety of the patient's previous SIHD drug regimen, if applicable.
- Identify medications that may interact with antianginal drug therapy.
- Assess adherence to medical therapy and recommended lifestyle modifications.
- Assess for the presence of SIHD-related complications.
- Assess preexisting and newly detected patient-specific risk factors for SIHD. (See Table 8–2 and Figure 8–4.)
- Determine patient-centered goals of therapy for SIHD.

Develop a Care Plan:

- Treat modifiable risk factors for SIHD; initiate appropriate lifestyle modifications.
- Treat hypertension, dyslipidemia, and diabetes.
- Initiate and/or modify therapy to prevent MACE. (See Figure 8–5.)
- Initiate and/or modify therapy to treat acute symptoms and prevent chronic angina symptoms. (See Figure 8–5.)

Implement the Care Plan:

- Refer patients with ACS to the hospital. (See Table 8–3.)
- Stress the importance of adherence to the care plan.
- Provide education on the following: consequences of untreated SIHD, lifestyle modifications, medication administration, potential adverse effects, potential drug interactions, signs and symptoms of worsening angina, signs and symptoms of IHD-related complications, and when to seek emergent care.

Follow-up: Monitor and Evaluate:

- Reassess the care plan at least every 4 to 12 months, more often if necessary (eg, first year of therapy, persistent symptoms, intolerance to medical therapy).
- During each subsequent visit, assess control of preexisting risk factors and development of new risk factors, control of angina symptoms, presence of SIHD complications, adherence to the care plan, development of adverse drug reactions, and drug interactions.
- Reevaluate the efficacy and safety of the medical regimen assuring it includes appropriate therapy to prevent MACE and prevent angina symptoms. (See Figures 8–4 and 8–5.)
- Reassess barriers to treatment affecting adherence and modify the care plan, if necessary.

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Abbreviations Introduced in This Chapter

ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndromes
AHA	American Heart Association
ARB	Angiotensin receptor blocker
ASCVD	Atherosclerotic cardiovascular disease
AV	Atrioventricular
BMS	Bare metal stent
BP	Blood pressure
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCB	Calcium channel blocker
cGMP	Cyclic guanosine monophosphate
CHD	Coronary heart disease
COX-2	Cyclooxygenase-2
CrCl	Creatinine clearance
CT	Computed tomography
CYP	Cytochrome P450
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stent
EBCT	Electron beam computed tomography
ECG	Electrocardiogram
FDA	Food and Drug Administration
GLP-1	Glucagon-like peptide 1
HDL	High-density lipoprotein
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
Hgb	Hemoglobin
HMG-CoA	3-Hydroxy-3-methylglutaryl coenzyme A
HRT	Hormone replacement therapy
HTN	Hypertension
IHD	Ischemic heart disease
IV	Intravenous
LDL	Low-density lipoprotein
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac events
MI	Myocardial infarction
MR	Magnetic resonance
MRA	Mineralocorticoid receptor antagonist
ms	Milliseconds
MVO_2	Myocardial oxygen consumption
NSTEMI	Non–ST-segment elevation myocardial infarction
NSAID	Nonsteroidal anti-inflammatory drug
OCT2	Organic cation transporter 2
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
P-gp	P-glycoprotein
PTCA	Percutaneous transluminal coronary angioplasty
SIHD	Stable ischemic heart disease
SGLT2	Sodium-glucose cotransporter 2
STEMI	ST-segment elevation myocardial infarction
TXA_2	Thromboxane A_2
UA	Unstable angina
WBC	White blood cell

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9 Acute Coronary Syndromes

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Define the role of atherosclerotic plaque, platelets, and the coagulation system in an acute coronary syndrome (ACS).
2. List key electrocardiographic (ECG), biomarker, and clinical features identifying a patient with non–ST-segment elevation (NSTE)-ACS and ST-segment elevation myocardial infarction (STEMI).
3. Devise an initial, early pharmacotherapy treatment and monitoring plan for a patient presenting with either NSTE-ACS or STEMI given patient-specific data.
4. Devise an antithrombotic pharmacotherapy treatment and monitoring plan for a patient with NSTE-ACS or STEMI undergoing percutaneous coronary intervention (PCI) given patient-specific data.
5. Devise an antithrombotic pharmacotherapy treatment and monitoring plan for a patient with NSTE-ACS or STEMI not undergoing PCI given patient-specific data.
6. Develop a pharmacotherapy and risk factor modification treatment plan for secondary prevention of coronary heart disease (CHD) events in a patient following NSTE-ACS or STEMI.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the United States and one of the major causes of death worldwide.[1] Acute coronary syndromes (ACSs), including unstable angina (UA) and myocardial infarction (MI), are a form of coronary heart disease (CHD) that comprises the most common cause of CVD death.[1] KEY CONCEPT ACS is primarily caused by rupture of an atherosclerotic plaque with subsequent platelet adherence, activation, aggregation, and the activation of the clotting cascade. Ultimately, a thrombus composed of fibrin and platelets may develop, resulting in incomplete or complete occlusion of a coronary artery.[2] ACS is a spectrum of disease encompassing ST-segment elevation MI (STEMI) or non–ST-segment elevation (NSTE)-ACS, which are classified according to electrocardiogram (ECG) changes and underlying pathophysiology.[3,4] The American Heart Association (AHA), American College of Cardiology (ACC), and American College of Cardiology Foundation (ACCF) recommend strategies or guidelines for ACS patient care for STEMI and NSTE-ACS which include both UA and non–ST-elevation MI (NSTEMI). In collaboration with the Society for Cardiovascular Angiography and Interventions (SCAI), the ACCF and AHA issue joint guidelines for percutaneous coronary intervention (PCI), including PCI in the setting of ACS. These practice guidelines are based on a review of available clinical evidence, have graded recommendations based on evidence and expert opinion, and are updated periodically. In the United States, these guidelines form the cornerstone for quality care of the ACS patient.[3-5]

EPIDEMIOLOGY

Each year, approximately 720,000 Americans will have a new coronary event, defined as a first hospitalization for MI or CHD death, while 335,000 will have a recurrent event.[1] The risks of CHD events, such as death, recurrent MI, and stroke, are higher for patients with established CHD and a history of MI than for patients without CHD.

The incidence rate of MI in the United States has been decreasing since 2007.[1] Particularly, patients presenting with STEMI have significantly decreased (from 133 to 50 cases per 100,000 person-years). Nevertheless, 110,346 Americans died of an MI in 2017.[1] One in seven deaths is secondary to CHD, which is the leading cause of hospitalization in the United States.[1] With median length of hospital stay being 3.1 days, the cost of CHD is high.[6] Estimated direct and indirect costs are more than $218.7 billion with both MI and CHD ranked in the top 10 most expensive conditions treated in the United States.[1]

Mortality rates have declined since the 1990s. Improvements in care that may have contributed to this reduction include greater use of guideline-recommended drugs (eg, aspirin [ASA], β-blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors [statins], $P2Y_{12}$ inhibitors); reductions in median times for administering fibrinolytics and performing primary PCI; and increased use of early coronary angiography and PCI for high-risk patients with NSTE-ACS.[1,7] In patients with STEMI, in-hospital death rates in the United States are approximately 3% in patients receiving primary PCI, 7% for patients treated with fibrinolytics, and 16% for patients who do not receive reperfusion therapy.[7] In patients with NSTEMI, in-hospital mortality is less than 4%.[7] Other than persistent ST-segment changes and troponin, predictors of in-hospital mortality include older age, elevated serum creatinine (SCr), tachycardia, and heart failure (HF).[8,9]

ETIOLOGY

Endothelial dysfunction, inflammation, and formation of fatty streaks contribute to the formation of atherosclerotic coronary artery plaques, the underlying cause of coronary artery disease (CAD).[10] **KEY CONCEPT** The predominant cause of ACS in more than 90% of patients is atheromatous plaque rupture, fissuring, or erosion of an unstable atherosclerotic plaque followed by thrombus formation that reduces blood flow and results in myocardial ischemia.[2,10] If the ischemia persists long enough, MI can occur. This is called MI type 1, which generally occurs in coronary arteries where the stenosis occludes less than 50% of the lumen prior to the event, rather than a more stable 70% to 90% stenosis of the coronary artery.[4,11] Stable stenoses are characteristic of stable angina, are not considered an ACS, and are discussed in Chapter 8, "Stable Ischemic Heart Disease." MI type 2 is related to a reduction in myocardial oxygen supply or an increase in myocardial demand in the absence of a coronary artery process (eg, severe anemia, coronary vasospasm, sustained tachycardia, coronary artery dissection). MI type 3 is defined as an MI resulting in sudden cardiac death when biomarker measurement is not possible, while MI types 4 and 5 occur during revascularization procedures, including PCI or coronary artery bypass graft (CABG) surgery, respectively.[11]

PATHOPHYSIOLOGY

The term ACS encompasses all clinical syndromes compatible with acute myocardial ischemia and/or MI resulting from an imbalance between myocardial oxygen demand and supply. In contrast to stable angina, an ACS results primarily from diminished myocardial blood flow secondary to an occlusive or partially occlusive coronary artery thrombus. ACSs are classified according to ECG changes into STEMI or NSTE-ACS (ie, NSTEMI and UA) (Figure 9–1).[3,4] An injury that transects the entire thickness of the myocardial wall results in a STEMI which will result in the release of biomarkers, mainly troponins T or I, from the necrotic myocytes into the bloodstream. An NSTEMI is limited to the subendocardial myocardium, and is usually smaller than a STEMI, resulting in lower mortality and complications. NSTEMI differs from UA in that ischemia is severe enough to result in the release of troponins. The clinical significance of serum markers is discussed in greater detail in later sections of this chapter.

Plaque Rupture and Clot Formation

Plaques that rupture are generally characterized by a soft lipid-rich necrotic core, a thin fibrous cap, adventitial and perivascular inflammation, intraplaque hemorrhage, angiogenesis, and

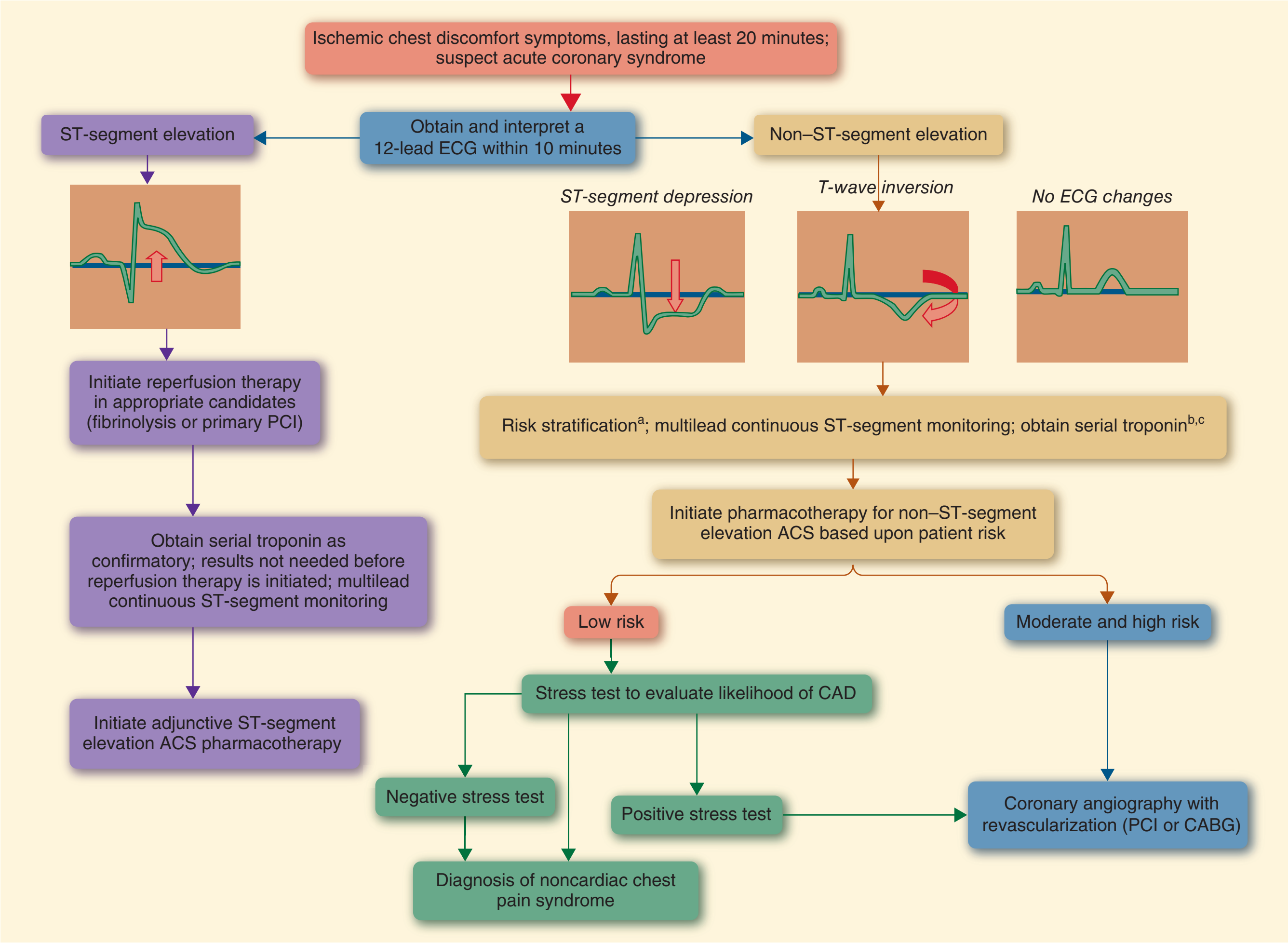
Ischemic chest discomfort symptoms, lasting at least 20 minutes; suspect acute coronary syndrome
Obtain and interpret a 12-lead ECG within 10 minutes
ST-segment elevation
Non–ST-segment elevation
ST-segment depression
T-wave inversion
No ECG changes
Initiate reperfusion therapy in appropriate candidates (fibrinolysis or primary PCI)
Risk stratification[a]; multilead continuous ST-segment monitoring; obtain serial troponin[b,c]
Obtain serial troponin as confirmatory; results not needed before reperfusion therapy is initiated; multilead continuous ST-segment monitoring
Initiate pharmacotherapy for non–ST-segment elevation ACS based upon patient risk
Low risk
Moderate and high risk
Initiate adjunctive ST-segment elevation ACS pharmacotherapy
Stress test to evaluate likelihood of CAD
Negative stress test
Positive stress test
Coronary angiography with revascularization (PCI or CABG)
Diagnosis of noncardiac chest pain syndrome

FIGURE 9–1. Evaluation of the acute coronary syndrome patient. [a]As described in Table 9–1. [b]"Positive": Above the myocardial infarction decision limit. [c]"Negative": Below the myocardial infarction decision limit. (ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; ECG, electrocardiogram; PCI, percutaneous coronary intervention.) (Reproduced with permission from: Rogers KC, de Denus S, Finks SW, Spinler SA. Acute coronary syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:167.)

expansive vascular remodeling. The latter explains why these plaques only show minimal luminal obstruction, despite being larger than plaques that characterize stable angina which are associated with more severe luminal narrowing.[2,10] Following plaque rupture, a clot (a partially or completely occlusive thrombus) forms on top of the ruptured plaque. The thrombogenic contents of the plaque are exposed to blood elements. Exposure of collagen and tissue factor induce platelet adhesion and activation, which promote the release of platelet-derived vasoactive substances, including adenosine diphosphate (ADP) and thromboxane A_2 (TXA_2).[10] These produce vasoconstriction and potentiate platelet activation. Furthermore, during platelet activation, a change in the conformation in the glycoprotein (GP) IIb/IIIa surface receptors of platelets occurs that cross-links platelets to each other through fibrinogen bridges. This is considered the final common pathway of platelet aggregation. Inclusion of platelets gives the clot a white appearance. Simultaneously, the extrinsic coagulation cascade pathway is activated as a result of exposure of blood components to the thrombogenic lipid core and disrupted endothelium, which are rich in tissue factor. This leads to the production of thrombin (factor IIa), which converts fibrinogen to fibrin through enzymatic activity. Fibrin stabilizes the clot and traps red blood cells, which gives the clot a red appearance. Therefore, the clot is composed of cross-linked platelets and fibrin strands.[2,10]

Ventricular Remodeling Following an Acute MI

Adverse ventricular remodeling is a process of structural and functional changes caused by loss of viable myocardium, enhanced inflammatory response, neurohormonal activation, and enhanced wall stress that occurs in several cardiovascular (CV) conditions including HF and MI. It is characterized by left ventricular dilation and reduced pumping function of the left ventricle, leading to cardiac failure.[12] Because HF represents one of the principal causes of morbidity and mortality following an MI, preventing ventricular remodeling is an important therapeutic goal. Infarct size is the greatest predictor of adverse ventricular remodeling and survival. Therefore, early reperfusion and blockade of neurohormonal activation play key roles in treatment.

Use of ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists can slow down or reverse ventricular remodeling through inhibition of the renin-angiotensin aldosterone system and/or through improvement in hemodynamics (decreasing preload or afterload).[12] These agents also significantly improve survival in patients with ACS.[3,4]

At some point during hospitalization, prior to discharge, patients with a definite ACS should have their left ventricular function (LVF) evaluated.[3,4] The most common way LVF is measured is using an echocardiogram to calculate the patient's left ventricular ejection fraction (LVEF, percent of blood pumped out of the left ventricle with each contraction). LVF, a measure of infarct size, is one of the strongest predictors of mortality following MI. Patients with LVEF less than 40% (0.40) are at high risk of death and ventricular arrhythmias.[3,4] LVEF is an important factor to consider when contemplating the use of several drugs, such as ACE inhibitors and aldosterone antagonists.

Complications

This chapter focuses on management of the uncomplicated ACS patient. However, it is important for clinicians to recognize complications of an acute MI as these may increase the risk of mortality. The most serious early complication of MI is cardiogenic shock, occurring in approximately 5% to 8% of hospitalized patients presenting with STEMI with mortality rates approaching 40%.[13] Other complications that may result from MI are HF, valvular dysfunction, bradycardia, heart block, **pericarditis**, stroke secondary to left ventricular thrombus embolization, venous thromboembolism, left ventricular free wall rupture, and ventricular and atrial tachyarrhythmias.[3] In fact, many patients die, presumably from ventricular fibrillation, prior to reaching the hospital. Patients with ventricular fibrillation or sustained ventricular tachycardia occurring more than 2 days following MI (which are not due to transient and reversible ischemia, reinfarction, or metabolic abnormalities), those with LVEF less than 30% (0.30; measured at least 40 days after STEMI) regardless of symptoms, or those with LVEF less than or equal to 35% (0.35) with New York Heart Association functional classes II to III may experience a mortality benefit against sudden cardiac death from placement of an implantable cardioverter-defibrillator (ICD).[3] Life-threatening bleeding secondary to fibrinolytics, anticoagulants and antiplatelets especially in the setting of catheterization and PCI, may also complicate the management of an MI.

CLINICAL PRESENTATION AND DIAGNOSIS

Symptoms and Physical Examination Findings

The classic symptom of ACS is severe new-onset or increasing substernal angina that is at least 10 minutes in duration, most often occurring at rest. The pain may radiate to the shoulder, down the left arm, and to the back or jaw, and this radiation pain may also occur without associated chest pain. Other symptoms include nausea, vomiting, **diaphoresis**, or shortness of breath. Although similar to stable angina, the duration may be longer and intensity may be greater.[3,4] Elderly, female patients, and patients with diabetes may present with a more atypical presentation, including epigastric pain, unexplained shortness of breath, or indigestion in the absence of chest pain which are often referred to as anginal equivalents. All healthcare professionals should review these warning symptoms with patients at high risk for CHD. On physical examination, no specific features are indicative of ACS. Patients with suspected ACS should be referred immediately to an emergency department (ED).

12-Lead ECG

KEY CONCEPT There are key features of a 12-lead ECG that identify and risk-stratify a patient with ACS. Within 10 minutes of presentation to an ED with symptoms of ischemic chest discomfort, a 12-lead ECG should be obtained and interpreted. If the first ECG is not diagnostic, additional ECGs should be performed every 15 to 30 minutes for the first hour if the patient is still symptomatic and the clinician has a high suspicion of ACS.[4] **KEY CONCEPT** When possible, an ECG should be performed by emergency medical system providers to reduce the delay until myocardial reperfusion. If available, a prior ECG should be reviewed to identify whether ischemic changes are new or old, with new findings being more indicative of an ACS. Key findings on review of an ECG that indicate myocardial ischemia or infarction are ST-segment elevation (STE), ST-segment depression, and T-wave inversion (see Figure 9–1).[3,4] ST-segment and/or T-wave changes in certain groupings of ECG leads help to identify the location of the coronary artery that is the cause of the ischemia or infarction. In addition, the appearance of a new left bundle-branch block accompanied by chest discomfort is highly specific for acute STEMI. Approximately one-third of patients diagnosed with MI present with STE on their ECG, with the remainder having ST-segment depression, T-wave inversion, or in some instances, no ECG changes.[4,7] According to the latest guidelines, the diagnosis of STE, in the absence of left bundle-branch block or left ventricular hypertrophy, is a new STE in at least two contiguous leads of greater than or equal to 2 mm in men and greater than or equal to 1.5 mm in women in leads V_2-V_3 and/or of greater than or equal to 1 mm in other leads. Some parts of the heart are more "electrically silent" than others, and myocardial ischemia may not be detected on an ECG. Therefore, it is important to review findings from the ECG in conjunction with biochemical markers of myocardial necrosis, such as high-sensitivity cardiac troponin I (hs-cTnI) or T (hs-cTnT), clinical symptoms, and other risk factors for CHD to determine the patient's risk for experiencing a new MI or having other complications.

Biochemical Markers/Cardiac Enzymes

Biochemical markers of myocardial cell death are important for confirming the diagnosis of MI. **KEY CONCEPT** Diagnosis of MI is confirmed when the following conditions are met in a clinical setting consistent with myocardial ischemia: "Detection of a rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit and with at least one of the following: (a) symptoms of ischemia; (b) ECG changes of new ischemia or development of pathological Q waves; (c) imaging evidence of new loss of viable myocardium; (d) new regional wall motion abnormality; or (e) identification of an intracoronary thrombus by angiography or autopsy."[11] The most recent guidelines indicate that only the use of troponin assays is recommended to assess myocardial necrosis.[4] Troponins are released into the bloodstream approximately 2 to 4 hours after an MI and generally peak around 18 to 24 hours. Troponins can stay elevated for up to 2 weeks. A single measurement of non–high-sensitivity troponin is not adequate to exclude a diagnosis of MI, as up to 15% of values that were initially below the level of detection (a "negative" test) rise to the level of detection (a "positive" test) in subsequent hours. Additionally, a single "positive" troponin may not be secondary to an MI as elevations can occur in other clinical conditions, such as pulmonary embolus, tachyarrhythmias, pericarditis, myocarditis, and sepsis, which can complicate diagnosis. Measurement of N-terminal pro B-type natriuretic peptide (BNP) may help predict long-term risk of mortality in patients with ACS but does not aid with acute diagnosis.[4]

The advent of hs-cTnI and hs-cTnT permits measurement well below the 99th percentile of the reference range. The lowest level the assay can detect is called the "level of detection." If the initial hs-cTn is below the level of detection, the diagnosis of MI can be excluded, and no further risk stratification is needed.

Clinical Presentation and Diagnosis

General

- The patient is typically in acute distress and may develop or present with acute HF, cardiogenic shock, or cardiac arrest.

Symptoms

- The classic symptom of ACS is acute onset of substernal chest pain or discomfort. Accompanying symptoms may include radiation of pain to either arm, back, or jaw, nausea, vomiting, diaphoresis, anxiety, or shortness of breath.
- Elderly, women, patients with diabetes, renal impairment, and dementia are more likely to present with atypical symptoms such as indigestion, epigastric pain, shortness of breath, or anxiety and less likely to present with classic symptoms.

Physical Signs

- There are no "classic" physical signs specific for ACS.
- Patients with ACS may present with signs of acute HF, including jugular venous distention, an S_3 sound on auscultation, or pulmonary edema on a chest X-ray.
- Patients may also present with arrhythmias such as tachycardia, bradycardia, or heart block.

Laboratory Tests

- High-sensitivity cardiac troponin I (hs-cTnI) or T (hs-cTnT) is measured at presentation and repeated at 1 to 6 hours to ascertain heart muscle damage, confirmatory for the diagnosis of an infarction. For patients with NSTE-ACS, an elevated troponin is diagnostic for MI, differentiating NSTEMI from UA. Patients presenting with suspected NSTE-ACS who do not have an MI undergo further diagnostic testing to determine whether they have UA or another diagnosis.
- Blood chemistry tests are performed with particular attention given to potassium and magnesium, which may affect heart rhythm.
- SCr is measured, and creatinine clearance (CrCl) is used to identify patients who may need dosing adjustments for medications, as well as those who are at high risk of morbidity and mortality.
- Baseline complete blood count (CBC) and coagulation tests (activated partial thromboplastin time [aPTT] and international normalized ratio [INR]) should be obtained because most patients will receive antithrombotic therapy that increases the risk for bleeding.
- Fasting lipid panel.

Other Diagnostic Tests

- The 12-lead ECG is the first step in management. Patients are risk-stratified into two groups: STEMI or NSTE-ACS.
- High-risk ACS patients, especially those with STEMI and those with recurrent chest discomfort will undergo coronary angiography via left heart catheterization and injection of contrast dye into the coronary arteries to determine the presence and extent of coronary artery stenoses and often undergo PCI to relieve the stenoses.
- During hospitalization, a measurement of LVF such as an echocardiogram is performed to identify patients with ejection fraction (EF) less than or equal to 40% (0.40) who are at high risk of death following hospital discharge.
- Selected low-risk patients may undergo early stress testing.

(Modified with permission from Rogers KC, de Denus S, Finks SW, Spinler SA. Acute coronary syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:168.)

For patients presenting with an hs-cTn above the level of detection but below the 99th percentile, a second level at 1 to 6 hours should be obtained and risk stratification performed (see "Risk Stratification" section). If there is no change when comparing the second hs-cTn level to the first, the diagnosis of MI can be reliably excluded. A third level is recommended if the first two levels are above the level of detection but below the 99th percentile, and the patient presented to the hospital less than 3 hours after the onset of symptoms. At any time, a level above the 99th percentile confirms the diagnosis of MI.[14,15]

Risk Stratification

KEY CONCEPT Patient symptoms, past medical history, ECG, and troponins are utilized to stratify patients into low, medium, or high risk of death, MI, or likelihood of failing pharmacotherapy and needing urgent coronary angiography and PCI (see Table 9–1). Initial treatment according to risk stratification should be performed as soon as possible to determine which patients may benefit from a reperfusion strategy for STEMI or an early invasive or medical management approach for NSTE-ACS and is depicted in Figure 9–1. For example, patients with STEMI are at the highest short-term risk of death; therefore, immediate reperfusion strategies should be initiated. The ACCF/AHA/SCAI PCI guidelines define a target time to initiate reperfusion treatment as less than or equal to 30 minutes of hospital arrival for fibrinolytics (eg, alteplase, reteplase, and tenecteplase) and within 90 minutes from first medical contact for primary PCI.[5] The sooner the infarct-related coronary artery is opened, the lower the mortality and the greater the amount of myocardium that is preserved. For patients who present to a facility without PCI capability, it is recommended they be transferred to another hospital within 120 minutes of first medical contact for primary PCI.[5] Although all patients should be evaluated for reperfusion therapy, not all patients may be eligible. Indications and contraindications for fibrinolytic therapy are described in the treatment section of this chapter and Table 9–2. If patients with STEMI are not eligible for reperfusion therapy, additional pharmacotherapy should be initiated in the ED and the patient transferred to a coronary intensive care unit.[3]

Risk-stratification of the patient with NSTE-ACS is more complex because outcomes may vary between UA and NSTEMI.

Table 9–1

Risk Stratification for Acute Coronary Syndromes[4,16]

TIMI Risk Score for NSTE-ACS

One point is assigned for each of the seven medical history and clinical presentation findings below. The point total is calculated, and the patient is assigned a risk for experiencing the composite endpoint of death, MI, or urgent need for revascularization

A clinical application tool is available at https://timi.org/calculators/timi-risk-score-calculator-for-ua-nstemi/

- Age 65 years or older
- Three or more CAD risk factors: smoking, hypercholesterolemia, HTN, DM, family history of premature CAD death/events
- Known CAD (50% or greater stenosis of at least one major coronary artery on coronary angiogram)
- Aspirin use within the past 7 days
- Two or more episodes of chest discomfort within the past 24 hours
- ST-segment depression 0.5 mm or greater
- Positive biochemical marker for infarction

High Risk	Intermediate Risk	Low Risk
TIMI Risk Score 5–7 points	TIMI Risk Score 3–4 points	TIMI Risk Score 0–2 points

TIMI Risk Score	Mortality, MI, or Severe Recurrent Ischemia Requiring Urgent Revascularization Through 14 Days
0/1	5%
2	8%
3	13%
4	20%
5	26%
6/7	41%

GRACE Risk Factors for Increased Mortality and the Composite of Death or MI in ACS

Signs and symptoms of HF
Low systolic BP
Elevated heart rate
Older age
Elevated SCr
Baseline risk factors on clinical evaluation: cardiac arrest at admission, ST-segment deviation, elevated troponin
A high-risk patient is defined as a GRACE Risk Score more than 140 points (for in-hospital mortality)
The clinical application tool is available at https://www.outcomes-umassmed.org/GRACE/default.aspx

HEART Score is composed of 5 components: History, **E**lectrocardiogram (ECG), **A**ge, **R**isk factors, and **T**roponin. For each component 0, 1, or 2 points are given.

Low Risk: 0–3 points
Intermediate Risk: 4–6 points
High Risk: ≥ 7 points
A clinical application tool is available at https://www.mdcalc.com/heart-score-major-cardiac-events

ACS, acute coronary syndrome; BP, blood pressure; CAD, coronary artery disease; DM, diabetes mellitus; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; HTN, hypertension; MI, myocardial infarction; NSTE, non–ST-segment elevation; SCr, serum creatinine; TIMI, thrombolysis in myocardial infarction.

Modified with permission from Rogers KC, de Denus S, Finks SW, Spinler SA. Acute coronary syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:169.

ALGRAWANY

Table 9–2

Indications and Contraindications to Fibrinolytic Therapy for Management of ST-Segment Elevation Myocardial Infarction[3]

Indications

1. Ischemic symptoms for at least 20 minutes in duration but 12 hours or less since symptom onset
   and
   ST-segment elevation of at least two contiguous leads of ≥ 2 mm in men and ≥ 1.5 mm in women in leads V_2-V_3 and/or of ≥ 1 mm in other leads, or new or presumed new left bundle-branch block
2. Ongoing ischemic chest discomfort at least 20 minutes in duration 12–24 hours since symptom onset
   and
   ST-segment elevation of at least two contiguous leads of ≥ 2 mm in men and ≥ 1.5 mm in women in leads V_2-V_3 and/or of ≥ 1 mm in other leads

Absolute Contraindications

- Active internal bleeding (not including menses)
- Previous intracranial hemorrhage or stroke of unknown origin at any time
- Previous ischemic stroke within 3 months
- Intracranial neoplasm or arteriovenous malformation
- Suspected aortic dissection
- Significant closed head or facial trauma within 3 months
- Intracranial or intraspinal surgery in prior 2 months
- Severe uncontrolled hypertension unresponsive to emergency therapy

Relative Contraindications

- History of ischemic stroke > 3 months prior
- Refractory hypertension (SBP >180 and/or DBP > 110 mm Hg)
- Oral anticoagulant therapy
- Active peptic ulcer
- Prolonged (> 10 minutes) or traumatic resuscitation
- Recent (within 2–4 weeks) internal bleeding
- Major surgery < 3 weeks prior
- Noncompressible vascular punctures
- Dementia
- Pregnancy

DBP, diastolic blood pressure; SBP, systolic blood pressure.

Modified with permission from Rogers KC, de Denus S, Finks SW, Spinler SA. Acute coronary syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:177.

Patients with a high likelihood of coronary ischemia have a greater risk of adverse cardiac events but not all patients presenting with suspected NSTE-ACS have CAD. Some are eventually diagnosed with chest discomfort and nonobstructive CAD or microvascular disease.[4] In general, patients with NSTE-ACS, those with ST-segment depression (see Figure 9–1) and/or elevated troponin are at higher risk of death or new/recurrent MI. Various risk scores are available and should be used at presentation to predict the short-term and long-term event rates of patients presenting with NSTE-ACS.[4] These include the Thrombolysis in Myocardial Infarction (TIMI) risk score for NSTE-ACS, the Global Registry of Acute Coronary Events (GRACE) score, and the History, ECG, Age, Risk factors, and Troponin (HEART) score (Table 9–1).[4,16] There is a linear relationship between increasing scores and short-term risk (2–6 weeks) of adverse cardiac events including mortality, new or recurrent MI, or need for urgent revascularization.[17]

Based on the risk assessment, a management strategy is chosen and patients are either treated using (1) an early invasive strategy, which involves coronary angiography in patients classified as high-risk of CV events based on clinical characteristics (eg, high TIMI score 5–7), or (2) an ischemia-guided strategy in which patients initially receive medication therapy only and will undergo an invasive evaluation if they fail medical therapy (eg, continued ischemia despite optimal medical treatment) or have objective evidence of ischemia on noninvasive stress testing.[4] The ischemia-guided strategy is generally reserved for patients stratified as low-risk (eg, TIMI score 0–3). Moderate- to high-risk patients are typically referred for an invasive strategy of early coronary angiography.[4]

TREATMENT

Desired Outcomes

Short-term desired outcomes in a patient with ACS are (a) early restoration of blood flow to the infarct-related artery to prevent infarct expansion (in the case of MI) or prevent complete occlusion and MI (in UA); (b) prevention of death and other MI complications; (c) prevention of coronary artery reocclusion; (d) relief of ischemic chest discomfort; and (e) resolution of ST-segment and T-wave changes on the ECG. Long-term desired outcomes are control of CV risk factors, prevention of additional CV events, including reinfarction, stroke, and HF, and improvement in quality of life.

General Approach to Treatment

Selecting evidence-based therapies described in the guidelines for patients without contraindications results in lower mortality.[3,4] Regardless of whether patients receive emergent PCI or a more conservative, ischemia-guided strategy, general treatment measures for intermediate- to high-risk patients include admission to hospital, initiation of antithrombotics, oxygen administration (if oxygen saturation is low (< 90% [0.90], or respiratory distress), continuous multilead ST-segment monitoring for arrhythmias and ischemia (termed "telemetry"), frequent measurement of vital signs, bed rest for 12 hours in hemodynamically stable patients, avoidance of the Valsalva maneuver (prescribe stool softeners routinely), and pain relief (Figures 9–2 and 9–3).[3,4]

It is important to triage and treat patients according to their risk category. Patients with STE are at high risk of death, and efforts to reestablish coronary perfusion as well as adjunctive pharmacotherapy should be initiated immediately beginning prehospital and in the ED. Features identifying low-, intermediate-, and high-risk patients with NSTE-ACS are described in Table 9–1.[4] Initial approaches to treatment of STEMI and NSTE-ACS patients are outlined in Figures 9–2 and 9–3.

Reperfusion Strategies for ACS

▶ *Reperfusion Strategies for STEMIs*

KEY CONCEPT Early reperfusion therapy with primary PCI of the infarct artery within 90 minutes from the time of first medical contact is the reperfusion treatment of choice for patients with STEMI who present within 12 hours of symptom onset (see Figure 9–2).[3] Patients may not often recognize the importance of seeking immediate medical care for a variety of reasons, which include self-treatment and preconception regarding the importance or presentation of a heart attack. Thus, education for patients and their families about the symptoms of ACS is paramount to reduce delays in reperfusion.

For primary PCI in STEMI, the patient is taken from the ED to the cardiac catheterization laboratory and undergoes coronary

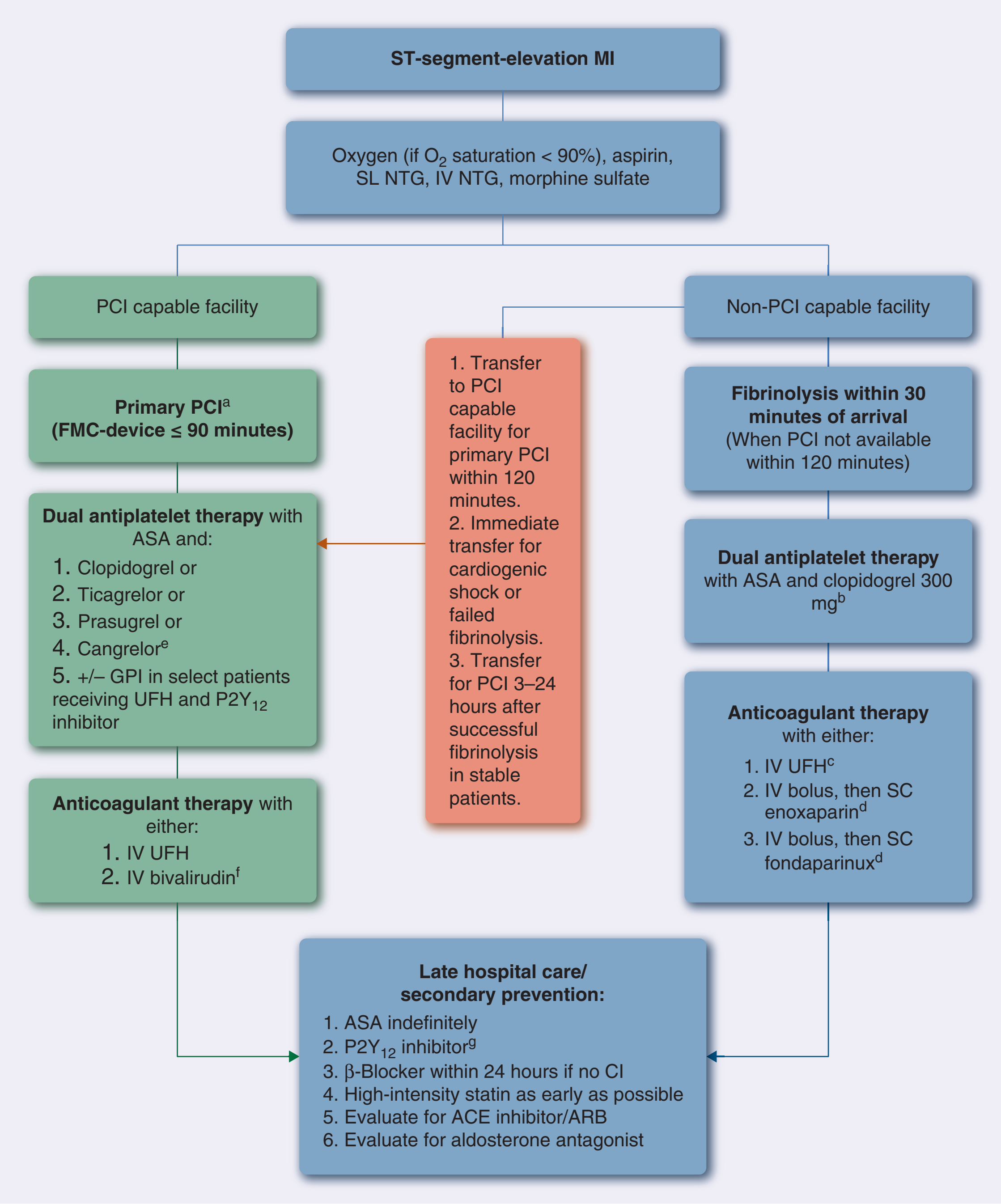
ST-segment-elevation MI
Oxygen (if O_2 saturation < 90%), aspirin, SL NTG, IV NTG, morphine sulfate
PCI capable facility
Primary PCI[a] (FMC-device ≤ 90 minutes)
Dual antiplatelet therapy with ASA and:
1. Clopidogrel or
2. Ticagrelor or
3. Prasugrel or
4. Cangrelor[e]
5. +/– GPI in select patients receiving UFH and $P2Y_{12}$ inhibitor
Anticoagulant therapy with either:
1. IV UFH
2. IV bivalirudin[f]
Non-PCI capable facility
1. Transfer to PCI capable facility for primary PCI within 120 minutes.
2. Immediate transfer for cardiogenic shock or failed fibrinolysis.
3. Transfer for PCI 3–24 hours after successful fibrinolysis in stable patients.
Fibrinolysis within 30 minutes of arrival (When PCI not available within 120 minutes)
Dual antiplatelet therapy with ASA and clopidogrel 300 mg[b]
Anticoagulant therapy with either:
1. IV UFH[c]
2. IV bolus, then SC enoxaparin[d]
3. IV bolus, then SC fondaparinux[d]
Late hospital care/ secondary prevention:
1. ASA indefinitely
2. $P2Y_{12}$ inhibitor[g]
3. β-Blocker within 24 hours if no CI
4. High-intensity statin as early as possible
5. Evaluate for ACE inhibitor/ARB
6. Evaluate for aldosterone antagonist

FIGURE 9–2. Initial pharmacotherapy for ST-segment elevation myocardial infarction (STEMI). See **Table 9–3** for dosing recommendations and contraindications to specific therapies. [a]Options after coronary angiography also include medical management alone or coronary artery bypass graft surgery. [b]Clopidogrel preferred $P2Y_{12}$ when fibrinolytic therapy is utilized. No loading dose recommended if age older than 75 years. [c]Given for up to 48 hours or until revascularization. [d]Given for the duration of hospitalization, up to 8 days or until revascularization. [e]For use as adjunct therapy during PCI only. Administer ticagrelor at any time prior to or during the cangrelor infusion. Administer prasugrel or clopidogrel after the cangrelor infusion. [f]If pretreated with UFH, stop UFH infusion for 30 minutes prior to administration of bivalirudin (bolus plus infusion). [g]In patients with STEMI receiving a fibrinolytic or who do not receive reperfusion therapy, administer clopidogrel for at least 14 days and ideally up to 1 year. (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, aspirin; CI, contraindication; FMC, first medical contact; GPI, glycoprotein IIb/IIIa inhibitor; IV, intravenous; MI, myocardial infarction; NTG, nitroglycerin; PCI, percutaneous coronary intervention; SC, subcutaneous; SL, sublingual; UFH, unfractionated heparin.)

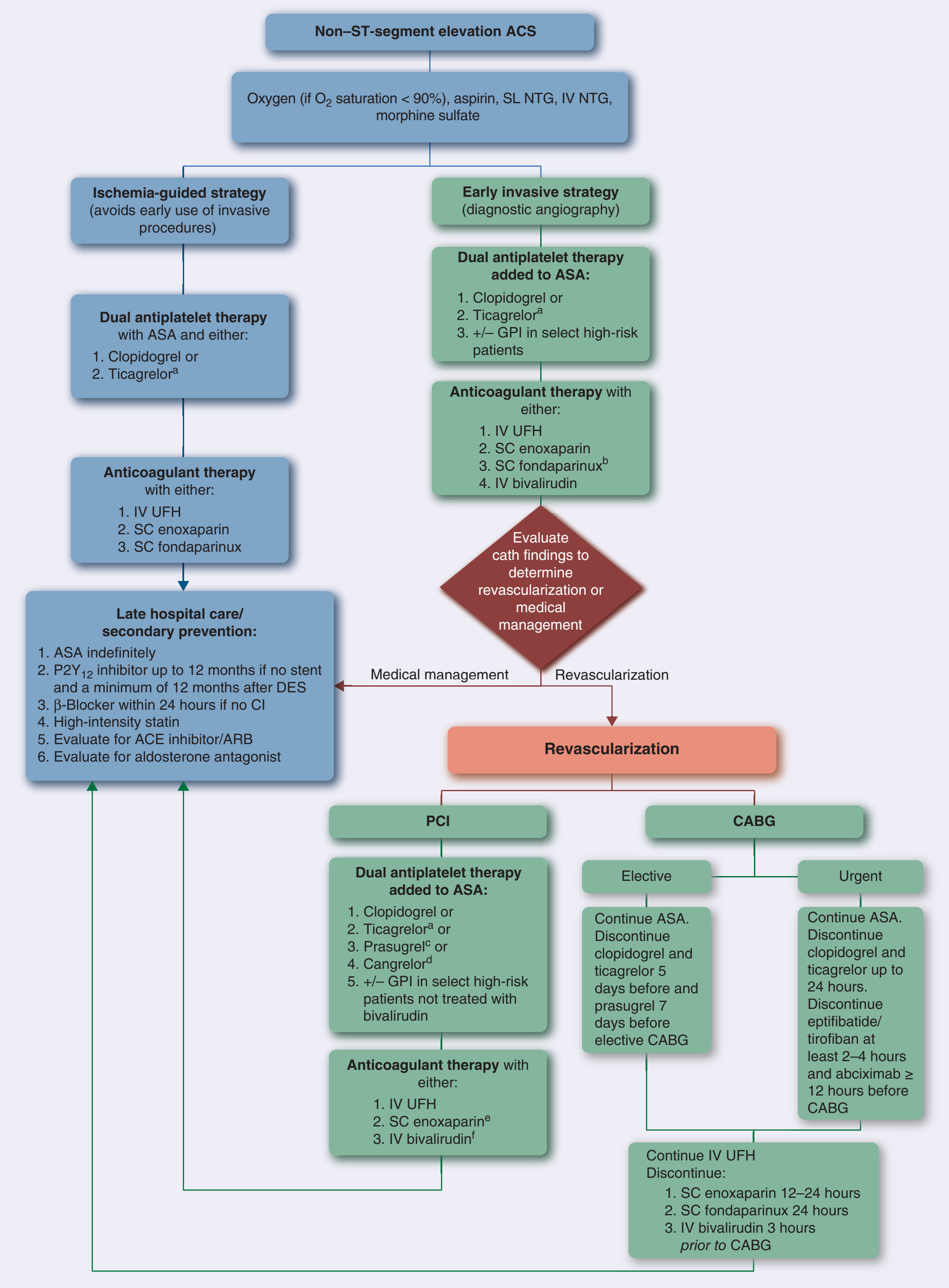
Non–ST-segment elevation ACS
Oxygen (if O_2 saturation < 90%), aspirin, SL NTG, IV NTG, morphine sulfate
Ischemia-guided strategy (avoids early use of invasive procedures)
Early invasive strategy (diagnostic angiography)
Dual antiplatelet therapy with ASA and either:
1. Clopidogrel or
2. Ticagrelor[a]
Anticoagulant therapy with either:
1. IV UFH
2. SC enoxaparin
3. SC fondaparinux
Dual antiplatelet therapy added to ASA:
1. Clopidogrel or
2. Ticagrelor[a]
3. +/– GPI in select high-risk patients
Anticoagulant therapy with either:
1. IV UFH
2. SC enoxaparin
3. SC fondaparinux[b]
4. IV bivalirudin
Evaluate cath findings to determine revascularization or medical management
Medical management
Revascularization
Late hospital care/ secondary prevention:
1. ASA indefinitely
2. $P2Y_{12}$ inhibitor up to 12 months if no stent and a minimum of 12 months after DES
3. β-Blocker within 24 hours if no CI
4. High-intensity statin
5. Evaluate for ACE inhibitor/ARB
6. Evaluate for aldosterone antagonist
Revascularization
PCI
CABG
Dual antiplatelet therapy added to ASA:
1. Clopidogrel or
2. Ticagrelor[a] or
3. Prasugrel[c] or
4. Cangrelor[d]
5. +/– GPI in select high-risk patients not treated with bivalirudin
Anticoagulant therapy with either:
1. IV UFH
2. SC enoxaparin[e]
3. IV bivalirudin[f]
Elective
Urgent
Continue ASA. Discontinue clopidogrel and ticagrelor 5 days before and prasugrel 7 days before elective CABG
Continue ASA. Discontinue clopidogrel and ticagrelor up to 24 hours. Discontinue eptifibatide/ tirofiban at least 2–4 hours and abciximab ≥ 12 hours before CABG
Continue IV UFH
Discontinue:
1. SC enoxaparin 12–24 hours
2. SC fondaparinux 24 hours
3. IV bivalirudin 3 hours
prior to CABG

FIGURE 9–3. Initial pharmacotherapy for non–ST-segment elevation (NSTE) ACS. See **Table 9–3** for dosing recommendations and contraindications to specific therapies. [a]Reasonable to choose ticagrelor over clopidogrel for maintenance $P2Y_{12}$ for NSTE-ACS patients treated with an early invasive or ischemia-guided strategy. [b]Not to be used as the sole anticoagulant during PCI. Give additional UFH 85 units/kg IV without GPI and 60 units/kg IV with GPI. [c]Reasonable to choose prasugrel over clopidogrel for maintenance $P2Y_{12}$ for NSTE-ACS patients undergoing PCI who are not at high risk for bleeding. Do not use if prior history of stroke/transient ischemic attack (TIA), age older than 75 years, or body weight less than or equal to 60 kg (132 lb). [d]Adjunct agent to be used during PCI only. Administer ticagrelor at any time prior to or during the cangrelor infusion. Administer prasugrel or clopidogrel after the cangrelor infusion. [e]May require IV supplemental dose of enoxaparin; see **Table 9–3**. [f]If pretreated with UFH, stop UFH infusion for 30 minutes prior to administration of bivalirudin bolus plus infusion. (ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; ASA, aspirin; CABG, coronary artery bypass graft; CI, contraindication; DES, drug-eluting stent; GPI, glycoprotein IIb/IIIa inhibitor; IV, intravenous; NTG, nitroglycerin; PCI, percutaneous coronary intervention; SC, subcutaneous; SL, sublingual; UFH, unfractionated heparin).

Patient Encounter 1, Part 1

A 71-year-old, 80 kg (176 lb) man developed substernal chest tightness and left arm and shoulder pain while shopping with his wife. When it was not relieved by rest, his wife called 911. Local paramedics arrived and ST-segment elevation was found on 12-lead ECG. He was given a total of three 0.4 mg sublingual nitroglycerin tablets by mouth over three successive doses, 325 mg ASA by mouth, and morphine 2-mg intravenous (IV) push without relief of discomfort upon transport to the ED. He was taken to a facility with a cardiac catheterization laboratory with the intent of performing primary PCI.

PMH: Hypertension (HTN) for 10 years; dyslipidemia for 10 years; diabetes mellitus (DM) type 2 for 15 years; chronic kidney disease (CKD) for 2 years

FH: Mother with DM; father with MI at age 55 years; siblings with HTN and DM

SH: Nonsmoker, never smoked

Allergies: NKDA

Meds: Ramipril 5 mg by mouth once daily; hydrochlorothiazide 25 mg by mouth once daily; ASA 81 mg by mouth once daily; atorvastatin 20 mg by mouth once daily

ROS: substernal chest discomfort

PE:

HEENT: Normocephalic atraumatic

CV: Regular rate and rhythm; S_1, S_2, no S_3, no S_4; no murmurs or rubs

VS: BP 150/90 mm Hg; HR 92 beats/min; T 37°C (98.6°F)

Lungs: Fine crackles at the lower bases

Abd: Nontender, nondistended

GI: Normal bowel sounds

GU: Stool guaiac negative

Exts: No bruits, no peripheral edema, pulses 2+, femoral pulses present, good range of motion

Neuro: Alert and oriented × 3, cranial nerves intact

Labs: Sodium 144 mEq/L (mmol/L), potassium 4.4 mEq/L (mmol/L), chloride 103 mEq/L (mmol/L), bicarbonate 21 mEq/L (mmol/L), SCr 1.6 mg/dL (141 μmol/L), glucose 155 mg/dL (8.6 mmol/L), WBC $8.9 \times 10^3/\text{mm}^3$ (8.9×10^9/L), hemoglobin 14.7 g/dL (147 g/L or 9.12 mmol/L), hematocrit 45% (0.45), platelets $210 \times 10^3/\text{mm}^3$ (210×10^9/L), hs-cTnI 8.9 ng/L (99th percentile 5 ng/L), oxygen saturation 98% (0.98) on room air, N-terminal proBNP 500 pg/mL (ng/L; 59 pmol/L)

ECG: Normal sinus rhythm, PR 0.16 seconds, QRS 0.08 seconds, QTc 0.38 seconds, 2-mm ST-segment elevation in two or more contiguous anterior leads

CXR: No active disease

Echo: Anterior wall dyskinesis, LVEF 40% (0.40)

What information is suggestive of acute MI?

Are any complications of MI present?

angiography with either balloon angioplasty or, preferably, placement of a drug-eluting intracoronary stent in the artery associated with the infarct. In most cases, drug-eluting stents are preferred over bare metal stents.[5,9] Because of the high likelihood of a complete coronary artery occlusion in patients presenting with symptoms and ST-segment elevation, results of a troponin blood test do not need to be available when the decision to proceed to primary PCI is made. Findings from a meta-analysis of trials comparing fibrinolysis with primary PCI indicate a lower mortality rate with primary PCI.[18] One reason for the superiority of primary PCI compared with fibrinolysis is that more than 90% of occluded infarct-related coronary arteries are opened with primary PCI compared with fewer than 60% with fibrinolytics.[3,5] In addition, intracranial hemorrhage (ICH) and major bleeding risks from primary PCI are lower than the risks of severe bleeding events following fibrinolysis.[19] A strategy of primary PCI is generally preferred in patients presenting to institutions with skilled interventional cardiologists and a catheterization laboratory immediately available, those in cardiogenic shock, those with contraindications to fibrinolytics, and those with continuing symptoms 12 to 24 hours after symptom onset.[3] Primary PCI is more commonly used in the United States compared to fibrinolysis. Current guidelines indicate the time from first medical contact-to-device should be less than or equal to 90 minutes, with every effort made to ensure the time to reperfusion is as short as possible.

Patients presenting to facilities that do not have interventional cardiology services can be transferred when a protocol that minimizes delays has been established between institutions and if primary PCI can be performed within the first 120 minutes of first medical contact.[3,19] Immediate transfer to a PCI-capable facility is recommended for patients who develop cardiogenic shock or acute severe HF, irrespective of the timing of presentation. PCI during hospitalization for STEMI, or transfer to a PCI-capable hospital, is also appropriate in those in whom fibrinolysis is not successful and those with persistent rest ischemia or signs of ischemia on stress testing following MI.[3,5]

▶ *Fibrinolytic Therapy for STEMI*

Administration of a fibrinolytic agent is indicated in patients with STEMI who present to the hospital within 12 hours of the onset of chest discomfort, who are initially seen at a non–PCI-capable hospital, and who have an anticipated time from first medical contact-to-device greater than 120 minutes if transferred to a PCI-capable hospital (see Figure 9–2).[3] The reduction in mortality with fibrinolysis is greatest with early administration and diminishes after 12 hours. The use of fibrinolytics between 12 and 24 hours after symptom onset should be limited to patients with ongoing ischemia. Fibrinolytic therapy is preferred over primary PCI when there is no cardiac catheterization laboratory in a hospital and the delay from first medical contact-to-device would exceed 120 minutes if the patient was transferred to a PCI-capable hospital.[3] Guidelines recommend the fibrinolytic agent be administered within 30 minutes of hospital arrival. All hospitals should have protocols addressing fibrinolysis eligibility, dosing, and monitoring. Medication errors are common in patients receiving fibrinolytics as dosing regimens are different for different indications (eg, alteplase dosing in acute ischemic stroke vs MI) and are less commonly used for MI. Indications and contraindications for

Patient Encounter 1, Part 2

Identify your acute treatment goals for this patient with STEMI.

What adjunctive pharmacotherapy should be administered in the ED prior to proceeding to the cardiac catheterization laboratory?

What additional pharmacotherapy should be initiated on the first day of this patient's hospitalization following successful PCI/intracoronary stenting?

fibrinolysis in MI are listed in Table 9–2. It is not necessary to obtain the results of biochemical markers before initiating fibrinolytic therapy.

Because administration of fibrinolytics results in clot lysis, patients who are at high risk of major bleeding (including ICH) presenting with an absolute contraindication should not receive fibrinolytic therapy; primary PCI is preferred. Alteplase, reteplase, and tenecteplase are fibrinolytics approved for treatment of MI. Streptokinase was formerly used but is no longer available in the United States. ICH and major bleeding are the most serious side effects of fibrinolytic agents. The risk of ICH was higher with alteplase versus tenecteplase in one study.[20] Fibrinolytic therapy is not indicated and should not be used in patients with NSTE-ACS because increased mortality has been reported with these agents compared with controls in clinical trials.[3,4]

▶ *Early Invasive Therapy for NSTE-ACS*

KEY CONCEPT Clinical practice guidelines recommend coronary angiography followed by either PCI or CABG surgery revascularization as an early treatment (early invasive strategy) for patients with NSTE-ACS at an elevated risk for death or MI including those with confirmed MI (by troponin or hs-troponin), a high-risk score (see Table 9–1) or patients with refractory angina, hemodynamic instability, or electrical instability (eg, ventricular arrhythmias) (see Figure 9–3).[4,5,9] Several clinical trials support an "invasive" interventional strategy with early angiography and PCI or CABG versus an ischemia-guided approach, whereby coronary angiography with revascularization is reserved for patients with symptoms refractory to pharmacotherapy and patients with signs of ischemia on stress testing.[4,21] An early invasive approach results in a long-term reduction in the rates of CV death or MI, with the largest absolute effect seen in higher-risk patients.[4] Several studies have also shown less angina, fewer hospitalizations, and improved quality of life with an invasive strategy.

All patients with ACS undergoing PCI should receive dual antiplatelet therapy (DAPT) with ASA and a $P2Y_{12}$ inhibitor antiplatelet (either clopidogrel, prasugrel, or ticagrelor) for at least 3 to 12 months following PCI regardless of stent type (Table 9–3).[3,4,22,23] A shorter duration of DAPT is suggested for patients at high risk of major bleeding, including patients requiring concomitant oral anticoagulation (eg, stroke prevention in atrial fibrillation), while a longer duration can be considered in patients who have tolerated DAPT without bleeding and are at higher risk of recurrent ischemic events (eg, second MI, DM, or multivessel CAD). After initial DAPT with aspirin and a $P2Y_{12}$ inhibitor, single antiplatelet therapy with either low-dose aspirin or a $P2Y_{12}$ inhibitor should be continued indefinitely. Clopidogrel is the preferred $P2Y_{12}$ inhibitor in patients with a high risk of bleeding as large comparative randomized trials demonstrated lower risk of major bleeding with clopidogrel compared to either prasugrel or ticagrelor.[4] The risk of ischemic events appears to be lower with prasugrel compared to ticagrelor with a similar risk of major bleeding.[24]

Ischemia-Guided Therapy ("Medical Management") for ACS

For patients with NSTE-ACS, an initial conservative ischemia-guided strategy is recommended for patients with a low-risk score, normal ECGs, and negative troponin who are without recurrence of chest discomfort (see Figure 9–3).[4] An ischemia-guided strategy may also be preferred in patients with extensive comorbidities in which the cumulative risks of comorbidities plus revascularization would outweigh the potential benefits of revascularization.

Stress testing (see Figure 9–1) is indicated in patients with NSTE-ACS when an initial ischemia-guided strategy is selected. It is also reasonable for STEMI patients who may be candidates for revascularization but did not undergo coronary angiography.[3,4] Following the stress test, patients experiencing recurrent ischemia or symptoms despite optimal medical treatment or who are considered high risk (see Table 9–1) should undergo left heart catheterization with coronary angiography and revascularization as indicated.[3,4] Patients with NSTE-ACS at low risk for recurrent CHD events following stress testing should be given low-dose ASA indefinitely and either clopidogrel or ticagrelor for up to 12 months following hospital discharge in addition to other secondary preventive pharmacotherapy described later in this chapter.[4] Patients with STEMI at low risk for recurrent CHD events should receive low-dose ASA indefinitely and clopidogrel for at least 14 days and up to 12 months in addition to other secondary preventive pharmacotherapy (see Figure 9–2).[3]

Early Pharmacologic Therapy for ACS

Pharmacotherapy for early treatment of ACS is outlined in Figures 9–2 and 9–3 and Table 9–3.[3-5] KEY CONCEPT According to ACC/ACCF/AHA STEMI and NSTE-ACS practice guidelines, pharmacotherapy that all patients should receive within the first day of hospitalization, and preferably in the ED, are intranasal oxygen (if oxygen saturation is low), sublingual (SL) nitroglycerin (NTG), ASA, a $P2Y_{12}$ inhibitor (agent and timing of administration dependent on reperfusion strategy), and anticoagulation (agent dependent on reperfusion strategy). Intravenous (IV) NTG may be given in select patients with either acute HF, severe hypertension, or who are still experiencing pain despite SL NTG. It is reasonable to administer morphine to patients with refractory angina as an analgesic and a venodilator. Oral β-blockers should be initiated within the first day in patients without cardiogenic shock or other contraindications.[3,4] ACE inhibitors (or ARB in ACE inhibitor-intolerant patients) should be initiated in select patients during hospitalization with ACS.[3] High-intensity statin therapy should be initiated or continued during hospitalization in all patients without contraindications. Dosing and contraindications for SL and IV NTG, ASA, clopidogrel, β-blockers, ACE inhibitors, statins, anticoagulants, and fibrinolytics are listed in Table 9–3.

▶ *Morphine*

While morphine is an effective analgesic and may reduce preload in patients presenting with ACS, administration has been found to delay the absorption of $P2Y_{12}$ inhibitors and their active metabolites resulting in a delay and attenuation of their antiplatelet effects.[25-27] The use of morphine has been associated with increased risk of recurrent in-hospital MI in some ACS studies

Table 9–3

Evidence-Based Pharmacotherapy for ST-Segment Elevation Myocardial Infarction (STEMI) and Non–ST-Segment Elevation Acute Coronary Syndrome (NSTE-ACS)[3,4,20]

Drug	Clinical Condition and Guideline Recommendations[a]	Contraindications[b]	Dose and Duration of Therapy
Antiplatelets			
Aspirin	STEMI, class I recommendation for all patients. NSTE-ACS, class I recommendation for all patients.	Hypersensitivity, active bleeding, severe bleeding risk.	162–325 mg orally once on hospital day 1. 81–325 mg orally once daily starting hospital day 2 and continued indefinitely in all patients. Aspirin dose of 81 mg is preferred. Limit dose to < 100 mg if using ticagrelor.
Clopidogrel	NSTE-ACS, class I recommendation added to aspirin. STEMI, class I recommendation added to aspirin. PCI in STEMI and NSTE-ACS, class I recommendation. In patients with aspirin allergy, class I recommendation.	Hypersensitivity, active bleeding, severe bleeding risk.	NSTE-ACS: 300- to 600-mg oral loading dose on hospital day 1 followed by a maintenance dose of 75 mg once daily starting on hospital day 2. STEMI: 300-mg oral loading dose followed by 75 mg orally daily in patients receiving a fibrinolytic or who do not receive reperfusion therapy; avoid loading dose in patients ≥ 75 years. 600-mg (class I recommendation) loading dose before or when PCI performed (unless within 24 hours of fibrinolytic therapy, a dose of 300 mg should be given). Discontinue at least 5 days before CABG surgery if bleeding risk outweighs benefit (class I recommendation). Administer indefinitely in patients with aspirin allergy (class I recommendation). Continue for at least 12 months (class I recommendation) and possibly beyond 12 months (class IIb recommendation) in patients with ACS managed with PCI/stent. In patients with NSTE-ACS treated medically, administer for up to 12 months (class I recommendation). In patients receiving a fibrinolytic or who do not receive reperfusion therapy, administer for at least 14 days (class I recommendation) and ideally up to 12 months. Genetic testing might be considered to identify patients at high risk of poor response (class IIb recommendation). In these patients, an alternative $P2Y_{12}$ inhibitor might be considered (class IIb recommendation). The routine use of genetic testing is not recommended (class III recommendation).
Prasugrel	PCI in STE and NSTE-ACS, added to aspirin, class I recommendation. Class IIa as preference over clopidogrel for those not at high risk of bleeding and do not have a history of stroke/TIA.	Active bleeding, prior stroke or TIA. Not recommended in patients not receiving PCI.	Initiate in patients with known coronary artery anatomy only (so as to avoid use in patients needing CABG surgery; class I recommendation). Give no later than 1 hour after PCI. Patients who have history of prior stroke/TIA, are 75 years of age or more, or weigh < 60 kg (132 lb) have higher risk of bleeding, and there is no added benefit compared with clopidogrel. 60-mg oral loading dose followed by 10 mg once daily for patients weighing 60 kg (132 lb) or more. Consider 5 mg once daily in patients weighing < 60 kg (132 lb) (based on limited data). Discontinue at least 7 days prior to CABG surgery if bleeding risk outweighs benefit (class I recommendation). Continue for at least 12 months (class I recommendation) and possibly beyond 12 months (class IIb recommendation) in patients with ACS managed with PCI/stent.

(Continued)

Table 9–3

Evidence-Based Pharmacotherapy for ST-Segment Elevation Myocardial Infarction (STEMI) and Non–ST-Segment Elevation Acute Coronary Syndrome (NSTE-ACS)[3,4,20] (*Continued*)

<table>
<tr><th>Drug</th><th>Clinical Condition and Guideline Recommendations[a]</th><th>Contraindications[b]</th><th>Dose and Duration of Therapy</th></tr>
<tr><td>Ticagrelor</td><td>PCI in STEMI and NSTE-ACS, added to aspirin, class I recommendation. Class IIa as preference over clopidogrel.</td><td>Active bleeding.</td><td>180-mg (class I recommendation) oral loading dose in patients undergoing PCI or ischemia-guided management, followed by 90 mg twice daily for at least 12 months (class I recommendation) and possibly beyond 12 months (class IIb recommendation) in patients with ACS managed with PCI/stent.
Current data are too limited to recommend use in patients with STEMI not undergoing primary PCI.
Discontinue at least 5 days prior to CABG surgery if bleeding risk outweighs benefit (class I recommendation).</td></tr>
<tr><td>Cangrelor</td><td>PCI-adjunct in patients not pre-treated with oral $P2Y_{12}$ inhibitor or GPI.</td><td>Active bleeding.</td><td>30 mcg/kg IV bolus initiated prior to PCI followed by 4 mcg/kg/min IV infusion for duration of PCI or 2 hours, whichever is longer. To maintain platelet inhibition after infusion, initiate oral $P2Y_{12}$ agent as follows: load ticagrelor 180 mg at any time during or immediately after infusion; load prasugrel 60 mg or clopidogrel 600 mg immediately after discontinuation of infusion. Do not administer prasugrel or clopidogrel during infusion of cangrelor. There is no antiplatelet effect of cangrelor 1 hour after discontinuation of infusion.</td></tr>
<tr><td>Glycoprotein IIb/IIIa receptor inhibitors</td><td>NSTE-ACS PCI, class I recommendation for high-bolus dose tirofiban or double-bolus eptifibatide at the time of PCI in high-risk patients already receiving aspirin and not adequately pretreated with a $P2Y_{12}$ inhibitor and not receiving bivalirudin as the anticoagulant; class IIa at the time of PCI for high-risk patients already receiving aspirin and pretreated with a $P2Y_{12}$ inhibitor and receiving UFH; class IIb for early invasive strategies in high-risk patients already receiving DAPT; eptifibatide or tirofiban preferred.
STEMI primary PCI, class IIa recommendation for high-bolus dose tirofiban or double-bolus eptifibatide in patients receiving UFH; IIb for administration of upstream GPI when PCI is intended.</td><td>Active bleeding, thrombocytopenia, prior stroke, renal dialysis (eptifibatide).</td><td>
<table>
<tr><th>Drug</th><th>Dose</th><th>Dosing Adjustment for CKD</th></tr>
<tr><td>Eptifibatide</td><td>180 mcg/kg IV bolus (max 22.6 mg) × 2, 10 minutes apart with an infusion of 2 mcg/kg/min (max 15 mg/hour) for 18–24 hours after PCI.</td><td>Reduce maintenance infusion to 1 mcg/kg/min for CrCl < 50 mL/min (0.83 mL/s); contraindicated if patient dependent on dialysis.</td></tr>
<tr><td>Tirofiban</td><td>25 mcg/kg IV bolus followed by an infusion of 0.15 mcg/kg/min for up to 18 hours.</td><td>Reduce maintenance infusion to 0.075 mcg/kg/min for patients with CrCl ≤ 60 mL/min (1.0 mL/s).</td></tr>
</table>
</td></tr>
</table>

Anticoagulants			
Unfractionated heparin	STEMI, class I recommendation in patients undergoing PCI and for those patients treated with fibrinolytics. NSTE-ACS, class I recommendation in combination with antiplatelet therapy for ischemia-guided or early invasive approach PCI, class I recommendation (NSTE-ACS and STEMI).	Active bleeding, history of heparin-induced thrombocytopenia, severe bleeding risk, recent stroke.	STEMI with fibrinolytics: initial 60-units/kg IV bolus (maximum 4000 units) followed by a constant IV infusion at 12 units/kg/hour (maximum 1000 units/hour). Titrate to therapeutic aPTT. STEMI primary PCI: administer 50- to 70 units/kg IV bolus if a GPI planned; 70–100 units/kg IV bolus if no GPI planned and supplement with IV bolus doses to maintain target ACT. NSTE-ACS: administer 60 units/kg IV bolus (maximum 4000 units) followed by a constant IV infusion at 12 units/kg/hour (maximum 1000 units/hour). Titrated to maintain an aPTT of 1.5–2.0 times control (~ 50–70 seconds) for STEMI with fibrinolytics and for NSTE-ACS. Titrated to ACT of 250–350 seconds for primary PCI without a GPI and 200–250 seconds in patients given a concomitant GPI. The first aPTT should be measured at 4–6 hours for NSTE-ACS and STEMI in patients not treated with fibrinolytics or undergoing primary PCI. The first aPTT should be measured at 3 hours in patients with STEMI who are treated with fibrinolytics. Continue for 48 hours or until revascularization.
Enoxaparin	STEMI class I recommendation in patients receiving fibrinolytics. NSTE-ACS, class I recommendation in combination with aspirin for ischemia-guided or early invasive strategy. For PCI, class I recommendation as an alternative to UFH in patients with NSTE-ACS.	Active bleeding, history of heparin-induced thrombocytopenia, severe bleeding risk, recent stroke, avoid enoxaparin if CrCl < 15 mL/min (0.25 mL/s), avoid if CABG surgery planned.	NSTE-ACS: Enoxaparin 1 mg/kg SC every 12 hours for patients (CrCl ≥ 30 mL/min [0.50 mL/s]). Enoxaparin 1 mg/kg SC every 24 hours (CrCl 15–29 mL/min [0.25–0.49 mL/s]). For all patients undergoing PCI following initiation of SC enoxaparin for NSTE-ACS or STEMI, a supplemental 0.3 mg/kg IV dose of enoxaparin should be administered at the time of PCI if the last dose of SC enoxaparin was given 8–12 hours prior to PCI or received < 2 therapeutic SC doses. STEMI with fibrinolytics: • Age < 75 years: Administer enoxaparin 30 mg IV bolus followed in 15 minutes by 1 mg/kg SC every 12 hours (maximum of 100 mg for first two doses). • Age ≥ 75 years: Administer enoxaparin 0.75 mg/kg SC every 12 hours (maximum of 75 mg for first two doses). • Continue throughout hospitalization, up to 8 days, or until revascularization. Continue for duration of hospitalization for NSTE-ACS or until revascularization. Discontinue at least 12–24 hours before CABG surgery.
Bivalirudin	NSTE-ACS class I recommendation for invasive strategy. PCI in STEMI (class I recommendation).	Active bleeding, severe bleeding risk.	NSTE-ACS planned early invasive strategy: Administer 0.1 mg/kg IV bolus followed by 0.25-mg/kg/hour infusion. PCI in NSTE-ACS: Administer a second bolus of 0.5 mg/kg IV and increase infusion rate to 1.75 mg/kg/hour if already receiving bivalirudin PCI in NSTE-ACS and STEMI: Administer 0.75-mg/kg IV bolus followed by 1.75 mg/kg/hour infusion if not already receiving bivalirudin If prior UFH given, discontinue UFH and wait 30 minutes before initiating bivalirudin. CrCl < 30 mL/min (0.50 mL/s): Adjust dose of infusion to 1 mg/kg/hour Hemodialysis: Adjust dose of infusion to 0.25 mg/kg/hour Lower bleeding rates are mitigated when administered with a GPI. Clopidogrel should be administered at least 6 hours before if a GPI is not used. Discontinue at least 3 hours prior to CABG surgery.

(*Continued*)

Table 9–3

Evidence-Based Pharmacotherapy for ST-Segment Elevation Myocardial Infarction (STEMI) and Non–ST-Segment Elevation Acute Coronary Syndrome (NSTE-ACS)[3,4,20] (*Continued*)

Drug	Clinical Condition and Guideline Recommendations[a]	Contraindications[b]	Dose and Duration of Therapy
Fondaparinux	STEMI class I recommendation receiving fibrinolytics. NSTE-ACS class I recommendation for ischemia-guided or early invasive strategy. Class III as sole agent in PCI.	Active bleeding, severe bleeding risk, SCr ≥ 3.0 mg/dL (265 μmol/L) or CrCl < 30 mL/min (0.50 mL/s).	STEMI: 2.5-mg IV bolus followed by 2.5-mg SC once daily starting on hospital day 2. NSTE-ACS: 2.5-mg SC once daily. Continue throughout hospitalization, up to 8 days, or until revascularization. For PCI, give additional doses of either UFH or bivalirudin as recommended above. Discontinue at least 24 hours prior to CABG surgery.
Fibrinolytic therapy	STEMI, class I recommendation for patients presenting within 12 hours following the onset of symptoms, class IIa in patients presenting between 12 and 24 hours following the onset of symptoms with continuing signs of ischemia. NSTE-ACS, class III recommendation.	Any prior ICH, known structural cerebrovascular lesions such as an arterial venous malformation, known intracranial malignant neoplasm, ischemic stroke within 3 months, active bleeding (excluding menses) or known bleeding diathesis, significant closed head or facial trauma within 3 months, severe uncontrolled HTN unresponsive to treatment.	Alteplase: 15-mg IV bolus followed by 0.75 mg/kg IV over 30 minutes (maximum 50 mg) followed by 0.5 mg/kg (max 35 mg) over 60 minutes (maximum total dose 100 mg). Reteplase: 10 units IVP over 2 minutes × 2 doses, 30 minutes apart. Tenecteplase: Single bolus administered over 5 seconds • < 60 kg: 30-mg IV bolus • 60–69 kg: 35-mg IV bolus • 70–79 kg: 40-mg IV bolus • 80–89 kg: 45-mg IV bolus • > 90 kg: 50-mg IV bolus • Consider reducing the dose by 50% in patients ≥ 75 years to reduce the risk of ICH
Nitroglycerin	STEMI and NSTE-ACS, class I recommendation in patients with ongoing ischemic discomfort, control of HTN, or management of HF.	Hypotension, sildenafil, avanafil, tadalafil, or vardenafil are all contraindicated with nitrates.	0.4-mg SL, repeated every 5 minutes × 3 doses then assess need for IV infusion. 5- to 10-mcg/min IV infusion titrated up to 75–100 mcg/min until relief of symptoms or limiting side effects (headache) with a systolic BP < 90 mm Hg or > 30% below starting mean arterial pressure levels if significant HTN is present. Topical patches or oral nitrates are acceptable alternatives for patients without ongoing or refractory symptoms. Discontinue IV infusion after 24–48 hours.
β-Blockers[c]	STEMI and NSTE-ACS, class I recommendation for oral β-blockers in all patients without contraindications in the first 24 hours, class IIa for IV β-blockers in STEMI patients with HTN or those with ongoing ischemia. Class III for IV β-blockers in patients with risk factors for shock.	PR ECG interval > 0.24 seconds, second-degree or third-degree atrioventricular heart block without a pacemaker, heart rate < 60 beats/min, systolic BP < 90 mm Hg, shock, left ventricular failure with decompensated HF, severe reactive airway disease.	Metoprolol 5-mg slow IV push (over 1–2 minutes), repeated every 5 minutes for a total of 15 mg followed in 1–2 hours by 25–50 mg orally every 6-12 hours; if a very conservative regimen is desired, initial doses can be reduced to 1–2 mg. Atenolol 5-mg IV dose followed in 5 minutes by a second 5-mg IV dose for a total of 10 mg followed in 1–2 hours by 50–100 mg orally once daily. Alternatively, initial IV therapy can be omitted and treatment started with oral dosing. For dosing of carvedilol, metoprolol succinate, and bisoprolol in patients with systolic HF, please refer to Chapter 7. Continue oral β-blocker for 3 years and possibly indefinitely.

Calcium channel blockers	NSTE-ACS class I recommendation for patients with ongoing ischemia or vasospasm who are already taking adequate doses of nitrates and β-blockers or in patients with contraindications or intolerance to β-blockers (diltiazem or verapamil preferred during initial presentation if EF > 40% [0.40]). NSTE-ACS, class IIb recommendation for diltiazem for patients with AMI.	Pulmonary edema, evidence of left ventricular dysfunction, systolic BP < 100 mm Hg, PR ECG segment to > 0.24 seconds second- or third-degree atrioventricular heart block for verapamil or diltiazem, pulse rate < 60 beats/min for diltiazem or verapamil.	Diltiazem 120–360 mg sustained release orally once daily. Verapamil 180–480 mg sustained release orally once daily. Amlodipine 5–10 mg orally once daily. Continue as indicated to manage angina, HTN, or arrhythmias.		
ACE inhibitors	NSTE-ACS and STEMI, class I recommendation for patients with HF, left ventricular dysfunction and EF < 40% (0.40), DM, HTN, or stable CKD in the absence of contraindications. Consider in all patients with CAD (class I recommendation, class IIb in low-risk patients). Indicated indefinitely for all patients with EF < 40% (0.40) (class I recommendation).	Systolic BP < 100 mm Hg, history of intolerance to an ACE inhibitor, bilateral renal artery stenosis, serum potassium > 5.5 mEq/L (mmol/L), acute renal failure, pregnancy.	**Drug**	**Initial Dose (mg)**	**Target Dose (mg)**
			Captopril	6.25–12.5	25–50 orally three times daily
			Enalapril	2.5–5.0	10 twice daily orally
			Lisinopril	2.5–5.0	10–20 once daily orally
			Ramipril	2.5	5 twice daily or 10 once daily orally
			Trandolapril	1.0	4 once daily orally
			Continue indefinitely.		
Angiotensin receptor blockers	NSTEMI and STEMI, class I recommendation in patients with HF or left ventricular EF < 40% (0.40) and intolerant of an ACE inhibitor, class IIa recommendation in patients with clinical signs of HF or EF < 40% (0.40) and no documentation of ACE inhibitor intolerance. Class I in other ACE inhibitor–intolerant patients with HTN.	Systolic BP < 100 mm Hg, bilateral renal artery stenosis, serum potassium > 5.5 mEq/L (mmol/L), acute renal failure, pregnancy.	**Drug**	**Initial Dose (mg)**	**Target Dose (mg)**
			Candesartan	4–8	32 once daily orally
			Valsartan	20	160 twice daily orally
			Losartan	12.5–25	150 daily
			Continue indefinitely.		
Aldosterone antagonists	NSTEMI and STEMI class I recommendation in patients with EF ≤ 40% (0.40) and either DM or HF who are already receiving an ACE inhibitor and β-blocker.	Hypotension, hyperkalemia, serum potassium > 5.0 mEq/L (mmol/L), SCr ≥ 2.5 mg/dL (221 μmol/L) for men and ≥ 2.0 mg/dL (177 μmol/L) for women and/or CrCl ≤ 30 mL/min (0.5 mL/s). Concomitant strong CYP3A inhibitors with eplerenone.	**Drug**	**Initial Dose (mg)**	**Target Dose (mg)**
			Eplerenone	25	50 once daily orally
			Spironolactone	12.5	25–50 once daily orally
			Continue indefinitely.		

(*Continued*)

Table 9–3

Evidence-Based Pharmacotherapy for ST-Segment Elevation Myocardial Infarction (STEMI) and Non–ST-Segment Elevation Acute Coronary Syndrome (NSTE-ACS)[3,4,20] (*Continued*)

Drug	Clinical Condition and Guideline Recommendations[a]	Contraindications[b]	Dose and Duration of Therapy	
Morphine sulfate	STEMI and NSTE-ACS class IIb recommendation for patients whose chest pain persists despite treatment with maximally tolerated anti-anginal drugs.	Hypotension, respiratory depression, confusion, obtundation.	1- to 5-mg IV bolus dose. May be repeated every 5–30 minutes as needed to relieve symptoms and maintain patient comfort.	
Statins	NSTE-ACS and STEMI class I recommendation to initiate or continue high-intensity statin therapy during early hospital care. For patients > 75 years of age, it is reasonable to initiate moderate- or high-intensity statin therapy.	Caution with use of fibrate and statin-specific drug interactions. Contraindicated in active liver disease.	**Dose Adjustment for CKD** Atorvastatin 40–80 mg daily. Rosuvastatin 20–40 mg daily. Continue indefinitely.	No adjustment needed. Reduce initial dose to 5 mg in CrCl < 50 mL/min (0.50 mL/s); max dose 10 mg daily.

[a] Class I recommendations are conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective. Class II recommendations are those conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment. For class IIa recommendations, the weight of the evidence/opinion is in favor of usefulness/efficacy. Class IIb recommendations are those for which usefulness/efficacy is less well established by evidence/opinion. Class III recommendations are those where the procedure or treatment is not useful and may be harmful.

[b] Allergy or prior intolerance is a contraindication for all categories of drugs listed in this chart.

[c] Choice of the specific agent is not as important as ensuring that appropriate candidates receive this therapy. If there are concerns about patient intolerance due to existing pulmonary disease, especially asthma, selection should favor a short-acting agent, such as metoprolol, or the ultra short-acting agent esmolol. Mild wheezing or a history of chronic obstructive pulmonary disease should prompt a trial of a short-acting agent at a reduced dose (eg, 2.5-mg IV metoprolol, 12.5-mg oral metoprolol, or 25-mcg/kg/min esmolol as initial doses) rather than complete avoidance of β-blocker therapy.

ACE, angiotensin-converting enzyme; ACT, activated clotting time; AMI, acute myocardial infarction; aPTT, activated partial thromboplastin time; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; CrCl, creatinine clearance; CYP, cytochrome P450; DAPT, dual antiplatelet therapy; DM, diabetes mellitus; ECG, electrocardiogram; EF, ejection fraction; GPI, glycoprotein IIb/IIIa inhibitor; HF, heart failure; HTN, hypertension; ICH, intracranial hemorrhage; IV, intravenous; IVP, intravenous push; PCI, percutaneous coronary intervention; SC, subcutaneous; SCr, serum creatinine; SL, sublingual; TIA, transient ischemic attack; UFH, unfractionated heparin.

Modified with permission from Rogers KC, de Denus S, Finks SW, Spinler SA. Acute coronary syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:173–176.

Patient Encounter 2, Part 1

A 55-year-old, 81 kg (178 lb) man presents to the ED by ambulance complaining of chest pressure and nausea for 4 hours after awakening from sleep. His symptoms were not relieved with two antacid tablets. Local paramedics were called who gave the patient a total of three 0.4 mg sublingual nitroglycerin tablets over three successive doses and 325 mg ASA by mouth without relief of chest discomfort. The patient is transferred to the hospital where an early invasive strategy is chosen.

PMH: Dyslipidemia and HTN for 5 years

FH: Father died after MI at age 50; mother and brother alive with HTN and dyslipidemia

SH: Nonsmoker

Allergies: NKDA

Meds: Atorvastatin 80 mg by mouth once daily at bedtime; aspirin 81 mg by mouth daily; amlodipine 10 mg by mouth once daily

ROS: Chest pressure and nausea

PE:

HEENT: Normocephalic atraumatic

CV: Regular rate and rhythm; S_1, S_2, no S_3, no S_4; no murmurs or rubs

VS: BP 150/88 mm Hg; HR 86 beats/min; T 37°C (98.6°F)

Lungs: Clear to auscultation and percussion

Abd: Nontender, nondistended

GI: Normal bowel sounds

GU: Stool guaiac negative

Exts: No bruits, no peripheral edema, pulses 2+, femoral pulses present, good range of motion

Neuro: Alert and oriented × 3, cranial nerves intact

Labs: Sodium 140 mEq/L (mmol/L), potassium 3.7 mEq/L (mmol/L), chloride 101 mEq/L (mmol/L), bicarbonate 24 mEq/L (mmol/L), SCr 0.8 mg/dL (71 μmol/L), glucose 88 mg/dL (4.9 mmol/L), WBC $4.9 \times 10^3/\text{mm}^3$ (4.9×10^9/L), hemoglobin 13.9 g/dL (139 g/L or 8.6 mmol/L), hematocrit 44% (0.44), platelets $220 \times 10^3/\text{mm}^3$ (220×10^9/L), hs-cTnI < 2 ng/L (99th percentile 5 ng/L), oxygen saturation 97% (0.97) on room air, BNP 550 pg/mL (ng/L; 159 pmol/L)

ECG: Normal sinus rhythm, PR 0.16 seconds, QRS 0.08 seconds, QTc 0.38 seconds, 1-mm ST-segment depression in inferior leads

CXR: Normal

Echo: Inferior wall dyskinesis, LVEF 55% (0.55)

What type of ACS is this?

What information is suggestive of acute MI?

but not all. Some clinicians advocate repeating the loading dose of the $P2Y_{12}$ inhibitor 6 to 8 hours after the last dose of opiate.

▶ Nitrates

Nitrates promote the release of nitric oxide from the endothelium, which results in venous and arterial vasodilation. Venodilation lowers preload and myocardial oxygen demand. Arterial vasodilation may lower blood pressure (BP), thus reducing myocardial oxygen demand. Arterial vasodilation also relieves coronary artery vasospasm, dilating coronary arteries to improve myocardial blood flow and oxygenation. Randomized clinical trials failed to show a mortality benefit for IV nitrate therapy followed by oral nitrate therapy in acute MI.[4]

In patients presenting with ACS, one SL NTG tablet should be administered every 5 minutes for up to three doses to relieve myocardial ischemia, unless contraindicated. IV NTG may be initiated in patients who have persistent ischemia, acute HF, or uncontrolled hypertension in the absence of contraindications.[3,4] IV NTG is typically continued until revascularization is performed or for approximately 24 hours following ischemia relief.

The most significant adverse effects of nitrates are tachycardia, flushing, headache, and hypotension. Nitrate administration is contraindicated in patients who have received oral phosphodiesterase-5 inhibitors.[4]

▶ Aspirin

ASA is the preferred antiplatelet agent in the treatment of ACS.[3,4] The antiplatelet effects of ASA are mediated by inhibiting the synthesis of TXA_2 through an irreversible inhibition of platelet cyclooxygenase-1.

In patients receiving fibrinolytics, ASA reduces mortality, and its effects are additive to fibrinolysis alone.[28] In patients undergoing PCI, ASA prevents acute thrombotic occlusion during the procedure. Additionally, in patients undergoing PCI, ASA, in addition to a $P2Y_{12}$ inhibitor, reduces the risk of stent thrombosis. ASA reduces the risk of death or MI by approximately 50% compared with no antiplatelet therapy in patients with NSTE-ACS.[28] Therefore, ASA remains the cornerstone of early treatment for all ACSs.

In patients experiencing an ACS, an initial dose of at least 162 mg nonenteric-coated ASA is recommended to achieve a rapid platelet inhibition. Current guidelines for STEMI and NSTE-ACS recommend an initial ASA dose of 162 to 325 mg (see Table 9–3).[3,4] This first dose can be chewed to achieve high blood concentrations and platelet inhibition rapidly. Current data suggest that although an initial dose of 162 to 325 mg is required, long-term therapy with doses of 75 to 150 mg daily are as effective as higher doses. Therefore, a daily maintenance dose of 81 mg is recommended as part of DAPT.[29] In patients receiving ticagrelor, the maximum recommended maintenance dose of ASA is 100 mg daily. Higher doses were associated with increased ischemic events in a large clinical trial and is a boxed warning in the product label.[4] The duration of DAPT was discussed previously in this chapter. The duration of single antiplatelet therapy with either ASA or a $P2Y_{12}$ inhibitor should be continued indefinitely following either STEMI or NSTE-ACS.[3,4,30]

The most frequent side effects of ASA are dyspepsia and nausea. Patients should be counseled about the risk of bleeding, especially gastrointestinal (GI) bleeding (see Table 9–3).[28] Nonsteroidal anti-inflammatory agents (NSAIDs) other than ASA as well as cyclooxygenase-2 (COX-2) selective anti-inflammatory agents are contraindicated and should be discontinued at the time of ACS secondary to increased risk of death, reinfarction, HF, and myocardial rupture.[3,4]

▶ Platelet P2Y$_{12}$ Inhibitors

Figures 9–2 and 9–3 and Table 9–4 outline the role of antiplatelets in ACS. Clopidogrel, prasugrel, ticagrelor, and cangrelor block the P2Y$_{12}$ receptor, a subtype of ADP receptor, on platelets which prevents the binding of ADP to the receptor and subsequent expression of platelet GP IIb/IIIa receptors and reduces platelet activation and aggregation. Both clopidogrel and prasugrel are thienopyridines and prodrugs that are converted to an active metabolite by a variety of cytochrome P-450 (CYP) isoenzymes, the most critical appearing to be CYP2C19 for clopidogrel (Table 9–4).[28] Both of these agents bind irreversibly to P2Y$_{12}$ receptors. Ticagrelor, which is not a thienopyridine, is a reversible, noncompetitive P2Y$_{12}$ receptor inhibitor. Ticagrelor's parent compound has antiplatelet effects and is also metabolized primarily by CYP3A4 to an active metabolite producing additional antiplatelet effects. Both prasugrel and ticagrelor are more potent ADP inhibitors than clopidogrel. Clopidogrel, ticagrelor, and prasugrel are administered orally with a loading dose followed by a maintenance dose. Cangrelor is the only intravenous P2Y$_{12}$ inhibitor approved as an adjunct to PCI in patients who did not receive prior oral P2Y$_{12}$ inhibitors or planned GP IIb/IIIa inhibitors (GPIs) to reduce the risk of periprocedural MI, revascularization, and stent thrombosis. Currently, there are no US guideline recommendations describing the role of cangrelor in ACS.

Prasugrel has the fewest significant drug–drug interactions of the oral agents. Moderate and strong inhibitors of CYP2C19 reduce the production of clopidogrel's active metabolite and consequently its antiplatelet effect, whereas strong inhibitors of CYP3A increase ticagrelor's exposure. Cangrelor is an active drug that undergoes rapid dephosphorylation in the circulation and has no drug–drug interactions involving the CYP system. A more detailed discussion of the drug interactions with clopidogrel and proton pump inhibitors (PPIs) may be found in Chapter 8, "Stable Ischemic Heart Disease."

Genetic variations in the gene coding for *CYP2C19* significantly modulate the antiplatelet effects of clopidogrel. Specifically, carriers of reduced-function allele (ie, *2 or *3) are not able to convert clopidogrel to its active metabolite to the extent of carriers of the wild-type allele. This results in decreased antiplatelet effects which could translate into higher rates of CV events, especially stent thrombosis and periprocedural MI.[28,31] As the efficacy of prasugrel and ticagrelor is not associated with *CYP2C19* genotype, these agents may be considered preferred agents in carriers of *CYP2C19* reduced-function alleles.[28,32] Nevertheless, due to the absence of a large randomized trial demonstrating the benefit of such genotype-based approach, the most recent clinical practice guidelines of the ACC/AHA/SCAI have not endorsed routine genotyping to guide the prescription of P2Y$_{12}$ inhibitors.[3,4] Most recently, the largest clinical trial comparing pharmacogenetic-guided therapy with ticagrelor for carriers and clopidogrel for noncarriers failed to show a benefit in the primary composite ischemic endpoint.[33] Administration of a P2Y$_{12}$ inhibitor, in addition to low-dose ASA, is recommended for all patients with ACS.[3,4,30] For patients with STEMI undergoing primary PCI, clopidogrel, prasugrel, ticagrelor, or cangrelor in addition to ASA, should be administered to prevent subacute stent thrombosis and long-term CV events (see Table 9–3 and Figure 9–2).[3-5,30] The more potent P2Y$_{12}$ inhbitors, ticagrelor or prasugrel, may be preferred in this setting.

In patients with STEMI receiving fibrinolytics, either clopidogrel or ticagrelor may be used.[3,24,34] Early therapy with clopidogrel 75 mg once daily administered during hospitalization and up to 28 days (mean: 14 days) reduced mortality and reinfarction without increasing the risk of major bleeding.[28] In adult patients 75 years or younger receiving fibrinolytics, a 300-mg loading dose of clopidogrel followed by 75 mg daily is recommended; in those older than 75 years, the loading dose should be omitted.[3] Clopidogrel should be continued for at least 14 days (and up to 1 year in the absence of bleeding) for patients presenting with STEMI who undergo reperfusion therapy with fibrinolysis.[3,34]

A large randomized trial demonstrated noninferiority of ticagrel to clopidogrel in patients with STEMI receiving fibrinolytics.[34] Most patients in the study received an initial clopidogrel loading dose and then were randomized to standard maintenance doses of either ticagrelor or clopidogrel which were continued for 12 months. Although prasugrel is recommended in the setting of STEMI and primary PCI, no studies have evaluated its use in conjunction with fibrinolytics.

In patients with NSTE-ACS who receive initial ischemia-guided therapy, ticagrelor is preferred over clopidogrel in patients not at high risk of bleeding.[4,30] In a large randomized clinical trial, ticagrelor compared with clopidogrel significantly reduced the rate of vascular death at 1 year by 22% (4% vs 5.1%), MI (5.8% vs 6.9%), and stent thrombosis (1.3% vs 1.9%).[35] There was no difference in the rate of total stroke. Although no increase in study-defined major bleeding was noted with ticagrelor, the frequency of non-CABG major bleeding was increased compared with clopidogrel (4.5% vs 3.8%). Therefore, ticagrelor is more efficacious than clopidogrel but also associated with an increased risk of bleeding. In addition, prasugrel has been compared to clopidogrel in patients with NSTE-ACS not undergoing planned revascularization.[36] There was no difference in ischemic or bleeding outcomes with prasugrel. Current guidelines recommend either clopidogrel or ticagrelor in these patients.[4]

A large randomized double-blind study demonstrated that prasugrel compared to clopidogrel for patients undergoing PCI significantly reduced the risk of CV death or MI by 19% (9.9% vs 12.1%), as well as MI and stent thrombosis, but increased the risk of major bleeding (not ICH) by 32% (2.4% vs 1.8%).[37] Patients with a history of prior stroke or transient ischemic attack (TIA) had an increased risk of ICH and net harm from prasugrel; therefore, prior stroke or TIA are contraindications to prasugrel. Patients 75 years and older as well as those weighing less than 60 kg (132 lb) are at increased risk of bleeding with prasugrel compared with clopidogrel and received no net clinical benefit from prasugrel.

Prasugrel demonstrated reduced ischemic events and similar major bleeding as ticagrelor in a large clinical trial in patients with either NSTE-ACS or STEMI where an initial strategy of PCI was planned.[24] However, the trial was open-label and had a large percentage of patient drop-outs. Therefore, whether or not prasugrel is preferred over ticagrelor is still a matter of debate.

Cangrelor is only administered intravenously as an adjunct agent during PCI; an oral P2Y$_{12}$ agent must be initiated after PCI if cangrelor is used. Specific dosing and contraindications of the P2Y$_{12}$ inhibitors are described in Tables 9–3 and 9–4.[3,4,22]

Although a variety of blood tests can assess functional platelet aggregation inhibition to P2Y$_{12}$ inhibitors, especially clopidogrel, there is no one gold standard test. Moreover, their benefit to personalize antiplatelet regimens has not been demonstrated. Therefore, the most recent practice guidelines do not recommend routine platelet aggregation testing to determine P2Y$_{12}$ inhibitor strategy.[3-5]

Table 9–4

Clinical Considerations When Choosing a P2Y$_{12}$ Receptor Inhibitor[3-5,20]

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Pharmacologic class	Thienopyridine	Thienopyridine	Cyclopentyl triazolopyrimidine	ATP analog
ADP receptor binding	Irreversible	Irreversible	Reversible	Reversible
Pharmacokinetics	Prodrug Metabolism: Hepatic Converted twice to active metabolite primarily through CYP 2C19; 3A4, 1A2, 2B6 Half-life 6 hours No dose adjustment necessary in CKD	Prodrug Metabolism: Hepatic Converted to active metabolite through CYP 3A4 and 2B6; 2C19, 2C9 Half-life 7 hours No dose adjustment necessary in CKD	Active drug Metabolism: Hepatic Converted to active metabolite through CYP 3A4/5; 2C9 Half-life 7–9 hours No dose adjustment necessary in CKD	Active drug Metabolism: Rapidly dephosphorylzed to inactive metabolite by ATPases in vascular endothelium Half-life 3–6 minutes No dose adjustment necessary in CKD
Dosing	300 mg loading dose with fibrinolytics; 600 mg loading dose for all other patients; 75 mg daily	60 mg loading dose; 10 mg daily < 60 kg (< 132 lb): consider 5 mg daily	180 mg loading dose; 90 mg twice daily. After 12 months, can use 60 mg twice daily in patients at low risk for bleeding	30 mcg/kg bolus; 4 mcg/kg/min IV infusion continued for at least 2 hours or the duration of PCI, whichever is longer
Onset of loading dose effect	Peak platelet inhibition occurs within 2–4 hours after 600 mg load and 6–8 hours after oral 300 mg load; 3–5 days after 75 mg dose	Peak platelet inhibition reached within 60 minutes after oral 60 mg load; 3 days after 10 mg dose	Peak platelet inhibition within 60 minutes after oral 180 mg load; 2–3 days after 90 mg dose	Peak platelet inhibition within 2 minutes after 30 mcg/kg bolus
Duration of effect	3–5 days	7–10 days	3–5 days	1–2 hours
Drug and disease considerations	Genetic polymorphisms may influence efficacy Enhanced bleeding with NSAIDs; avoid use Enhanced bleeding with parenteral anticoagulants, DOACs and warfarin; monitor carefully for bleeding; target INR to 2.0–2.5 for most indications Avoid use with moderate or strong CYP2C19 inhibitors (omeprazole, esomeprazole, chloramphenicol, cimetidine, efavirenz, etravirine felbamate, fluoxetine, fluconazole, fluvoxamine, isoniazid, oxcarbazepine, ketoconazole, voriconazole); select alternative noninteracting P2Y$_{12}$ inhibitor or alternative noninteracting drug	Enhanced bleeding with parenteral anticoagulants, warfarin, DOACs, and NSAIDs, avoid use	Enhanced bleeding with parenteral anticoagulants, DOACs, warfarin, and NSAIDs Use aspirin doses < 100 mg daily Avoid use with strong CYP3A inhibitors (atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ketoconazole, ritonavir, saquinavir, telithromycin, voriconazole) Avoid use with potent CYP3A inducers (carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin) Avoid simvastatin and lovastatin doses > 40 mg daily (ticagrelor inhibits CYP3A4 and increases statin concentration) Monitor digoxin serum concentrations with any change in ticagrelor dose (ticagrelor inhibits P-glycoprotein) Unique side effects including dyspnea and bradycardia	Do not administer clopidogrel or prasugrel prior to the discontinuation of cangrelor infusion Ticagrelor may be given at any time during cangrelor infusion or immediately after the discontinuation of cangrelor infusion
Contraindications	Any active pathological bleeding	Any active pathological bleeding; any history of TIA/stroke	Any active pathological bleeding; ICH or severe hepatic disease	Significant active bleeding or hypersensitivity
Surgery hold time	5 days for elective surgery; 24 hours for urgent	7 days	5 days for elective surgery; 24 hours for urgent	1 hour
NSTE-ACS indication	May be used regardless of treatment strategy; additional non-ACS indications	Reasonable over clopidogrel in patients treated with PCI who are not at high risk for bleeding and who have no history of stroke/TIA	Reasonable over clopidogrel for NSTE-ACS patients treated with invasive or ischemia-guided approach	No US guideline recommendation; may be considered in P2Y$_{12}$ inhibitor–naïve patients undergoing PCI

(Continued)

Table 9–4

Clinical Considerations When Choosing a $P2Y_{12}$ Receptor Inhibitor[3-5,20] (*Continued*)

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
STEMI indication	Preferred when fibrinolytics used	Superior to clopidogrel in STEMI or in other high-risk patients like DM; not studied in patients receiving fibrinolytic therapy	Superior to clopidogrel; not studied in patients receiving fibrinolytic therapy	No US guideline recommendation; may be considered in $P2Y_{12}$ inhibitor–naïve patients undergoing PCI
Risk benefit considerations	Gold standard for reducing CV death and stent thrombosis compared to placebo Consider alternative if documented clopidogrel ineffectiveness (ie, poor metabolism, stent thrombosis during clopidogrel therapy)	Superior to clopidogrel with a significant increase in bleeding risk (driven mainly by reductions in MI and stent thrombosis); no clinical benefit when age ≥ 75 years or weight < 60 kg (132 lb); net harm in patients with history of TIA or stroke	Superior to clopidogrel with modest increase in major non–CABG-related bleeding; associated with an all-cause mortality reduction; consider compliance with twice daily dosing	Demonstrated better efficacy than post-PCI clopidogrel with minor increases in bleeding Has potential use as a bridge to CABG surgery in high-risk patients

ACS, acute coronary syndrome; ADP, adenosine diphosphate; ATP, adenosine triphosphate; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CV, cardiovascular; CYP, cytochrome P-450; DM, diabetes mellitus; DOAC, direct oral anticoagulant; ICH, intracranial hemorrhage; INR, international normalized ratio; IV, intravenous; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack.

From Rogers KC, de Denus S, Finks SW, Spinler SA. Acute coronary syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:179–180, with permission.

Bleeding should be carefully monitored when using $P2Y_{12}$ inhibitors. If it is recommended that a $P2Y_{12}$ inhibitor be discontinued prior to elective surgery, clopidogrel and ticagrelor should be withheld preferably for 5 days, prasugrel at least 7 days, and cangrelor for 1 hour to reduce the risk of postoperative bleeding, unless the need for revascularization outweighs the bleeding risk. If urgent CABG is necessary, discontinue clopidogrel and ticagrelor up to 24 hours before CABG to reduce the risk of major bleeding.[4,5] Rarely, thrombotic thrombocytopenic purpura (TTP) has been reported with clopidogrel.[38] In addition, the use of ticagrelor is associated with dyspnea and, rarely, ventricular pauses and bradyarrhythmias. Small nonclinically significant increases in SCr and serum uric acid have also been reported with ticagrelor.[35]

▶ *Glycoprotein IIb/IIIa Receptor Inhibitors*

GP IIb/IIIa receptor inhibitors block the final common pathway of platelet aggregation, namely cross-linking of platelets by fibrinogen bridges between the GP IIb and IIIa receptors on the platelet surface. In patients with STEMI undergoing primary PCI who are treated with unfractionated heparin (UFH), eptifibatide or tirofiban may be administered on an individual basis.[3,5] Investigations of GPIs precede the widespread use of oral DAPT and thus their benefit in modern settings is not as clear. Their use appears most appropriate and beneficial in patients who are not adequately treated with a $P2Y_{12}$ inhibitor or in those with a large thrombus burden. Routine use of a GPI is not recommended in patients who have received fibrinolytics or bivalirudin secondary to increased bleeding risk. For patients treated with bivalirudin as the anticoagulant, GPIs should only be used in select cases as clinically indicated. These agents should not be administered for medical management of patients with STEMI who will not be undergoing PCI.[3]

The role of GPIs in NSTE-ACS has diminished since $P2Y_{12}$ inhibitors are used earlier in therapy, and bivalirudin is commonly selected as the anticoagulant in patients receiving an early intervention approach. Current evidence indicates no benefit of routine use of GPIs in patients treated with an ischemia-guided approach because the bleeding risk exceeds the benefit.[4] Nevertheless, in select patients treated with an ischemia-guided approach who experience recurrent ischemia (chest discomfort and ECG changes), HF, or arrhythmias after initial medical therapy necessitating a change in strategy to angiography and revascularization, a GPI may be added to ASA prior to the angiogram, particularly if the patient is (1) not adequately pretreated with clopidogrel or ticagrelor and (2) not treated with bivalirudin.

In patients who undergo an early invasive strategy and are adequately pretreated with clopidogrel or ticagrelor, routine upstream (prior to coronary angiography) administration of a GPI is not recommended, although eptifibatide or tirofiban may be considered in select high-risk patients (troponin positive). Clinical trials have shown that eptifibatide (added to ASA and clopidogrel) prior to angiography and PCI (ie, "upstream" use) in NSTE-ACS does not reduce ischemic events and increases bleeding risk.[4,39] In patients undergoing PCI, a GPI (double-bolus eptifibatide 180 mcg/kg or high-dose bolus tirofiban 25 mcg/kg) should be used in patients presenting with high-risk features who are not adequately pretreated with clopidogrel or ticagrelor (and who are not treated with bivalirudin as the anticoagulant), and may be considered in select individuals adequately pretreated with clopidogrel.[4]

Dosing and contraindications for GPIs are described in Table 9–3. Bleeding is the most significant adverse effect associated with administration of GPIs; therefore, they should not be administered to patients with a prior history of hemorrhagic stroke or recent ischemic stroke. The risk of bleeding is increased in patients with CKD. Eptifibatide is contraindicated in patients dependent on dialysis and requires a 50% reduced infusion rate in patients with CrCl less than 50 mL/min (0.83 mL/s).[3] The rate of tirofiban infusion should also be halved in patients with CrCl less than or equal to 60 mL/min (1.0 mL/s).[3]

▶ *Anticoagulants*

All patients should receive an anticoagulant in addition to DAPT regardless of ACS type or initial treatment strategy.[3,4] Options for anticoagulant therapy are outlined in Figures 9–2 and 9–3. For patients with STEMI undergoing primary PCI, either UFH or bivalirudin is preferred.[3] Bivalirudin monotherapy reduces CV and overall mortality while minimizing bleeding compared to UFH plus a GPI. However, direct head-to-head comparisons of monotherapy with UFH and bivalirudin have not shown this bleeding advantage.[40] Anticoagulant therapy is generally discontinued after primary PCI unless a compelling reason to continue exists. When fibrinolytic therapy is utilized in STEMI, anticoagulation with either UFH, enoxaparin, or fondaparinux are administered concomitantly. In this case, anticoagulant therapy should be maintained for a minimum of 48 hours (for UFH) and preferably for the duration of the hospitalization (with enoxaparin and fondaparinux) up to 8 days after fibrinolysis or until reperfusion is performed to support patency and prevent reocclusion of the affected artery.[3] Enoxaparin dosing is adjusted for body weight and renal function, and when administered in combination with fibrinolysis, it has special dosing requirements for older patients and those weighing more than 100 kg (220 lb) (see Table 9–3).

The choice of anticoagulant for a patient with NSTE-ACS is guided by risk stratification and initial treatment strategy, either an early invasive approach with coronary angiography and PCI or an ischemia-guided strategy with angiography in select patients guided by relief of symptoms and stress testing (see Figure 9–3). For patients treated by an early invasive strategy, UFH, enoxaparin, fondaparinux, or bivalirudin are options.[4] However, due to an increased risk of catheter-related thrombosis, fondaparinux is not indicated as an anticoagulant for use during PCI. Additional heparin must be administered during PCI if fondaparinux was initially chosen for anticoagulation. Clinical trials with bivalirudin have demonstrated similar efficacy in preventing CV ischemic events with a lower bleeding rate compared to UFH or enoxaparin plus a GPI in moderate- and high-risk patients with NSTE-ACS undergoing an early invasive strategy.[28] Use of enoxaparin during PCI is considered reasonable in patients treated with upstream subcutaneous enoxaparin. Unless there is an indication for chronic oral anticoagulation (eg, stroke prevention in atrial fibrillation), therapeutic anticoagulation is not continued following PCI. Venous thromboembolism prophylaxis anticoagulation is then started and continued for the duration of hospitalization.[4] Dosing considerations for initial treatment and during PCI are outlined in Table 9–3.

In NSTE-ACS patients in whom an initial ischemia-guided strategy is planned, enoxaparin, UFH, or low-dose fondaparinux is recommended.[4] Bivalirudin has not been studied as initial therapy in this setting. When added to ASA, UFH and low-molecular-weight heparins (LMWHs) reduce the frequency of death or MI in patients presenting with NSTE-ACS compared with control/placebo in patients primarily managed with an ischemia-guided strategy.[4,28] Compared with enoxaparin, fondaparinux showed similar ischemic outcomes with a lower bleeding rate in patients with NSTE-ACS primarily managed with an ischemia-guided strategy and may be preferred in patients at high risk for bleeding.[28] However, if fondaparinux is chosen for a patient who subsequently undergoes angiography and PCI, it should be administered in combination with UFH to avoid catheter thrombosis.[4] Guideline-recommended dosing and contraindications are described in Table 9–3.

UFH is preferred following angiography in patients proceeding to CABG during the same hospitalization because it has a short duration of action following discontinuation. Because enoxaparin is eliminated renally and patients with renal insufficiency generally have been excluded from clinical trials, UFH should be considered for patients with CrCl rates of less than 30 mL/min (0.50 mL/s) (where CrCl is estimated using total patient body weight in the Cockroft–Gault equation).[4] Although recommendations for dosing adjustment of enoxaparin in patients with CrCl between 10 and 30 mL/min (0.17 and 0.50 mL/s) are listed in the product manufacturer's label, the safety and efficacy of enoxaparin in this patient population remain vastly understudied. Administration of enoxaparin should be avoided in dialysis patients with ACS. While the duration of bivalirudin infusion is generally short (several hours only), few patients with significant renal impairment have been included in clinical trials. Dose adjustments for bivalirudin in patients with CrCl less than 30 mL/min (0.50 mL/s) or on hemodialysis are recommended. Patients with SCr greater than 3.0 mg/dL (265 μmol/L) were excluded from ACS trials with fondaparinux. Fondaparinux is contraindicated in patients with CrCl less than 30 mL/min (0.50 mL/s).[4]

UFH is monitored and the dose adjusted to a target aPTT or antifactor Xa (anti-Xa) levels, whereas the dose of enoxaparin is based on actual body weight without routine monitoring of anti-Xa levels. No routine monitoring of coagulation is recommended for enoxaparin, bivalirudin, or fondaparinux. Some experts recommend anti-Xa monitoring for LMWHs (eg, enoxaparin, fondaparinux) in patients with renal impairment during prolonged courses of administration of more than several days.

Besides bleeding, the most serious adverse effect of UFH and enoxaparin is **heparin-induced thrombocytopenia**; however, the frequency is rare.[28] Bivalirudin would be the preferred anticoagulant for patients with a history of heparin-induced thrombocytopenia undergoing PCI.[5]

▶ *β-Blockers*

Oral β-blockers should be administered early in the care of patients with an ACS and continued for at least 3 years in patients with normal LVF.[3,4] In ACS, the benefit of β-blockers results mainly from the competitive blockade of β_1-adrenergic receptors located on the myocardium. β_1-Blockade produces a reduction in heart rate, myocardial contractility, and BP, decreasing myocardial oxygen demand. In addition, the reduction in heart rate increases diastolic time, thus improving ventricular filling and coronary artery perfusion. As a result of these effects, β-blockers reduce the risk for recurrent ischemia, infarct size, risk of reinfarction, and occurrence of ventricular arrhythmias in the hours and days following MI.[3,4]

The role of early β-blocker therapy in reducing MI mortality was established in the 1970s and 1980s before routine use of early reperfusion therapy. Data in the reperfusion era are derived mainly from a large clinical trial that suggests IV initiation followed by oral β-blockers early in the course of MI is associated with a lower risk of reinfarction or ventricular fibrillation. However, there may be an early risk of cardiogenic shock in patients presenting with advanced age (> 70 years), heart rate greater than 100 beats/min, systolic BP less than 120 mm Hg, or late presentation.[3,4] Therefore, initiation of β-blockers (oral preferred) should be limited to patients who are hemodynamically stable, not at increased risk for cardiogenic shock, and without signs or symptoms of acute HF. Careful assessment for any contraindications to β-blockers should be performed following initiation and prior to any dose titration. The most serious side effects of β-blocker administration early in ACS are hypotension, acute HF, bradycardia, and heart block.[3,4]

Patients already taking β-blockers can continue taking them. Patients with contraindications to their use in the first 24 hours of presentation should be reevaluated and treated with β-blockers at a later time if they become eligible. In patients presenting with acute HF, use of β-blockers should be delayed until they are stabilized. Initiation of β-blockers may be attempted before hospital discharge in most patients following resolution of acute HF. Patients with HF secondary to reduced LVF should receive one of three β-blockers: bisoprolol, sustained-release metoprolol succinate, or carvedilol.[3,4]

▶ *Additional Therapies*

Oral ACE inhibitors have been shown to decrease nonfatal and fatal major CV events.[3,4] The benefit of ACE inhibitors in patients with MI most likely comes from their ability to prevent cardiac remodeling and ultimately development of HF. The largest reduction in mortality is observed in patients with left ventricular dysfunction (low LVEF) or HF symptoms. Early initiation (within 24 hours) of an oral ACE inhibitor is recommended as benefit can be seen as early as 24 hours post-MI, especially in patients with high-risk features such as HF, low LVEF, or STEMI in the anterior location.[3,4] However, these agents should be used cautiously in the first 24 hours to avoid renal dysfunction or hypotension. The use of IV ACE inhibitors is not recommended because mortality may be increased. Administration of ACE inhibitors should be continued indefinitely in those patients without contraindications with LVEF less than 40% (0.40) and in those with HTN, stable CKD, or DM.[3,4]

To accurately assess baseline low-density lipoprotein (LDL), it is recommended to obtain a lipid panel within 24 hours, or as soon as possible, in patients presenting with an ACS.[3,4] The administration of high-intensity statins prior to PCI may reduce the risk of periprocedural MI, and hence statins should be initiated as early as possible in ACS.[5] Additionally, statins reduce the risk of CV death, recurrent MI, stroke, and the need for revascularization when initiated early in the treatment of ACS.[3,4,41] Although the primary effect of statins is to decrease LDL cholesterol, statins are believed to produce many non–lipid-lowering or "pleiotropic" effects such as anti-inflammatory and antithrombotic properties. Based on current evidence, the most recent guidelines for the management of blood cholesterol in adults recommend that patients who experience an ACS should receive high-intensity statin therapy (atorvastatin 40–80 mg daily; rosuvastatin 20–40 mg daily) if they are less than or equal to 75 years of age or those greater than 75 if considered at very high risk. For patients greater than 75, either moderate-to high-intensity statins are recommended. Moderate-intensity statins (eg, atorvastatin 10–20 mg; pravastatin 40–80 mg; rosuvastatin 5–10 mg; simvastatin 20–40 mg) would be appropriate for any patient who is not a candidate for high-intensity statins because of contraindications, at risk for statin intolerance, or have a history of statin-associated adverse drug reactions. High- and moderate-intensity statins are defined as daily statin doses required to reduce LDL cholesterol greater than or equal to 50% and 30% to 49%, respectively.[41] Thus, in the absence of contraindications and depending on age, moderate- to high-intensity statin therapy should be initiated early during hospitalization to all patients experiencing ACS.[3,4]

Patient Encounter 2, Part 2

Is reperfusion therapy with fibrinolysis indicated at this time for this patient?

What adjunctive pharmacotherapy should be administered to this patient in the ED?

▶ *Calcium Channel Blockers*

Calcium channel blockers in the setting of ACS are used for relief of continued ischemia despite β-blocker and nitrate therapy, vasospastic angina, additional need for BP lowering (ie, amlodipine), or in patients with contraindications to β-blockers. Data suggest little benefit on clinical outcomes beyond symptom relief for calcium channel blockers in the setting of ACS especially in patients with reduced LVEF.[3,4] Therefore, calcium channel blockers should be avoided in the acute management of ACS unless there is a clear symptomatic need or contraindication to β-blockers. Agent selection is based on presenting heart rate and left ventricular dysfunction (diltiazem and verapamil are contraindicated in patients with bradycardia, heart block, or reduced LVEF). Immediate-release nifedipine should be avoided because it has demonstrated reflex sympathetic activation, tachycardia, and worsened myocardial ischemia.[3,4] Dosing and contraindications are described in Table 9–3.

Secondary Prevention Following MI

The long-term goals following ACS are to (a) control modifiable CHD risk factors; (b) prevent the development of HF; (c) prevent new or recurrent MI and stroke; (d) prevent death, including sudden cardiac death; and (e) prevent stent thrombosis following PCI. Pharmacotherapy, which has been proven to decrease mortality, HF, reinfarction, stroke, and stent thrombosis should be initiated prior to hospital discharge for secondary prevention. **KEY CONCEPT** Secondary prevention therapies following MI include long-term treatment with ASA, and/or a $P2Y_{12}$ inhibitor, β-blocker, an ACE inhibitor, and a statin for secondary prevention of death, stroke, or recurrent infarction.[4] A $P2Y_{12}$ inhibitor should be continued for at least 12 months for patients undergoing PCI and for patients with NSTE-ACS receiving an ischemia-guided treatment strategy.[3-5,30] Clopidogrel should be continued for at least 14 days and ideally up to 1 year in patients with STEMI receiving thrombolytics. Other $P2Y_{12}$ inhibitors have not been studied in combination with thrombolytics; however, prasugrel may be an alternative to clopidogrel in patients who undergo delayed PCI after thrombolytics.[3] An ACE inhibitor or ARB and an aldosterone antagonist should be given to select patients. Dosing and contraindications of medication therapy are described in detail in Table 9–3. For all patients with ACS, treatment and control of modifiable risk factors such as HTN, dyslipidemia, obesity, smoking, and DM are essential.[3,4] Patients should receive proper counseling and education, both verbal and written, regarding these treatments and recommendations prior to discharge. At follow-up appointments, medication reconciliation and dose optimization improve drug adherence.[42] Use of ICDs for the prevention of sudden cardiac death following MI in patients with reduced LVF and nonsustained ventricular arrhythmias is discussed in more detail in Chapter 10, "Arrhythmias."

▶ *Aspirin*

ASA decreases the risk of death, recurrent infarction, and stroke following MI. All patients should receive daily low-dose ASA as part of DAPT.[3,4,30] The risk of major bleeding from chronic ASA therapy is approximately 2% and is dose related. Higher doses of ASA, 160 to 325 mg, are not more effective than ASA doses of 75 to 81 mg but have higher rates of bleeding. Therefore, the guidelines recommend 81 mg daily as a preferred strategy in ACS patients with or without PCI.[3,4,30]

▶ *P2Y$_{12}$ Inhibitors*

For patients with either STEMI or NSTE-ACS, clopidogrel decreases the risk of CV events and stent thrombosis compared with placebo. Compared with clopidogrel, either prasugrel or ticagrelor lowers the risk of CV death, MI, or stroke by an additional 20% to 30% depending on the patient population studied. The frequency of stent thrombosis following PCI is also lower with prasugrel or ticagrelor compared with clopidogrel. However, the rate of bleeding not related to CABG surgery is higher with both prasugrel and ticagrelor compared with clopidogrel.[35,37]

The ACC/AHA Dual Antiplatelet Therapy Focused Update recommends continuation of a P2Y$_{12}$ inhibitor for at least 12 months following PCI for ACS.[30] However, more recent data suggest that major bleeding is reduced and anti-ischemic efficacy preserved with a shorter (3–6 months) duration of DAPT.[23] Continuation of P2Y$_{12}$ inhibitors longer than 12 months may be considered in patients who have not experienced any bleeding episodes and are not at high risk for bleeding.[30] Single antiplatelet therapy with either low-dose ASA or a P2Y$_{12}$ inhibitor should be continued indefinitely. For patients with STEMI receiving fibrinolytics, clopidogrel should be continued for at least 14 days and ideally up to 1 year.[3] Ticagrelor should be continued for up to 1 year.[34] For NSTE-ACS patients who do not receive a coronary stent, clopidogrel or ticagrelor should be continued up to 1 year.[4,30]

Bleeding is an inherent risk with long-term DAPT. In fact, oral antiplatelet agents are the third leading cause of adverse drug reaction–associated hospital admissions after ED visits among seniors.[43] Therefore, patients should be counseled on the risks and sites of potential bleeding and should be told to seek medical care immediately if significant bleeding is noticed. Some patients who are at increased risk of GI bleeding (eg, patients taking concomitant oral anticoagulants) may benefit from the addition of a PPI.[30,44,45]

Evidence for duration of DAPT is evolving in the setting of ACS with or without PCI. Clinical trials are investigating a shorter duration of DAPT with different strategies of stopping aspirin and continuing a P2Y$_{12}$ inhibitor to reduce risk of bleeding in patients.

▶ *β-Blockers, Nitrates, and Calcium Channel Blockers*

Current treatment guidelines recommend that following an ACS, patients with normal LVF should receive a β-blocker for at least 3 years, indefinitely for those with reduced LVF, and may be considered longer if needed for the treatment of HTN or angina.[3,4,46] Overwhelming data support the use of β-blockers in patients with a previous MI to improve long-term survival. Currently, there are no data to support the superiority of one β-blocker over another in the absence of HF with reduced LVF.

Although β-blockers should be initially avoided in patients with decompensated HF from left ventricular systolic dysfunction complicating an acute MI, clinical trial data suggest it is safe to initiate β-blockers prior to hospital discharge in these patients once HF symptoms have resolved.[3,4] In patients who cannot tolerate or have a contraindication to a β-blocker, a calcium channel blocker can be used to prevent anginal symptoms but nondihydropyridines should not be used in patients with reduced LVF.[3,4]

Chronic long-acting nitrate therapy has not been shown to reduce CHD events following MI and is not indicated in ACS patients who have undergone revascularization, unless the patient has stable ischemic heart disease, refractory angina, coronary vasospasm, or significant coronary stenoses that were not revascularized. All patients should be prescribed short-acting SL NTG tablets or spray to relieve any anginal symptoms when necessary and instructed on its use.[3,4] If ischemic chest discomfort persists for more than 5 minutes after the first dose, the patient should be instructed to contact emergency medical services. Nitrates should not be administered to patients with hypotension or who have recently received a phosphodiesterase inhibitor (see Table 9–3).[3,4]

▶ *ACE Inhibitors and ARBs*

ACE inhibitors reduce mortality, decrease reinfarction, and prevent the development of HF with recent ACS, especially in those with reduced LVF.[3,4] Additional trials suggest that most patients with CAD, not just ACS or HF patients, benefit from ACE inhibitors. Therefore, ACE inhibitors should be considered in all patients (eg, those with HTN, DM, or stable CKD) following an ACS in the absence of a contraindication.

Besides hypotension, the most frequent adverse reaction to an ACE inhibitor is cough, which may occur in up to 30% of patients. Patients who cannot tolerate an ACE inhibitor may be prescribed an ARB. Other, less common but more serious adverse effects of ACE inhibitors and ARBs include acute renal failure, hyperkalemia, and angioedema.[3]

▶ *Aldosterone Antagonists*

Aldosterone plays an important role in HF and in MI because it promotes vascular and myocardial fibrosis, endothelial dysfunction, HTN, left ventricular hypertrophy, sodium retention, potassium and magnesium loss, and arrhythmias. Aldosterone antagonists have been shown to attenuate these adverse effects and reduce mortality in patients who are already receiving an ACE inhibitor (or ARB) and β-blocker and have an LVEF less than or equal to 40% (0.40) and either HF symptoms or DM.[3,4]

Eplerenone and spironolactone are aldosterone antagonists that block the mineralocorticoid receptor. In contrast to spironolactone, eplerenone has no effect on the progesterone or androgen receptor, thereby minimizing the risk of gynecomastia, sexual dysfunction, and menstrual irregularities. In a large clinical trial, eplerenone significantly reduced mortality as well as hospitalization for HF in post-MI patients with an LVEF less than 40% (0.40) and symptoms of HF at any time during hospitalization.[47]

The risk of hyperkalemia increases with the use of aldosterone antagonists when added to an ACE inhibitor or ARB. Therefore, patients with serum potassium concentrations greater than 5.0 mmol/L (mEq/L) should not receive these agents. Specific contraindications for spironolactone include SCr greater than or equal to 2.5 mg/dL (221 μmol/L) for men or 2.0 mg/dL (177 μmol/L) for women, or CrCl less than or equal to 30 mL/min (0.50 mL/s). Contraindications for eplerenone include SCr greater than or equal to 2.0 mg/dL (177 μmol/L) for men or 1.8 mg/dL (159 μmol/L) for women, or CrCl less than or equal to 50 mL/min (0.83 mL/s). Currently, there are no data to support that eplerenone is superior or preferred to spironolactone but it may be an option in patients who experience adverse effects including gynecomastia, breast pain, or impotence while receiving spironolactone.

▶ *Lipid-Lowering Agents*

Following MI, statins reduce total mortality, CV mortality, need for revascularization, and stroke. According to practice guidelines, all patients who have experienced ACS should receive high-intensity statin therapy provided that no contraindications exist.[4,41] Indeed, results from landmark clinical trials have unequivocally demonstrated the value of statins in secondary prevention. High-intensity statin therapy, which typically lowers LDL cholesterol by 50% or greater, is preferred because of the greatest reduction in outcomes. The current evidence indicates that higher-intensity statin therapy, such as atorvastatin 40 to 80 mg daily and rosuvastatin 10 to 20 mg daily, produces a greater reduction in CV events such as MI, ischemic stroke, and revascularization than less intensive statin regimens (such as simvastatin 20–40 mg daily). Moderate-intensity statin therapy is recommended for those who are 75 years or older if high-intensity therapy is not tolerated, or in those who have a high risk for statin-associated adverse effects such as those with drug–drug interactions.

In patients for whom a 50% reduction of LDL cholesterol is not achieved by statin therapy alone (or in whom LDL cholesterol remains ≥ 70 mg/dL [1.81 mmol/L]), nonstatin therapy may be added to the statin for therapy intensification.[41] The addition of either ezetimibe or a proprotein convertase subtilisin/kexin type (PCSK9) inhibitor to statin therapy is recommended in very high-risk patients with clinical atherosclerotic cardiovascular disease (ASCVD) after considering desired LDL reduction, potential for additional CV risk reduction, adverse events or drug–drug interactions, and patient preference.[41] Based on randomized data, ezetimibe added to statin therapy after ACS produced a modest benefit (~10% reduction) on CV outcomes.[41] Both evolocumab and alirocumab (PCSK9 inhibitors) have also demonstrated improved CV outcomes in patients with ASCVD added to maximal statin therapy with or without ezetimibe and is a reasonable alternative.[41]

▶ *Other Modifiable Risk Factors*

Smoking cessation, managing HTN, weight loss, exercise, and glucose control for patients with DM, in addition to treatment of dyslipidemia, are important treatments for secondary prevention of CHD events.[4] Referral to a comprehensive CV risk reduction program for cardiac rehabilitation is recommended.[3] HTN should be strictly controlled according to published guidelines.[46] Patients who are overweight, hypertensive, or who require cholesterol lowering should be educated on the importance of regular exercise, healthy eating habits, and reaching and maintaining an ideal weight.

Patient Encounter 2, Part 3

The patient undergoes coronary angiography and is found to have a 95% stenosis in his right coronary artery. PCI is performed and a drug-eluting stent is placed without complications.

What additional pharmacotherapy should be initiated on the first day of this patient's hospitalization following successful reperfusion with PCI?

Identify the long-term treatment goals for this patient.

Create a care plan for this patient for hospital discharge that includes pharmacotherapy, desired treatment outcomes, and monitoring for efficacy and adverse effects.

Because patients with DM have up to a fourfold increased mortality risk compared with patients without DM, the importance of blood glucose control, as well as other CHD risk factor modifications, cannot be overstated.[4] Sodium-glucose cotransporter 2 (SGLT2) inhibitors (depending on renal function) and glucagon-like peptide-1 receptor agonists (GLP-1RA) are recommended first- or second-line agents (to metformin) for managing both hyperglycemia and CV risk reduction in patients with type 2 DM.[48,49] Proposed CV risk reduction mechanisms with SGLT2 inhibitors include weight loss, blood pressure lowering, improved endothelial function, and reductions in preload and afterload, in addition to glycemic control. In clinical trials, dapagliflozin, empagliflozin, and canagliflozin have all demonstrated reduction in adverse cardiac events (composite of CV death, nonfatal MI or stroke) as well as hospitalizations for HF in patients with ASCVD. GLP1-RAs, specifically dulaglutide, liraglutide, injectable semaglutide, also have CV benefits such as weight loss, anti-inflammatory and natriuretic effects with observed reductions in blood pressure. Only liraglutide has shown reductions in cardiovascular outcomes or all-cause mortality.[50] Selection of specific agents and monitoring for adverse effects is discussed in Chapter 44 "Diabetes Mellitus."

Finally, influenza vaccination is recommended in all patients with CVD. Additionally, vaccination with the 23-valent pneumococcal polysaccharide vaccine (PCV) is recommended in those 65 years and older, as well as all high-risk individuals presenting with CVD.[4] The use of PCV-13 is reserved for patients with certain risk factors, and its use should be determined after discussion with the patient.

In patients who require treatment for musculoskeletal pain, a stepped-care approach should be taken in the selection of treatment. Acetaminophen, tramadol, and nonacetylated salicylates are preferred. Use of small doses of narcotics for short periods can be added if the aforementioned are not adequate to relieve the patient.[4] If these agents are insufficient, NSAIDs can be considered and should be used at the lowest effective dose and for the shortest possible time. Existing evidence suggests that naproxen may have the lowest risk to induce CV ischemic events, but the quality of the evidence available limits the definitiveness of assessment of its safety, particularly when it is used for long term. Importantly, all NSAIDs increase the risk of HF. If NSAIDs are used in combination with antiplatelets or anticoagulants, a PPI should be added to reduce risk of GI bleeding.[45]

OUTCOME EVALUATION

- **KEY CONCEPT** To determine the efficacy of nonpharmacologic and pharmacotherapy for both STEMI and NSTE-ACS, monitor patients for (a) relief of ischemic discomfort; (b) return of ECG changes to baseline; and (c) absence or resolution of HF signs and symptoms.
- Monitoring parameters for recognition and prevention of adverse effects from ACS pharmacotherapy are described in Table 9–5. In general, the most common adverse reactions from ACS therapies are hypotension and bleeding. To treat bleeding and hypotension, discontinue the offending agent(s) until symptoms resolve. Severe bleeding resulting in hypotension secondary to hypovolemia may require blood transfusion.
- Because poor medication adherence of secondary prevention medications following MI leads to worsened CV outcomes, patients should receive medication

Table 9–5

Therapeutic Drug Monitoring of Pharmacotherapy for Acute Coronary Syndromes

Drug	Adverse Effects	Monitoring
Aspirin	Dyspepsia, bleeding, gastritis	Clinical signs of bleeding[a]; GI upset; baseline and every 6 months: Hgb, HCT, platelet count
Clopidogrel and prasugrel	Bleeding, diarrhea, rash, TTP (rare)	Clinical signs of bleeding[a]; baseline and every 6 months: Hgb, HCT, platelet count
Ticagrelor	Bleeding, dyspnea, diarrhea, rash, elevated SCr, elevated serum uric acid	Clinical signs of bleeding[a]; baseline and every 6 months: Hgb, HCT, platelet count
Unfractionated heparin	Bleeding, heparin-induced thrombocytopenia	Clinical signs of bleeding[a]; baseline aPTT, INR, Hgb, HCT, and platelet count; ACT during cardiac catheterization; aPTT every 6 hours until target then every 24 hours; daily Hgb, HCT, and platelet count
Enoxaparin	Bleeding, heparin-induced thrombocytopenia	Clinical signs of bleeding[a]; baseline SCr, aPTT, INR, Hgb, HCT, and platelet count; daily SCr, Hgb, HCT, and platelet count
Fondaparinux	Bleeding	Clinical signs of bleeding[a]; baseline SCr, aPTT, INR, Hgb, HCT, and platelet count; daily SCr, Hgb, HCT, and platelet count
Bivalirudin	Bleeding	Clinical signs of bleeding[a]; baseline SCr, aPTT, INR, Hgb, HCT, and platelet count
Fibrinolytics	Bleeding, especially ICH	Clinical signs of bleeding[a]; baseline aPTT, INR, Hgb, HCT, and platelet count; mental status every 2 hours for signs of ICH; daily Hgb, HCT, and platelet count
GPIs	Bleeding, acute profound thrombocytopenia	Clinical signs of bleeding[a]; baseline SCr (for eptifibatide and tirofiban), Hgb, HCT, and platelet count; platelet count at 4 hours after initiation; daily Hgb, HCT, and platelet count (and SCr for eptifibatide and tirofiban)
IV nitrates	Hypotension, flushing, headache, tachycardia	BP and HR every 2 hours
β-Blockers	Hypotension, bradycardia, heart block, bronchospasm, HF, fatigue, depression, sexual dysfunction	BP, RR, HR, 12-lead ECG, and clinical signs of HF every 5 minutes with bolus IV dosing; BP, RR, HR, and clinical signs of HF every shift with oral therapy, then BP and HR every 6 months following hospital discharge
Diltiazem and verapamil	Hypotension, bradycardia, heart block, HF, constipation, gingival hyperplasia	BP and HR every shift with oral therapy, then every 6 months following hospital discharge; dental examination and teeth cleaning every 6 months
Amlodipine	Hypotension, dose-dependent peripheral edema, gingival hyperplasia	BP every shift with oral therapy, then every 6 months following hospital discharge; dental examination and teeth cleaning every 6 months
ACE inhibitors and ARBs	Hypotension, cough (with ACE inhibitors), hyperkalemia, prerenal azotemia, acute renal failure, angioedema (ACE inhibitors more so than ARBs)	BP every 4 hours × 3 for first dose, then every shift with oral therapy, then once every 6 months following hospital discharge; baseline SCr and potassium; daily SCr and potassium while hospitalized, then every 6 months (or 1–2 weeks after each outpatient dose titration); closer monitoring required in patients receiving spironolactone or eplerenone or if renal insufficiency; counsel patient on symptoms of angioedema including throat, tongue, and facial swelling
Aldosterone antagonists	Hypotension, hyperkalemia, increased SCr	BP and HR every shift with oral therapy, then once every 6 months; SCr and serum potassium concentration at baseline then at 48 hours, at 7 days, monthly for 3 months, then every 3 months thereafter
Morphine	Hypotension, respiratory depression	BP and RR 5 minutes after each bolus dose and resolution of pain
Statins	GI upset, myopathy, hepatotoxicity	Liver function tests at baseline. Lipid panel for adherence. Only repeat liver function tests if patients present with sign/symptoms of liver failure. Check a CK if muscle symptoms; counsel patient on myalgia; consider CK at baseline if adding a fibrate or niacin

[a] Clinical signs of bleeding include bloody stools, melena, hematuria, hematemesis, bruising, and oozing from arterial or venous puncture sites.

ACE, angiotensin-converting enzyme; ACT, activated clotting time; aPTT, activated partial thromboplastin time; ARB, angiotensin receptor blocker; BP, blood pressure; CK, creatine kinase; ECG, electrocardiogram; GI, gastrointestinal; GPI, glycoprotein IIb/IIIa inhibitor; HCT, hematocrit; HF, heart failure; Hgb, hemoglobin; HR, heart rate; ICH, intracranial hemorrhage; INR, international normalized ratio; IV, intravenous; RR, respiratory rate; SCr, serum creatinine; TTP, thrombotic thrombocytopenic purpura.

Modified with permission from Rogers KC, de Denus S, Finks SW, Spinler SA. Acute coronary syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:188.

counseling (including counseling prior to hospital discharge) and be monitored for medication persistence.[3,4,42] Counseling should include assessment of health literacy level, assessment of barriers to adherence, assessment of access to medications, written and verbal instructions about the purpose of each medication, changes to previous medication regimen, optimal time to take each medication, new allergies or medication intolerances, need for timely prescription fill after discharge, anticipated duration of therapy, consequences of nonadherence, common and/or serious adverse reactions that may develop, drug–drug and drug–food interactions, and an assessment of instruction understanding.

Patient Care Process

Collect Information:

- Perform a medication history for use of prescriptions, over-the-counter medications, and dietary supplements. Identify allergies to medications and other substances.
- Review the medical history and physical assessment findings for possible causes and risk factors for ACS including other symptoms and what may have relieved the patient's angina.
- Review results of the ECG which should be performed and interpreted within 10 minutes.
- Review relevant laboratory tests (eg, serial cardiac troponin levels, renal function, lipids, CBC) (Figure 9–1 and Clinical Presentation and Diagnosis textbox).
- Speak with the patient to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Risk-stratify the NSTE-ACS patient (Table 9–1).
- For patients already receiving pharmacotherapy for ACS, assess efficacy and safety including any significant drug interactions.
- Document existing contraindications and adverse events to medications in the medical record.
- Assess refill history to determine medication adherence and to identify any barriers to adherence.
- Review relevant laboratory tests.

Develop a Care Plan:

- Use risk stratification to select antithrombotic therapies for patients with NSTE-ACS and STEMI (Figures 9–2 and 9–3).
- Initiate secondary prevention therapies as appropriate before discharge.
- Ensure all patients without contraindications receive oral β-blockers, preferably within the first 24 hours of admission. Patients with initial contraindications in the first 24 hours should be reevaluated prior to discharge.
- Ensure all patients receive aspirin and statins at discharge and continue indefinitely as long as no contraindication exists.
- Initiate prescription of PPI therapy as appropriate for those at increased risk of bleeding or those requiring triple therapy with aspirin, a $P2Y_{12}$ receptor inhibitor, and an oral anticoagulant.
- Determine appropriate vaccinations prior to discharge.

Implement the Care Plan:

- Verify orders for anti-ischemic, antiplatelet, and analgesic medications where appropriate early in care and prior to discharge.
- Initiate appropriate antithrombotic medications based on ACS type and treatment strategy (Figures 9–2 and 9–3).
- Appropriately adjust all medications based on renal function, as well as baseline coagulation tests for antithrombotics (Table 9–3).
- Monitor for signs and symptoms of bleeding.
- Educate patient on discharge prescriptions. Discuss the importance of DAPT (especially in the patient receiving a stent), which should be given for 12 months after ACS regardless of stenting.
- Ensure patients receive a prescription for SL NTG at the time of discharge with instructions for use.
- Discontinue NSAIDs and select COX-2 inhibitor agents taken prior to ACS.
- Educate patient regarding appropriate secondary prevention therapies including lifestyle management with easily understandable and culturally sensitive verbal and written instructions.

Follow-up: Monitor and Evaluate:

- Follow-up within 2 weeks to assess angina symptoms and interventional success.
- Ensure appropriate use of evidence-based pharmacotherapy.
- Determine presence of any adverse events or drug interactions.
- Discuss and review adherence to medication/treatment plan.

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Abbreviations Introduced in This Chapter

ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
ACT	Activated clotting time
ADP	Adenosine diphosphate
AHA	American Heart Association
AMI	Acute myocardial infarction
aPTT	Activated partial thromboplastin time
ARB	Angiotensin receptor blocker
ASA	Aspirin
ASCVD	Atherosclerotic cardiovascular disease
ATP	Adenosine triphosphate
BNP	B-type natriuretic peptide
BP	Blood pressure
CABG	Coronary artery bypass graft (surgery)
CAD	Coronary artery disease
CBC	Complete blood count
CHD	Coronary heart disease
CKD	Chronic kidney disease
CK	Creatine kinase
COX-2	Cyclooxygenase-2
CrCl	Creatinine clearance
CV	Cardiovascular
CVD	Cardiovascular disease
CYP	Cytochrome P-450
DAPT	Dual antiplatelet therapy
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DOAC	Direct oral anticoagulant

ECG	Electrocardiogram
ED	Emergency department
EF	Ejection fraction
GI	Gastrointestinal
GLP-1RA	Glucagon-like peptide-1 receptor agonist
GP	Glycoprotein
GPI	Glycoprotein IIb/IIIa inhibitor
GRACE	Global Registry of Acute Coronary Events
HCT	Hematocrit
HEART	History, Electrocardiogram (ECG), Age, Risk factors, and Troponin
HF	Heart failure
Hgb	Hemoglobin
HMG CoA	3-Hydroxy-3-methylglutaryl coenzyme A
HR	Heart rate
HTN	Hypertension
hs-cTnI	High-sensitivity cardiac troponin I
hs-cTnT	High-sensitivity cardiac troponin T
ICD	Implantable cardioverter-defibrillator
ICH	Intracranial hemorrhage
INR	International normalized ratio
IV	Intravenous
IVP	Intravenous push
LDL	Low-density lipoprotein
LMWH	Low-molecular-weight heparin
LVEF	Left ventricular ejection fraction
LVF	Left ventricular function
MI	Myocardial infarction
NSAID	Nonsteroidal anti-inflammatory drug
NSTE	Non–ST-segment elevation
NSTEMI	Non–ST-elevation myocardial infarction
NTG	Nitroglycerin
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCV	Pneumococcal polysaccharide vaccine
PPI	Proton pump inhibitor
RR	Respiratory rate
SBP	Systolic blood pressure
SC	Subcutaneous
SCAI	Society for Cardiovascular Angiography and Interventions
SCr	Serum creatinine
SGLT2	Sodium-glucose cotransporter 2
SL	Sublingual
STE	ST-segment elevation
STEMI	ST-segment elevation myocardial infarction
TIA	Transient ischemic attack
TIMI	Thrombolysis in myocardial infarction
TTP	Thrombotic thrombocytopenic purpura
TXA_2	Thromboxane A_2
UA	Unstable angina
UFH	Unfractionated heparin

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10 Arrhythmias

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the phases of the cardiac action potential, cardiac myocyte ion currents corresponding to each phase, and the relationship between the cardiac action potential and the electrocardiogram (ECG).
2. Describe the modified Vaughan Williams classification of antiarrhythmic drugs and compare and contrast the effects of these drugs on cardiac electrophysiology.
3. Determine risk factors for and mechanisms, etiologies, symptoms, and goals of therapy of (a) sinus bradycardia, (b) atrioventricular (AV) block, (c) atrial fibrillation (AF), (d) paroxysmal supraventricular tachycardia (PSVT), (e) premature ventricular complexes (PVCs), (f) ventricular tachycardia (VT, including torsades de pointes [TdP]), and (g) ventricular fibrillation (VF).
4. Compare and contrast mechanisms of action of drugs used for ventricular rate control, conversion to sinus rhythm, and maintenance of sinus rhythm in patients with AF.
5. Compare and contrast the advantages and disadvantages of warfarin and the direct oral anticoagulants (DOACs) for prevention of stroke and systemic embolism in patients with AF.
6. Discuss nonpharmacologic methods for termination of PSVT and compare and contrast mechanisms of action of drugs used for acute termination of PSVT, as well as treatment options for long-term prevention of PSVT recurrence.
7. Describe the role of drug therapy for management of asymptomatic and symptomatic PVCs.
8. Compare and contrast mechanisms of action of drugs used for treatment of acute episodes of VT and describe options and indications for nonpharmacologic treatment of VT and VF.
9. Design individualized drug therapy treatment plans for patients with (a) sinus bradycardia, (b) AV block, (c) AF, (d) PSVT, (e) PVCs, (f) VT (including TdP), and (g) VF.

NORMAL AND ABNORMAL CARDIAC CONDUCTION AND ELECTROPHYSIOLOGY

The two primary functions of the heart are mechanical and electrical activity. Mechanical activity refers to atrial and ventricular contraction, the mechanism by which blood is delivered to tissues. Deoxygenated blood returns to the heart via the venous circulation and enters the right atrium. Right atrial contraction delivers blood to the right ventricle through the tricuspid valve. Right ventricular contraction pumps blood through the pulmonic valve and pulmonary arteries to the lungs, where it is oxygenated. The oxygenated blood then flows through the pulmonary veins into the left atrium. Left atrial contraction pumps blood through the mitral valve into the left ventricle (LV), contraction of which delivers blood through the aortic valve and to the body's tissues.

The heart's mechanical activity stems from its electrical activity. The heart possesses an intrinsic electrical conduction system (Figure 10–1). Normal function of the heart's electrical conduction system is required for normal myocardial contraction. Atrial depolarization causes atrial contraction, and ventricular depolarization produces ventricular contraction. Perturbation of the heart's electrical conduction system may result in dysfunctional atrial and/or ventricular contraction and reduce cardiac output.

Cardiac Conduction System

The sinoatrial (SA) node (frequently referred to as the sinus node), located in the upper portion of the right atrium, normally serves as the heart's pacemaker and generates the electrical impulses that

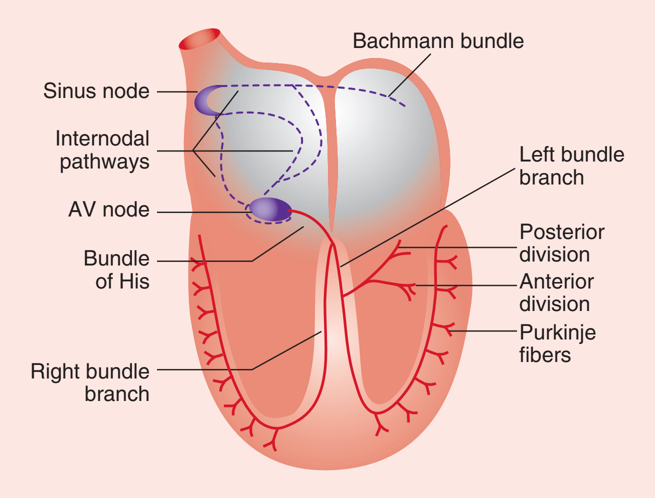

FIGURE 10–1. The cardiac conduction system. (AV, atrioventricular.)

result in atrial and ventricular depolarization (see Figure 10–1). The sinus node serves as the heart's dominant pacemaker because it has the greatest degree of automaticity, defined as the ability of a cardiac fiber or tissue to initiate depolarizations spontaneously. In adults at rest, normal intrinsic depolarization rate of the sinus node is 60 to 100 per minute. Other cardiac fibers also possess automaticity, but normally the intrinsic depolarization rates are slower than that of the sinus node. For example, normal depolarization rate of the atrioventricular (AV) node and ventricular tissue is 40 to 60 per minute and 30 to 40 per minute, respectively. As a result of greater automaticity, the sinus node normally serves as the heart's pacemaker. However, if the sinus node fails to depolarize faster than the AV node, the AV node may take over as the pacemaker. If both the sinus and AV nodes fail to depolarize faster than 30 to 40 per minute, ventricular tissue may take over.

Following initiation of the electrical impulse from the sinus node, the impulse travels through internodal pathways of the specialized atrial conduction system and the Bachmann bundle. Upon excitation via the internodal pathways and the Bachmann bundle, atrial depolarization spreads as a wave through atrial tissues, conceptually similar to throwing a pebble into water. As the impulse is conducted across the atria, each depolarized cell depolarizes the surrounding connected cells, until both atria have been completely depolarized. Atrial contraction follows normal atrial depolarization.

Following atrial depolarization, impulses are conducted through the AV node, located in the lower right atrium (Figure 10–1). The impulse then enters the bundle of His and is conducted through the ventricular conduction system, consisting of the left and right bundle branches. The LV requires a larger conduction system than the right ventricle due to its larger mass; therefore, the left bundle branch bifurcates into the left anterior and posterior divisions (also known as "fascicles"). The bundle branches further divide into the Purkinje fibers through which impulse conduction results in ventricular depolarization, initiating ventricular contraction.

Ventricular Action Potential

Ventricular action potential is depicted in Figure 10–2. Ventricular myocyte resting membrane potential is −70 to −90 mV, due to the function of the sodium–potassium adenosine triphosphatase (ATPase) pump, which maintains relatively high extracellular sodium concentrations and low extracellular potassium concentrations. During each action potential cycle, the membrane potential slowly increases due to a slow influx of sodium into the cell, raising the threshold to −60 to −80 mV. When the membrane potential reaches this threshold, the fast sodium channels open and sodium ions rapidly enter the cell. This rapid influx of positive ions creates a vertical upstroke of the action potential, which reaches 20 to 30 mV. This is phase 0, representing ventricular depolarization. At this point, the fast sodium channels become inactivated, and ventricular repolarization begins, consisting of phases 1 through 3. Phase 1 repolarization occurs primarily as a result of an efflux of potassium ions. During phase 2, potassium ions continue to exit the cell, but the membrane potential is balanced by an influx of calcium and sodium ions, transported through slow calcium and slow sodium channels, resulting in a plateau. During phase 3, the efflux of potassium ions greatly exceeds calcium and sodium influx, resulting in the major component of ventricular repolarization. During phase 4, sodium ions gradually enter the cell, increasing the threshold again to −60 to −80 mV and initiating another action potential. Understanding the ion fluxes responsible for the action potential facilitates understanding of the effects of specific drugs. Drugs that primarily inhibit ion flux through sodium channels influence phase 0 (ventricular depolarization), whereas drugs that primarily inhibit

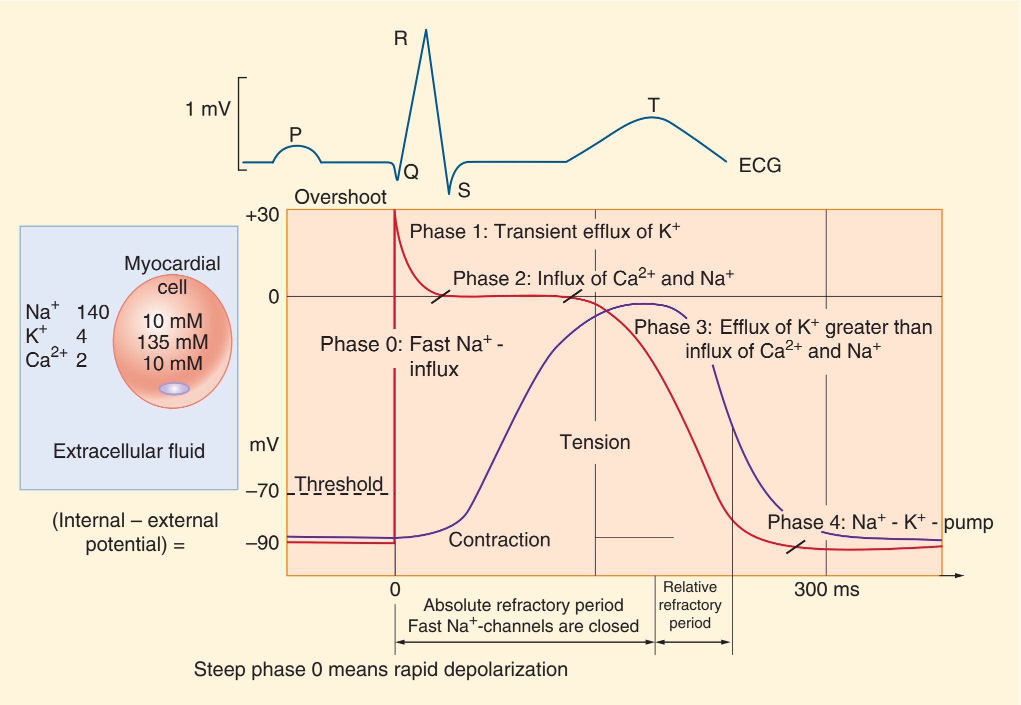
R
1 mV
P
T
Q
S
ECG
Overshoot
+30
Phase 1: Transient efflux of K⁺
Myocardial cell
Phase 2: Influx of Ca²⁺ and Na⁺
0
Na⁺ 140
K⁺ 4
Ca²⁺ 2
10 mM
135 mM
10 mM
Phase 3: Efflux of K⁺ greater than influx of Ca²⁺ and Na⁺
Phase 0: Fast Na⁺ - influx
Extracellular fluid
mV
Tension
-70
Threshold
(Internal – external potential) =
-90
Contraction
Phase 4: Na⁺ - K⁺ - pump
0
Relative refractory period
300 ms
Absolute refractory period
Fast Na⁺-channels are closed
Steep phase 0 means rapid depolarization

FIGURE 10–2. The ventricular action potential depicting the flow of specific ions responsible for each phase. The phases of the action potential that correspond to the absolute and relative refractory periods are portrayed, and the relationship between phases of the action potential and the electrocardiogram (ECG) are shown. The red line represents the ventricular action potential, and the purple line represents ventricular contraction. (Ca, calcium; K, potassium; Na, sodium.)

ion flux through potassium channels influence the repolarization phases, particularly phase 3.

Electrocardiogram

The electrocardiogram (ECG) is a noninvasive means of measuring the heart's electrical activity. The relationship between the ventricular action potential and the ECG is depicted in Figure 10–2. The P wave on the ECG represents atrial depolarization (not depicted in Figure 10–2, which shows only the ventricular action potential). Phase 0 of the action potential corresponds to the QRS complex and represents ventricular depolarization. Atrial repolarization is not visible on the ECG because it occurs during ventricular depolarization and is obscured by the QRS complex. The T wave on the ECG corresponds to phase 3 ventricular repolarization.

Several ECG intervals and durations are measured routinely. The PR interval is the time from the start of the P wave to the beginning of the QRS complex and represents conduction through the AV node. The normal PR interval in adults is 0.12 to 0.2 seconds (120–200 ms). The QRS duration represents the time required for ventricular depolarization, which is normally 0.08 to 0.12 seconds (80–120 ms) in adults. The QT interval is the time from the start of the QRS complex to the end of the T wave and is an indicator of ventricular repolarization time. The normal QT interval in adults is 0.32 to 0.4 seconds (320–400 ms). The QT interval varies with heart rate—the faster the heart rate, the shorter the QT interval, and vice versa. A number of formulas are used to correct the QT interval for heart rate (QTc). Normal QTc interval in adults is 0.36 to 0.47 seconds (360–470 ms) in men and 0.36 to 0.48 seconds (360–480 ms) in women.[1]

Refractory Periods

After an impulse is initiated and conducted, there is a period during which cells and fibers cannot be depolarized again, termed the absolute refractory period (Figure 10–2), and corresponds to phases 1, 2, and approximately the first one-third of phase 3 repolarization. The absolute refractory period corresponds to the period from the Q wave to approximately the first half of the T wave on the ECG (Figure 10–2). During this period, electrical impulses cannot be conducted because the tissue is absolutely refractory to conduction. However, there is a period following the absolute refractory period during which a premature electrical stimulus can be conducted and is often conducted abnormally, which is called the relative refractory period, corresponding to the latter two-thirds of phase 3 repolarization on the action potential and to the latter half of the T wave on the ECG. If a premature electrical stimulus is initiated during the relative refractory period (sometimes referred to as the "vulnerable period"), it can be conducted abnormally, potentially resulting in an arrhythmia.

Mechanisms of Cardiac Arrhythmias

KEY CONCEPT Cardiac arrhythmias are caused by (a) abnormal impulse initiation, (b) abnormal impulse conduction, or (c) both.

▶ *Abnormal Impulse Initiation*

Abnormal initiation of electrical impulses occurs due to abnormal automaticity. Increased automaticity is associated with an increased slope of phase 4 depolarization whereas decreased automaticity is linked to a decrease in phase 4 depolarization slope. A decrease in sinus node automaticity results in a reduced rate of impulse generation and a slow heart rate (sinus bradycardia). Conversely, an increase in sinus node automaticity results in an increased rate of impulse generation and a rapid heart rate (sinus tachycardia). If other cardiac fibers become abnormally automatic, such that the rate of spontaneous impulse initiation exceeds that of the sinus node, or premature impulses are generated, other tachyarrhythmias may occur. Many cardiac fibers possess the capability for automaticity, including atrial tissue, the AV node, the Purkinje fibers, and ventricular muscle. Also, tissue in the pulmonary veins in the left atrium can initiate and conduct electrical impulses. Abnormal atrial automaticity may result in premature atrial depolarizations or may precipitate atrial tachycardia or atrial fibrillation (AF); abnormal AV nodal automaticity may result in "junctional tachycardia" (so named because the AV node is also sometimes referred to as the AV junction). Abnormal automaticity originating from the pulmonary veins is a precipitant of AF. In addition, abnormal automaticity in the ventricles may result in premature ventricular complexes (PVCs) or may precipitate ventricular tachycardia (VT) or ventricular fibrillation (VF).

Cardiac fiber automaticity is controlled in part by sympathetic and parasympathetic nervous system activity. Enhanced sympathetic nervous system activity increases automaticity of the sinus node or other automatic cardiac fibers. Enhanced parasympathetic nervous system activity suppresses automaticity, while parasympathetic nervous system activity inhibition increases automaticity. Other factors may increase automaticity of extrasinus node tissues, including hypoxia, atrial or ventricular stretch (such as following long-standing hypertension or during and after development of heart failure [HF]), electrolyte abnormalities such as hypokalemia or hypomagnesemia, and certain drugs including digoxin and adrenergic agonists.

▶ *Abnormal Impulse Conduction*

The mechanism of abnormal impulse conduction is termed **reentry**. Reentry is often triggered as a result of an abnormal premature electrical impulse (abnormal automaticity); therefore, in these situations, the arrhythmia mechanism is both abnormal impulse formation (automaticity) and abnormal impulse conduction (reentry). For reentry to occur, three conditions must be present: (a) at least two pathways down which an electrical impulse may travel; (b) a "unidirectional block" in one of the conduction pathways ("unidirectional block" reflects prolonged refractoriness in this pathway, or increased "dispersion of refractoriness," defined as substantial variation in refractory periods between cardiac fibers); and (c) slowed impulse conduction velocity down the other conduction pathway.

The reentry process is depicted in Figure 10–3.[2] Normally, when a premature impulse is initiated, it cannot be conducted in either direction down either pathway because the tissue is in its absolute refractory period from the previous impulse. A premature impulse may be conducted down both pathways if it is only slightly premature and arrives after the tissue is no longer refractory. However, when refractoriness is prolonged down one of the pathways, a precisely timed premature beat can conduct down one pathway but cannot be conducted in either direction in the pathway with prolonged refractoriness because the tissue is still in its absolute refractory period.[2] Refractoriness may be prolonged more in one pathway than in the other due to increased dispersion of repolarization. When the third condition for reentry is present, the impulse traveling forward down the other pathway still cannot be conducted. However, because the impulse in one pathway is traveling more slowly than normal, by the time it circles around and travels upward along the other pathway, sufficient time has passed so the pathway is no longer in its absolute

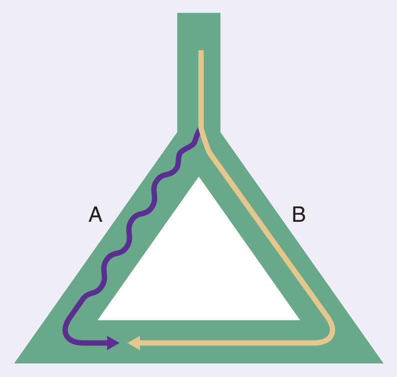

FIGURE 10–3. The process of initiation of reentry. There are two pathways for impulse conduction: slowed impulse conduction down pathway A and a longer refractory period in pathway B. A precisely timed premature impulse initiates reentry; the premature impulse cannot be conducted down pathway B because the tissue is still in the absolute refractory period from the previous, normal impulse. However, because of dispersion of refractoriness (ie, different refractory periods down the two pathways), the impulse can be conducted down pathway A. Because conduction down pathway A is slowed by the time the impulse reaches pathway B in a retrograde direction, the impulse can be conducted retrogradely up the pathway since the pathway is now beyond its refractory period from the previous impulse. This creates reentry, in which the impulse continuously and repeatedly travels in a circular fashion around the loop.

refractory period, and now the impulse may travel upward in that pathway. In other words, the electrical impulse "reenters" a previously stimulated pathway in the reverse (retrograde) direction. This results in circular movement of electrical impulses; as the impulse travels in this circular fashion, it depolarizes each cell around it, and if the impulse is traveling at a rate faster than the intrinsic rate of the sinus node, a tachycardia occurs. Reentry may occur in numerous tissues, including the atria, the AV node, and the ventricles.

Prolonged refractoriness and/or slowed impulse conduction velocity may be present in cardiac tissues for a variety of reasons. Myocardial ischemia may alter ventricular refractory periods or impulse conduction velocity, facilitating reentry. In patients with past myocardial infarction (MI), the infarcted myocardium is dead and cannot conduct impulses. However, there is typically a border zone of tissue that is damaged and in which refractory periods and conduction velocity are aberrant, facilitating ventricular reentry. In patients with left atrial or LV hypertrophy as a result of hypertension, refractory periods and conduction velocity are often perturbed. In patients with HF with reduced ejection fraction (HFrEF), ventricular refractoriness and conduction velocity are often altered due to LV hypertrophy, collagen deposition, and other anatomical and structural changes. Antiarrhythmic drugs, or other drugs affecting cardiac electrophysiology, can also alter the balance between conduction velocity and refractory periods and precipitate reentrant arrhythmias.

Vaughan Williams Classification of Antiarrhythmic Drugs

The Vaughan Williams classification of antiarrhythmic drugs is the most commonly used method for categorizing antiarrhythmic drugs (Table 10–1).[3,4] This classification is primarily based on the effects of these drugs on sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}) channels and the resultant effects on conduction velocity, repolarization/refractoriness, and automaticity. Class I drugs all block the fast Na+ channel during phase 0 depolarization resulting in decreases in ventricular automaticity and conduction velocity. However, due to differences in potency of the drugs to reduce conduction velocity, the class I drugs are subdivided into classes IA, IB, and IC. The class IC drugs are the most potent Na^+ channel blockers and markedly slow ventricular conduction but have minimal effects on refractory periods. The class IA drugs have intermediate potency and also block K^+ channels to prolong the refractory period. Class IB drugs have the lowest potency for the Na^+ channel with minimal effects on conduction velocity at normal heart rates. Class II drugs are the β-adrenergic receptor inhibitors (β-blockers). Class III drugs primarily block K^+ channels during phase 3 repolarization resulting in prolonged ventricular repolarization and refractoriness. The class IV drugs are the nondihydropyridine calcium channel blockers (CCBs) diltiazem and verapamil that predominantly block the slow Ca^{2+} channel in the sinus and AV nodes.

The Vaughan Williams classification of antiarrhythmic drugs has notable limitations. The classification is based on the effects of drugs on laboratory preparations of normal, rather than diseased, myocardium. In addition, many of the drugs affect multiple ion channels (eg, Na^+ and K^+) and may be placed into more than one class. For example, the class IA drugs, in addition to blocking Na+ channels, also block K+ channels and prolong repolarization/refractoriness, either via the parent drug or an active metabolite. The class III agent sotalol is also a β-blocker and therefore could fit into class II. Amiodarone inhibits Na^+, K^+, and Ca^{2+} channels and is also a noncompetitive inhibitor of β-receptors and therefore may be placed into any of the four classes. Thus, drugs within each class cannot be considered interchangeable. Despite these limitations, the Vaughan Williams classification continues to be widely used because of its simplicity.

CARDIAC ARRHYTHMIAS

Arrhythmias are classified into two broad categories: supraventricular (those occurring above the ventricles) and ventricular (those occurring in the ventricles). Names of specific arrhythmias are generally composed of two words, the first of which indicates location of the electrophysiological abnormality resulting in the arrhythmia (sinus node, AV node, atrial, or ventricular), and the second describes the arrhythmia as abnormally slow (bradycardia) or fast (tachycardia) or type of arrhythmia (block, fibrillation, or flutter).

SUPRAVENTRICULAR ARRHYTHMIAS

Sinus Bradycardia

Sinus bradycardia is defined by a sinus rate less than 60 beats/min.[5]

▸ *Epidemiology and Etiology*

Many individuals, particularly those who engage in regular vigorous exercise, have resting heart rates less than 60 beats/min. For those individuals, sinus bradycardia is normal and healthy, and does not require evaluation or treatment. However, some people develop symptomatic sinus node dysfunction. In the absence of correctable underlying causes, idiopathic sinus node dysfunction is referred to as sick sinus syndrome. Incidence of sick sinus syndrome is about 0.8 per 1000 person-years of follow-up, increases with advancing age, and is higher in White versus Black individuals.[6] Sinus node dysfunction accounts for roughly 50% of pacemaker implantations in the United States[6] and may also

Table 10–1

Vaughan Williams Classification of Antiarrhythmic Agents[a,3,4]

Class	Drug	Conduction Velocity[b]	Repolarization/Refractoriness[b]	Automaticity[b]	Ion Channel Block
IA	Quinidine Procainamide Disopyramide	↓	↑	↓	Na^+/K^+
IB	Lidocaine Mexiletine	0/↓	↓/0	↓	Na^+
IC	Flecainide Propafenone	↓↓	0	↓	Na^+
II	β-Blockers[c] Acebutolol Atenolol Betaxolol Bisoprolol Carteolol Carvedilol[d] Esmolol Labetalol[d] Metoprolol Nadolol Nebivolol Penbutolol Pindolol Propranolol Timolol	0	0	0	N/A
III	Amiodarone[e] Dofetilide Dronedarone[e] Ibutilide Sotalol	0	↑	0	K^+
IV	CCBs[c] Diltiazem Verapamil	0	0	0	Ca^{+2}

[a] Adenosine and digoxin are agents used for management of arrhythmias that do not fit into the Vaughan Williams classification.

[b] In ventricular tissue only; effects may differ in atria, sinus node, or atrioventricular node.

[c] Slow conduction, prolong refractory period, and reduce automaticity in sinoatrial node and atrioventricular node tissue but generally not in the ventricles.

[d] Combined α- and β-blocker.

[e] Amiodarone and dronedarone also slow conduction velocity and inhibit automaticity. Amiodarone also blocks Na^+ and Ca^{+2} channels and β-receptors.

Ca, calcium; CCB, calcium channel blocker; K, potassium; Na, sodium; ↑, increase/prolong; ↓, decrease; 0, no effect; 0/↓, does not change or may decrease: ↓/0, decreases or does not change.

Clinical Presentation and Diagnosis of Sinus Bradycardia

Symptoms

- Many patients are asymptomatic, particularly those with resting heart rates less than 60 beats/min as a result of physical fitness due to regular exercise
- Susceptible patients may develop symptoms, depending on degree of heart rate lowering
- Symptoms include dizziness, fatigue, light-headedness, syncope, chest pain (in patients with underlying coronary artery disease [CAD]), and shortness of breath and other symptoms of HF (in patients with underlying LV dysfunction)

Diagnosis

- Cannot be made on the basis of symptoms alone because the symptoms of all bradyarrhythmias are similar
- History of present illness, presenting symptoms, and 12-lead ECG showing sinus bradycardia
- Assess possible correctable etiologies, including myocardial ischemia, serum potassium concentration (for hyperkalemia), and thyroid function tests (for hypothyroidism)
- Determine whether patient is taking any drugs known to cause sinus bradycardia and discontinue if possible

manifest as the bradycardia-tachycardia syndrome (also known as tachy-brady syndrome), characterized by alternating periods of supraventricular tachyarrhythmias and bradycardia.[5]

Sick sinus syndrome leading to sinus bradycardia may be caused by degenerative changes in the sinus node that occur with advancing age. However, there are other possible etiologies of sinus bradycardia including drugs (Table 10–2).[5]

▶ *Pathophysiology*

Sick sinus syndrome leading to sinus bradycardia is due to replacement of normal sinus node tissue with fibrotic tissue.[5]

▶ *Treatment*

Desired Outcomes Desired treatment outcomes are to restore normal heart rate and alleviate patient symptoms.

Pharmacologic Therapy KEY CONCEPT Treatment of sinus bradycardia is only necessary in symptomatic patients. Any medication(s) that may cause symptomatic sinus bradycardia should be discontinued whenever possible. If the patient remains in sinus bradycardia after drug discontinuation and after five half-lives of the drug(s) have elapsed, then drug(s) can usually be excluded as the etiology. In certain circumstances, however, discontinuation may be undesirable, even if the drug causes symptomatic sinus bradycardia. For example, if the patient has a history of MI or HFrEF, discontinuation of a β-blocker may be necessary in the short term but undesirable long term because β-blockers reduce mortality and prolong life in patients with these diseases, and benefits of therapy outweigh risks associated with sinus bradycardia. In this situation, clinicians and patients may elect to implant a permanent pacemaker to allow continuation of β-blocker therapy.

Table 10–2

Etiologies of Sinus Bradycardia[5]

Idiopathic ("sick sinus syndrome")
Myocardial ischemia
Carotid sinus hypersensitivity
Neurocardiac syncope
Electrolyte abnormalities: hypokalemia or hyperkalemia
Hypothyroidism
Hypothermia
Hypoxia
Amyloidosis
Sarcoidosis
Systemic lupus erythematosus
Scleroderma
Sleep apnea
Drugs:
  Adenosine
  Amiodarone
  β-Blockers
  Cannabis
  Cisplatin
  Citalopram
  Clonidine
  Cocaine
  Dexmedetomidine
  Digoxin
  Diltiazem
  Dipyridamole
  Disopyramide
  Donepezil
  Dronedarone
  Fingolimod
  Flecainide
  Fluoxetine
  Halothane
  Isradipine
  Ivabradine
  Ketamine
  Lithium
  Methyldopa
  Neostigmine
  Nicardipine
  Nitroglycerin
  Opioid analgesics
  Paclitaxel
  Pregabalin
  Propafenone
  Propofol
  Remifentanil
  Sotalol
  Succinylcholine
  Thalidomide
  Verapamil

KEY CONCEPT Acute treatment of the symptomatic and/or hemodynamically unstable patient with sinus bradycardia includes administration of the anticholinergic drug atropine, given in doses of 0.5 mg intravenous (IV) every 3 to 5 minutes to a maximum recommended total dose of 3 mg.[5] Atropine is used to achieve acute symptom control while awaiting placement of a transcutaneous or transvenous pacemaker. Where necessary, transcutaneous pacing can be initiated during atropine administration. Atropine should be used cautiously in patients with myocardial ischemia or MI because increasing heart rate and myocardial oxygen demand may aggravate ischemia or extend the infarct. Atropine should not be used in patients post-heart transplant.[5]

In patients with hemodynamically unstable sinus bradycardia unresponsive to atropine, transcutaneous pacing may be initiated. In patients with hemodynamically unstable or severely symptomatic sinus bradycardia unresponsive to atropine and in whom temporary or transvenous pacing is not available or is ineffective, or while awaiting pacemaker placement, dopamine (5–20 mcg/kg/min starting at 5 mcg/kg/min and increasing the dose by 5 mcg/kg/min every 2 minutes based on response), epinephrine (2–10 mcg/min or 0.1–0.5 mcg/kg/min, titrate to response), or isoproterenol (20–60 mcg IV bolus followed by doses of 10–20 mcg or continuous infusion of 1–20 mcg/min, titrate to heart rate response) may be administered to increase heart rate.[5]

In patients with sinus bradycardia due to underlying correctable disorders such as electrolyte abnormalities or hypothyroidism, management consists of correcting those disorders.

Nonpharmacologic Therapy Long-term management of patients with sick sinus syndrome requires implantation of a permanent pacemaker.[5]

▶ *Outcome Evaluation*

- Monitor heart rate, goal is symptom alleviation.
- Monitor for adverse effects of medications such as atropine (dry mouth, mydriasis, urinary retention, and tachycardia).

AV Block

AV block occurs when conduction of electrical impulses through the AV node is impaired to varying degrees. AV block is classified into three categories. First-degree (1°) AV block is prolongation of the PR interval to greater than 0.2 seconds. Here, all impulses initiated by the sinus node are conducted through the AV node, but more slowly than normal, resulting in PR interval prolongation.[5,7] Second-degree (2°) AV block is subdivided into two types: Mobitz type I (also known as Wenckebach) and Mobitz type II. Mobitz type I is due to progressive lengthening of the PR interval until a P wave is not followed by a QRS complex (dropped beat). In contrast, Mobitz type II is not associated with a progressive lengthening of the PR interval prior to or after the nonconducted P wave. In both types, some of the sinus node impulses are not conducted through the AV node. This often occurs in a regular pattern; for example, there may be absence of AV nodal conduction of every third or fourth impulse. Mobitz type II has a higher risk for progression to third-degree (3°) AV block. During 3° AV block, also called "complete heart block," impulses generated by the sinus node are not conducted through the AV node. This results in AV dissociation, during

Table 10–3

Etiologies of Atrioventricular (AV) Block[5,7]

Idiopathic degeneration of the AV node
Myocardial ischemia or infarction
Neurocardiac syncope
Carotid sinus hypersensitivity
Electrolyte abnormalities: hypokalemia or hyperkalemia
Hypothyroidism
Hypothermia
Infectious diseases: Chagas disease, endocarditis, Lyme disease
Amyloidosis
Sarcoidosis
Systemic lupus erythematosus
Scleroderma
Obstructive sleep apnea
Myocarditis
Drugs:
  Adenosine
  Amiodarone
  β-Blockers
  Bupivacaine
  Carbamazepine
  Chloroquine
  Digoxin
  Diltiazem
  Dronedarone
  Fingolimod
  Flecainide
  Hydroxychloroquine
  Paclitaxel
  Propafenone
  Propofol
  Sotalol
  Thioridazine
  Tricyclic antidepressants
  Verapamil

which the atria continue to depolarize normally as a result of normal impulses initiated by the sinus node; however, the ventricles initiate their own depolarizations because no sinus node-generated impulses are conducted to the ventricles. Therefore, on the ECG, there is no relationship (dissociation) between the P waves and the QRS complexes.

▶ *Epidemiology and Etiology*

Overall incidence of AV block is unknown. AV block may occur as a result of age-related AV node degeneration. There are many other possible etiologies of AV block including drugs (Table 10–3).[5,7]

▶ *Pathophysiology*

1° AV block is due to inhibition of conduction within the upper portion of the node.[5,7] Mobitz type I 2° AV block results from inhibition of conduction further down within the node.[5,7] Mobitz type II 2° AV block is caused by inhibition of conduction within or below the level of the bundle of His.[5,7] 3° AV block may be a result of inhibition of conduction either within the AV node or within the bundle of His or the His-Purkinje system.[5,7]

▶ *Treatment*

Desired Outcomes Desired treatment outcomes are to restore normal sinus rhythm and alleviate patient symptoms.

Pharmacologic Therapy **KEY CONCEPT** Treatment of 1° AV block is rarely necessary because symptoms rarely occur. However, ECGs of patients with 1° AV block should be monitored to assess the possibility of progression to 2° or 3° block, which requires treatment because bradycardia often results in symptoms. If the patient is taking any medication(s) that may cause AV block, the drug(s) should be discontinued whenever possible. If the patient's rhythm still exhibits AV block after discontinuing the medication(s) and after five half-lives of the drug(s) have elapsed, then drug(s) can usually be excluded as the etiology. However, in certain circumstances, discontinuation of a medication that is inducing AV block may be undesirable. For example, if the patient has a history of MI or HFrEF, discontinuation of a β-blocker is undesirable, as the benefits of therapy outweigh risks associated with AV block. Here, permanent pacemaker placement to enable the patient to continue β-blocker therapy is often considered.

Clinical Presentation and Diagnosis of AV Block

Symptoms

- 1° AV block is rarely symptomatic because it rarely results in bradycardia
- 2° AV block may cause bradycardia because not all impulses generated by the sinus node are conducted through the AV node to the ventricles
- In 3° AV block, heart rate is often 30 to 40 beats/min, resulting in symptoms
- Symptoms vary from asymptomatic to dizziness, fatigue, light-headedness, syncope, chest pain (in patients with underlying CAD), and shortness of breath and other symptoms of HF (in patients with underlying HF).

Diagnosis

- Made on the basis of patient presentation, including history of present illness and presenting symptoms, as well as a 12-lead ECG that reveals AV block
- Assess potentially correctable etiologies, including myocardial ischemia, serum potassium concentration (for hyperkalemia), and thyroid function tests (for hypothyroidism)
- Determine whether the patient is taking any drugs known to cause AV block and discontinue if possible

KEY CONCEPT Acute treatment of patients with 2° or 3° AV block consists primarily of administration of atropine, given in the same doses as recommended for management of sinus bradycardia. In patients with hemodynamically unstable or severely symptomatic AV block unresponsive to atropine and in whom temporary or transvenous pacing is not available or is ineffective, epinephrine (2–10 mcg/min, titrate to response) and/or dopamine (5–20 mcg/kg/min) may be administered.[5]

In patients with 2° or 3° AV block due to underlying correctable disorders (such as electrolyte abnormalities or hypothyroidism), management consists of correcting those disorders.

Nonpharmacologic Therapy Long-term treatment of most patients with 2° or 3° AV block due to nonreversible causes requires permanent pacemaker implantation.[5]

▶ *Outcome Evaluation*

- Monitor for AV block termination and restoration of normal sinus rhythm, heart rate, and symptom alleviation.
- If atropine is administered, monitor for adverse effects, including dry mouth, mydriasis, urinary retention, and tachycardia.

Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. Understanding AF is important because it is associated with substantial morbidity and mortality, and because many strategies for drug therapy are available. Some drugs used to treat AF have a narrow therapeutic index and numerous adverse effects.

▶ *Epidemiology and Etiology*

Approximately 5.2 million Americans have AF, and as many as 8.8 million in the European Union.[6] Prevalence and incidence of AF increase with advancing age; roughly 8% of patients between 80 and 89 years old have AF. AF occurs more commonly in men than women.

Etiologies of AF are presented in Table 10–4.[8-10] The common feature of most etiologies is left atrial hypertrophy development. Hypertension may be the most important risk factor for AF development. However, AF also occurs commonly in patients with CAD. HF is increasingly recognized as a cause; approximately 25% to 30% of patients with New York Heart Association (NYHA) class III HF and as many as 50% of patients with NYHA class IV HF have AF.[11] AF is responsible for more than 467,000 annual hospitalizations in the United States.[10]

Drug-induced AF is relatively uncommon but is reported (Table 10–4).[8,12-14] Use of some bisphosphonate drugs is associated with new-onset AF, but this potential relationship requires further study.[12] Recent evidence suggests that both acute and chronic alcohol ingestion are associated with an increased risk of AF and that alcohol abstinence reduces AF recurrences.[13,14]

▶ *Pathophysiology*

AF may be caused by both abnormal impulse formation and abnormal impulse conduction. Traditionally, AF was believed to be initiated by premature impulses initiated in the atria. However, in most patients AF is triggered by electrical impulses generated within the pulmonary veins.[15] These impulses initiate the reentry process within the atria, and AF is believed to be sustained by multiple reentrant wavelets operating simultaneously within the atria. In some patients, the increased automaticity in the pulmonary veins may be the sole mechanism of AF. However, the concept of multiple simultaneous reentrant wavelets remains the predominant hypothesis regarding the mechanism of AF.[9,10]

AF leads to electrical remodeling of the atria. Episodes that are of longer duration and occur with increasing frequency result in progressive shortening of atrial refractory periods, further potentiating atrial reentry.[9] Therefore, it is often said that "atrial fibrillation begets atrial fibrillation"; that is, AF causes atrial electrophysiological alterations that further promote AF.[9,10] AF is associated with chaotic, disorganized atrial electrical activity, resulting in no atrial contraction.

AF occurs due to structural and/or electrophysiological abnormalities that promote abnormal atrial and/or pulmonary vein automaticity and/or atrial reentry.[9,10] Atrial structural abnormalities include fibrosis, dilation, ischemia, infiltration, and hypertrophy.[9,10] Other contributing factors include inflammation, oxidative stress, activation of the renin-angiotensin-aldosterone system, autonomic nervous system activation, and genetic variants in myocardial ion channels and those leading to cardiomyopathy.[9,10] A substantial amount of the atrial electrical activity occurring during AF is conducted through the AV node into the ventricles, resulting in ventricular rates ranging from 100 to 200 beats/min.

Table 10–4

Etiologies of and Risk Factors for Atrial Fibrillation (AF)[8-10]

- Older age
- Hypertension
- Myocardial infarction
- Heart failure
- Diabetes mellitus
- Hyperthyroidism
- Rheumatic heart disease
- Diseases of the heart valves:
  - Mitral stenosis or regurgitation
  - Mitral valve prolapse
- Obesity
- Smoking
- Obstructive sleep apnea
- Critical Illness
- Pericarditis
- Amyloidosis
- Myocarditis
- Pulmonary embolism
- Idiopathic
- Family history
- Genetic predisposition
- Thoracic surgery:
  - Coronary artery bypass graft surgery
  - Pulmonary resection
  - Thoracoabdominal esophagectomy
- Drugs:
  - Adenosine
  - Albuterol
  - Alcohol
  - Alendronate
  - Dobutamine
  - Dopamine
  - Doxorubicin
  - Enoximone
  - Epinephrine
  - Fingolimod
  - Interleukin-2
  - Ivabradine
  - Methylprednisolone
  - Milrinone
  - Mitoxantrone
  - Morphine
  - Paclitaxel
  - Propafenone
  - Theophylline
  - Verapamil
  - Zoledronic acid

Patient Encounter Part 1

A 67-year-old man presents to the emergency department (ED) complaining of his heart racing, shortness of breath, and fatigue. He states that this started a few hours ago and occurred at rest. He also complains of occasional light-headedness. His pulse is irregular, with a rate of 150 beats/min.

What information suggests AF?

What additional information do you need to develop a treatment plan?

Clinical Presentation and Diagnosis of AF

Symptoms

- Approximately 20% to 30% of patients with AF remain asymptomatic
- Symptoms include fatigue, palpitations, dizziness, lightheadedness, dyspnea, chest pain (if underlying CAD is present), near-syncope, and syncope. Patients commonly complain of palpitations; often the complaint is "I can feel my heart beating fast" or "I can feel my heart fluttering" or "It feels like my heart is going to beat out of my chest"
- Other symptoms depend on the degree of cardiac output reduction, which in turn depends on ventricular rate and the degree to which **stroke volume** is reduced by the rapidly beating heart
- In some patients, the first symptom of AF is stroke

Diagnosis

- Symptoms of all tachyarrhythmias depend on heart rate and can be similar, therefore diagnosis depends on presence of AF on the ECG
- Characterized on ECG by an absence of P waves (an undulating baseline that represents chaotic atrial electrical activity) and an irregularly irregular rhythm (meaning the intervals between the R waves are irregular with no pattern to the irregularity)
- Sometimes first diagnosed in patients presenting with ischemic stroke

AF is categorized into several classifications.[10] *Paroxysmal AF* terminates spontaneously or with interventions within 7 days of onset.[10] Episodes begin suddenly and spontaneously, last minutes to hours, or sometimes as long as several days, and terminate spontaneously. The frequency of recurrence in patients with paroxysmal AF is variable. *Persistent AF* is defined as continued AF of duration longer than 7 days.[10] *Long-standing persistent AF* is defined as continuous AF lasting longer than 12 months.[10] The term *permanent AF* is used when patient and clinician jointly decide to terminate further attempts to restore and/or maintain sinus rhythm.[10] Acceptance of AF represents a specific therapeutic viewpoint from the patient and clinician rather than a pathophysiological characteristic of AF and may change as symptoms, efficacy of treatments, and patient and clinician preferences develop and evolve.[10]

AF is associated with substantial morbidity and mortality, including risk of ischemic stroke of approximately 5% per year.[10] Stroke risk is increased two- to sevenfold in patients with AF compared to patients without this arrhythmia.[6] AF is the cause of roughly one of every six strokes. During AF, atrial contraction is absent. Because atrial contraction is responsible for approximately 30% of LV filling, blood that is not ejected from the left atrium to the LV pools in the atrium, particularly in the left atrial appendage. Blood pooling facilitates thrombus formation, which subsequently may travel across the mitral valve into the LV and be ejected during ventricular contraction. The thrombus then may travel through a carotid artery into the brain, resulting in an ischemic stroke. Patients with AF are also at increased risk for systemic thromboembolism. Note that risk of thromboembolism is more complex than simply blood stasis in the left atrium and likely involves many factors including inflammation, endothelial dysfunction, atrial myopathy, and many others.[9]

AF is associated with a threefold increase in risk of HF as a result of tachycardia-induced cardiomyopathy.[10] AF increases risk of dementia and mortality approximately twofold compared to patients without AF[10]; cause of death is likely stroke or HF.

▶ *Treatment*

Desired Outcomes KEY CONCEPT The goals of individualized therapy for AF are (a) ventricular rate control; (b) termination of AF and restoration of sinus rhythm (commonly referred to as "cardioversion" or "conversion to sinus rhythm"); (c) maintenance of sinus rhythm, or reduction in the frequency of episodes of paroxysmal AF; and/or (d) prevention of stroke and systemic embolism. These goals of therapy do not necessarily apply to all patients; the specific goal(s) depend on the patient's AF classification (Table 10–5).

Hemodynamically Unstable AF For patients with hemodynamically unstable AF, emergent conversion to sinus rhythm is necessary using **direct current cardioversion** (DCC). Hemodynamic instability is defined as the presence of any of the following: (a) acutely altered mental status; (b) hypotension (systolic blood pressure < 90 mm Hg) or other signs of shock; (c) ischemic chest discomfort; and/or (d) acute HF.[16]

DCC is the process of administering a synchronized electrical shock to the chest. The purpose of DCC is to simultaneously depolarize all of the myocardial cells, resulting in interruption and termination of the multiple reentrant circuits and restoration of normal sinus rhythm. The recommended initial energy level for conversion of AF to sinus rhythm is 120 to 200 Joules (J) for biphasic shocks or 200 J for monophasic shocks. If the DCC attempt is unsuccessful, DCC energy should be increased in a stepwise fashion.[11] Shock delivery is synchronized to the ECG by the cardioverter machine, such that the electrical charge is not delivered during the latter portion of the T wave (ie, the relative refractory period) to avoid delivering an electrical impulse

Table 10–5

Treatment Goals According to Atrial Fibrillation (AF) Classification

Paroxysmal AF	Persistent AF	Long-Standing Persistent AF	Permanent AF
Ventricular rate control Prevention of stroke and systemic embolism Maintenance of sinus rhythm *if ventricular rate control is not sufficient to control symptoms*	Ventricular rate control Prevention of stroke and systemic embolism Conversion to sinus rhythm	Ventricular rate control Prevention of stroke and systemic embolism Conversion to sinus rhythm	Ventricular rate control Prevention of stroke and systemic embolism

that may be conducted abnormally, which may result in a life-threatening ventricular arrhythmia ("R-on-T phenomenon").

The remainder of this section is devoted to pharmacologic management of hemodynamically stable AF.

Ventricular Rate Control Ventricular rate control can be achieved by inhibiting the proportion of electrical impulses conducted from the atria to the ventricles through the AV node. Drugs that are effective for ventricular rate control inhibit AV node impulse conduction: β-blockers, diltiazem, verapamil, digoxin, and amiodarone (Tables 10–6[10] and 10–7).

In patients who present to the ED with an episode of symptomatic persistent AF or paroxysmal AF for which intervention is desired, ventricular rate control is usually initially achieved using IV drugs. A decision algorithm for selecting a specific drug for ventricular rate control is presented in Figure 10–4.[10] In general, an IV CCB or β-blocker is preferred for ventricular rate control in patients with normal LV function because ventricular rate control can often be achieved within minutes. In patients with acute decompensated HF (ADHF) or HFrEF, IV diltiazem and verapamil should be avoided, as these drugs have negative inotropic effects and may exacerbate HFrEF.[10] An IV β-blocker may be administered in these patients, but only following stabilization of ADHF, due to potential for exacerbation. Amiodarone or digoxin may be considered as alternatives for rate control in patients with AF associated with severe LV dysfunction and HF or hemodynamic instability. However, caution is warranted with amiodarone due to the potential for chemical cardioversion. Therefore, patients must either be anticoagulated or evaluated by echocardiography to rule out thrombus prior to amiodarone use.[17]

For patients requiring long-term rate control with oral medications, the treatment algorithm is the same (Figure 10–4). Although digoxin is effective for rate control in patients at rest,

Table 10–6

Drugs for Ventricular Rate Control in Atrial Fibrillation (AF)[10]

Drug	Mechanism of Action	Intravenous Administration	Usual Oral Maintenance Dose	Drug Interactions
Amiodarone	β-Blocker CCB	300 mg over 1 hour, then 10–50 mg/hour over 24 hours via continuous infusion	100–200 mg once daily	Inhibits clearance of warfarin, some statins, and other drugs. Increases digoxin bioavailability and reduces clearance
β-Blockers[a]	Inhibit AV nodal conduction by slowing AV nodal conduction and prolonging AV nodal refractoriness	Esmolol 500 mcg/kg over 1 minute, then 50–300 mcg/kg/min continuous infusion Propranolol 1 mg over 1 minute, up to 3 doses at 2-minute intervals Metoprolol tartrate 2.5–5 mg over 2 minutes; up to 3 doses	Atenolol 25–100 mg once daily Bisoprolol 2.5–10 mg once daily Carvedilol 3.125–25 mg twice daily Metoprolol tartrate 25–100 mg twice daily Metoprolol XL (succinate) 50–400 mg once daily Nadolol 10–240 mg once daily Propranolol 10–40 mg three or four times daily	
Diltiazem	Inhibits AV nodal conduction by slowing AV nodal conduction and prolonging AV nodal refractoriness	0.25 mg/kg bolus over 2 minutes, then 5–15 mg/hour continuous infusion	120–360 mg once daily (extended release)	Increases carbamazepine, cyclosporine, midazolam, triazolam, theophylline, atorvastatin, lovastatin, simvastatin concentrations Cimetidine, ranitidine, diazepam, grapefruit juice may increase serum diltiazem concentrations Dantrolene (combination may lead to ventricular arrhythmias)
Verapamil	Inhibits AV nodal conduction by slowing AV nodal conduction and prolonging AV nodal refractoriness	0.075–0.15 mg/kg bolus over 2 minutes. If no response after 30 minutes, may give an additional 10 mg, then 0.005 mg/kg/min continuous infusion	180–480 mg daily (extended release)	Increases digoxin, carbamazepine, cyclosporine, theophylline, atorvastatin, lovastatin, simvastatin concentrations Dantrolene (combination may lead to ventricular arrhythmias)
Digoxin	Inhibits AV nodal conduction by (a) vagal stimulation, (b) directly slowing AV nodal conduction, and (c) prolonging AV nodal refractoriness	0.25 mg every 2 hours, up to 1.5 mg over 24 hours	0.125–0.25 mg once daily	Amiodarone, verapamil inhibit digoxin elimination and increase bioavailability

[a] In patients with acute decompensated heart failure, therapy with intravenous β-blockers should be initiated only after the patient has been stabilized. Diltiazem and verapamil should be avoided in these patients.

AV, atrioventricular; CCB, calcium channel blocker.

Table 10–7

Adverse Effects of Drugs Used to Treat Arrhythmias

Drug	Adverse Effects
Adenosine	Chest pain, flushing, dyspnea, transient sinus bradycardia/AV block
Amiodarone	IV: Hypotension, sinus bradycardia, phlebitis, QT interval prolongation, torsades de pointes Oral: Blue–gray skin discoloration, photosensitivity, corneal microdeposits, pulmonary fibrosis, hepatotoxicity, sinus bradycardia, hypo- or hyperthyroidism, peripheral neuropathy, weakness, AV block
Atenolol	Hypotension, bradycardia, AV block, HF exacerbation[a]
Atropine	Tachycardia, urinary retention, blurred vision, dry mouth, mydriasis
Bisoprolol	Hypotension, bradycardia, AV block, HF exacerbation[a]
Carvedilol	Hypotension, bradycardia, AV block, HF exacerbation[a]
Digoxin	Nausea, vomiting, anorexia, visual changes such as green–yellow halos around objects, AV block, ventricular arrhythmias
Diltiazem	Hypotension, sinus bradycardia, HF exacerbation, AV block
Dofetilide	Torsades de pointes
Dronedarone	Diarrhea, asthenia, nausea and vomiting, abdominal pain, bradycardia, GI distress, hepatotoxicity
Esmolol	Hypotension, sinus bradycardia, AV block, bronchospasm, HF exacerbation
Flecainide	Dizziness, blurred vision, HF exacerbation, torsades de pointes, life-threatening ventricular tachycardia (in patients with underlying CAD)
Ibutilide	Torsades de pointes
Lidocaine	Slurred speech, diminished consciousness, seizures, bradycardia
Metoprolol	Hypotension, sinus bradycardia, AV block, fatigue, bronchospasm, HF exacerbation[a]
Mexiletine	Nausea, vomiting, GI distress, tremor, dizziness, fatigue, seizures (if dose too high)
Nadolol	Hypotension, bradycardia, AV block, HF exacerbation[a]
Procainamide	Hypotension, HF exacerbation, QT interval prolongation, torsades de pointes
Propafenone	Dizziness, blurred vision, life-threatening ventricular tachycardia (in patients with underlying CAD)
Propranolol	Hypotension, sinus bradycardia, AV block, bronchospasm, HF exacerbation[a]
Sotalol	Sinus bradycardia, AV block, fatigue, torsades de pointes
Verapamil	Hypotension, HF exacerbation, bradycardia, AV block, constipation (oral)

[a] Associated with intravenous administration (metoprolol, propranolol), inappropriately high oral doses at initiation of therapy, or overly aggressive and rapid dose titration.

AV, atrioventricular; CAD, coronary artery disease; GI, gastrointestinal; HF, heart failure; IV, intravenous.

it is less effective than CCBs or β-blockers in patients undergoing physical activity, including activities of daily living. This is likely because activation of the sympathetic nervous system during exercise and activity overwhelms the stimulating effect of digoxin on the parasympathetic nervous system. Digoxin may be associated with increased mortality risk in patients with AF, and this risk may be associated with higher digoxin plasma concentrations.[18,19] Overall, in patients with normal LV function, CCBs or β-blockers are preferred for long-term ventricular rate control. Diltiazem may be preferable to verapamil in older patients due to a lower incidence of constipation. However, in patients with HFrEF, oral diltiazem and verapamil are contraindicated due to their negative inotropic activity and propensity to exacerbate HFrEF. Therefore, the options in this population are β-blockers or digoxin. Most patients with HFrEF should receive an oral β-blocker to reduce mortality risk. In patients with HFrEF who develop rapid AF while receiving therapy with β-blockers, digoxin can be administered for ventricular rate control. The combination of digoxin and β-blockers is effective for ventricular rate control, likely as a result of β-blocker–induced attenuation of the inhibitory effects on the sympathetic nervous system.[20]

Conversion to Sinus Rhythm Antiarrhythmic drug therapy or elective DCC can be used to terminate AF in hemodynamically stable patients. Drugs effective for conversion to sinus rhythm are presented in Table 10–8.[10] These agents slow atrial conduction velocity and/or prolong refractoriness, interrupting reentrant

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Hypertension × 30 years; MI 2 years ago; HFrEF × 1 year (left ventricular ejection fraction [LVEF] 35% [0.35])

Meds: Aspirin 81 mg once daily; atorvastatin 40 mg orally once daily; sacubitril/valsartan 49 mg/51 mg orally twice daily; carvedilol 12.5 mg orally twice daily; bumetanide 2 mg orally once daily; eplerenone 25 mg orally once daily.

PE:

Ht 5 ft 11 in (180 cm), Wt 98 kg (216 lb), BP 115/78 mm Hg, P 150 beats/min, RR 20 breaths/min; remainder of physical examination noncontributory

Labs: All within normal limits. Serum creatinine 1.1 mg/dL (97 μmol/L)

CXR: Mild pulmonary edema

ECG: Atrial fibrillation

What is your assessment of the patient's condition?

What are your treatment goals?

What pharmacologic or nonpharmacologic alternatives are available for each treatment goal?

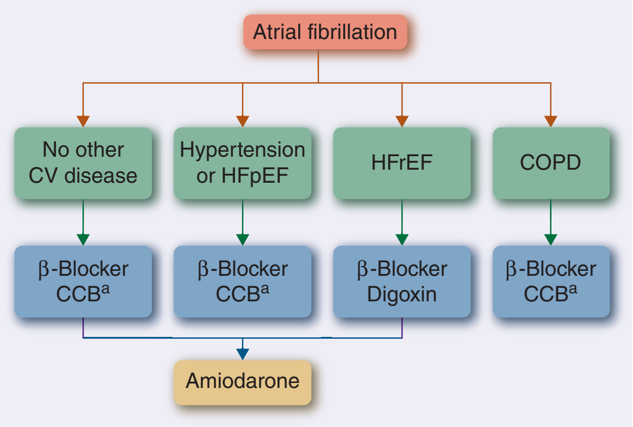

FIGURE 10–4. Decision algorithm for selecting drug therapy for ventricular rate control. In boxes where multiple medications are listed, drugs are listed alphabetically, not in order of preference. [a]When administered intravenously, diltiazem is generally preferred over verapamil because of a lower risk of severe hypotension. (CCB, calcium channel blocker [diltiazem or verapamil]; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.) (Adapted with permission from January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. J Am Coll Cardiol. 2014;64:e1–e76).

circuits and restoring sinus rhythm. DCC is generally more effective than drug therapy for converting AF to sinus rhythm. However, patients undergoing elective DCC must be sedated and/or anesthetized to avoid the discomfort associated with delivery of electrical shock to the chest. Therefore, it is important that patients undergoing elective DCC not eat within approximately 8 to 12 hours of the procedure to avoid aspiration of stomach contents and resulting aspiration pneumonitis during the period of sedation/anesthesia.

A decision strategy for conversion of AF to sinus rhythm is presented in Figure 10–5.[10] The cardioversion decision strategy primarily depends on AF duration. If the AF episode began within 48 hours, conversion to sinus rhythm is safe and may be attempted with elective DCC or drug therapy. However, if the duration of the AF episode is 48 hours or longer, or if there is uncertainty regarding duration, two strategies for conversion may be considered. A thrombus may form in the left atrium during AF episodes of 48 hours or longer; if an atrial thrombus is present, conversion to sinus rhythm, whether with DCC or drugs, can dislodge the atrial thrombus, leading to embolization and a stroke. Therefore, in patients experiencing an AF episode of 48 hours or longer, conversion to sinus rhythm should be deferred unless it is known that an atrial thrombus is not present. One option in patients with AF of duration 48 hours or longer, or of unknown duration, is to anticoagulate with warfarin (maintaining an international normalized ratio [INR] of 2–3) or a direct oral anticoagulant (DOAC; dabigatran, rivaroxaban, apixaban, or edoxaban) for 3 weeks, after which cardioversion may be performed. Patients should subsequently be anticoagulated for a minimum of 4 weeks following restoration of sinus rhythm. An alternative approach is to perform a transesophageal echocardiogram (TEE) to determine

Table 10–8

Drugs for Conversion of Atrial Fibrillation (AF) to Normal Sinus Rhythm[10]

Treatment	IV Administration	Oral Administration	Drug Interactions
Amiodarone	150 mg over 10 minutes, then 1 mg/min for 6 hours, then 0.5 mg/min for 18 hours or change to oral dosing	600–800 mg daily in divided doses up to a total load of 10 g, then maintenance dose of 200 mg daily	Inhibits clearance of warfarin, some statins, and other drugs. Increases digoxin bioavailability and reduces clearance
Dofetilide	Not available IV	CrCl (mL/min)[a,b]: > 60 mL/min: 500 mcg twice daily 40–60 mL/min: 250 mcg twice daily 20–40 mL/min: 125 mcg twice daily < 20 mL/min: Not recommended	Cimetidine, hydrochlorothiazide, ketoconazole, dolutegravir, megestrol, prochlorperazine, promethazine, trimethoprim, verapamil (all inhibit dofetilide elimination, most by inhibition of renal cation transport)
Flecainide	Not available IV in the United States	200–300 mg × one dose[c]	Quinidine, fluoxetine, tricyclic antidepressants increase flecainide concentrations
Ibutilide	1 mg IV over 10 minutes, followed by a second 1 mg IV dose if necessary. If weight < 60 kg (132 lb), dose should be 0.01 mg/kg	Not available orally	—
Propafenone	Not available IV	450–600 mg × one dose[c]	Quinidine, fluoxetine, tricyclic antidepressants increase propafenone concentrations Increases serum digoxin concentrations Inhibits CYP2C9, inhibits warfarin metabolism

[a] Creatinine clearance of > 60, 40–60, 20–40, and < 20 mL/min corresponds to > 1, 0.67–1, 0.33–0.67, and < 0.33 mL/s, respectively.

[b] Dofetilide therapy must be initiated in hospital, due to risk of QT interval prolongation that may lead to torsades de pointes.

[c] It is recommended that a β-blocker or nondihydropyridine calcium channel blocker be administered ≥ 30 minutes prior to administering flecainide or propafenone to avoid accelerated atrioventricular (AV) node conduction and increased heart rate.

CrCl, creatinine clearance; CYP, cytochrome P450; IV, intravenous.

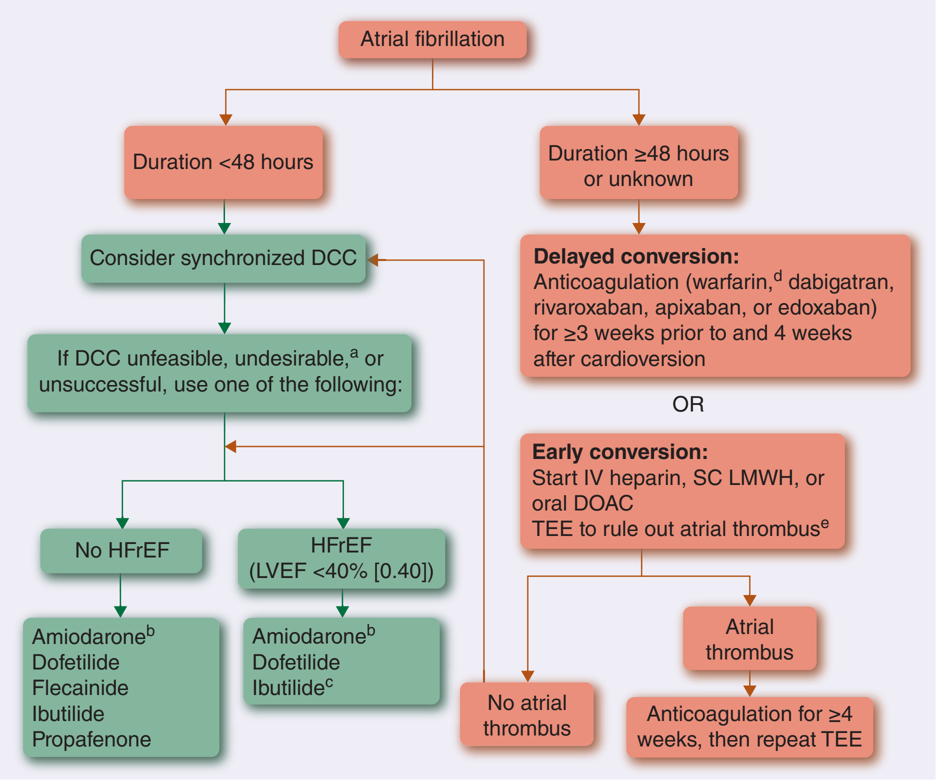
Atrial fibrillation
Duration <48 hours
Duration ≥48 hours or unknown
Consider synchronized DCC
Delayed conversion: Anticoagulation (warfarin,d dabigatran, rivaroxaban, apixaban, or edoxaban) for ≥3 weeks prior to and 4 weeks after cardioversion
If DCC unfeasible, undesirable,a or unsuccessful, use one of the following:
OR
Early conversion: Start IV heparin, SC LMWH, or oral DOAC TEE to rule out atrial thrombuse
No HFrEF
HFrEF (LVEF <40% [0.40])
Amiodaroneb Dofetilide Flecainide Ibutilide Propafenone
Amiodaroneb Dofetilide Ibutilidec
Atrial thrombus
No atrial thrombus
Anticoagulation for ≥4 weeks, then repeat TEE

FIGURE 10–5. Decision algorithm for conversion of hemodynamically stable atrial fibrillation to normal sinus rhythm. [a]Patients should not be sedated for synchronized DCC if they have eaten a meal within 12 hours, due to risk of aspiration. [b]Drugs are listed in alphabetical order, not order of preference. [c]Ibutilide can be administered to patients with LVEF 30%–40% (0.30–0.40) but should be avoided in patients with LVEF < 30% (0.30) due to risk of ventricular proarrhythmia. [d]International normalized ratio (INR) of 2–3. [e]Anticoagulation must be achieved prior to TEE and maintained for more than or equal to 4 weeks after TEE. (DCC, direct current cardioversion; DOAC, direct oral anticoagulant; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LVEF, left ventricular ejection fraction; LMWH, low-molecular-weight heparin; SC, subcutaneous; TEE, transesophageal echocardiogram.)

whether an atrial thrombus is present; if no thrombus is present, DCC or pharmacologic cardioversion may be performed. If this strategy is selected, hospitalized patients should undergo anticoagulation with IV unfractionated heparin, with the dose targeted to an activated partial thromboplastin time (aPTT) of 60 seconds (range: 50–70 seconds), low-molecular-weight heparin, or oral anticoagulation therapy with warfarin (target INR range: 2–3) or a DOAC during hospitalization prior to the TEE and cardioversion procedure. If a thrombus is not present during TEE and cardioversion is successful, patients should remain on oral anticoagulation therapy for at least 4 weeks. If a thrombus is observed during TEE, then cardioversion should be postponed and anticoagulation continued indefinitely. Another TEE should be performed prior to a subsequent cardioversion attempt.[10]

Conversion of hemodynamically stable AF to sinus rhythm may be performed in patients with a symptomatic episode of persistent or paroxysmal AF. For patients in permanent AF, a joint decision has been made by the patient and clinician to forego further attempts to restore and/or maintain sinus rhythm, therefore conversion to sinus rhythm is not attempted.[10]

Maintenance of Sinus Rhythm/Reduction in the Frequency of Episodes of Paroxysmal AF Many patients experience AF recurrences after cardioversion, thus permanent maintenance of sinus rhythm after cardioversion is an unrealistic goal. Similarly, in patients with paroxysmal AF, complete maintenance of sinus rhythm without recurrent AF episodes is often not achievable. A more realistic goal for these patients is not permanent maintenance of sinus rhythm, but rather reduction in frequency or duration of episodes of paroxysmal AF. Maintenance of sinus rhythm is more likely to be successful in patients with AF duration of less than 6 months.

Numerous studies compared whether drug therapy for maintenance of sinus rhythm is preferred to ventricular rate control.[21-24] In these studies, patients were assigned randomly to receive drug therapy either for rate control or rhythm control (Table 10–9). No significant differences in mortality were found between the two strategies.[21-24] However, patients assigned to the rhythm control strategy were more likely to be hospitalized[21,22,24] and to experience adverse effects associated with drug therapy.[23,24]

KEY CONCEPT Therefore, drug therapy to maintain sinus rhythm or reduce the frequency of AF episodes should be initiated only in patients with paroxysmal AF who continue to experience symptoms despite maximum tolerated doses of drugs for ventricular rate control. A decision strategy for maintenance therapy of sinus rhythm is presented in Figure 10–6.[10] Therapy with dofetilide or sotalol should be initiated in the hospital with patients undergoing continuous ECG monitoring due to the risk of torsades de pointes (TdP). Drug therapy for maintenance of sinus rhythm and/or reduction in the frequency of episodes of paroxysmal AF should not be initiated in patients with underlying correctable causes of AF, such as hyperthyroidism; rather, the underlying cause should be corrected. Drug therapy for maintenance of sinus rhythm should be discontinued when AF becomes designated as permanent.

Table 10–9

Drugs for Maintenance of Sinus Rhythm/Reduction in the Frequency of Episodes of Atrial Fibrillation[10]

Drug	Dose
Amiodarone	400–600 mg orally in 2–3 divided doses for 2–4 weeks; maintenance dose 100–200 mg orally once daily
Dofetilide[a]	As described in Table 10–8
Dronedarone	400 mg orally every 12 hours with food
Flecainide	50–200 mg orally every 12 hours
Propafenone	Immediate release: 150–300 mg orally every 8 hours Extended release: 225–425 mg orally every 12 hours
Sotalol[a]	Initial dose, CrCl[b] > 60 mL/min: 80 mg orally twice daily Initial dose, CrCl[b] 40–60 mL/min: 80 mg orally once daily CrCl[b] < 40 mL/min: Contraindicated Maintenance dose: If 80-mg doses are tolerated and QTc interval remains < 500 ms after 3 days, patients can be discharged. Alternatively, dose can be increased to 120 mg orally once or twice daily as appropriate during hospitalization and patient followed for 3 days on this dose IV available as substitute for oral sotalol Note: 75 mg IV over 5 hours twice daily equivalent to 80 mg orally twice daily; 112.5 mg IV over 5 hours twice daily equivalent to 120 mg orally twice daily; 150 mg IV over 5 hours twice daily equivalent to 160 mg orally twice daily

[a] Dofetilide and sotalol therapy must be initiated in the hospital due to the risk of QT interval prolongation that may lead to torsades de pointes.

[b] CrCl of > 60, 40–60, and < 40 mL/min corresponds to > 1, 0.67–1, and < 0.67 mL/s, respectively.

CrCl, creatinine clearance; IV, intravenous; ms, milliseconds; QTc, corrected QT interval.

Catheter ablation is a nonpharmacologic treatment for rhythm control in patients with paroxysmal AF. During this procedure, a catheter is introduced transvenously and directed to the left atrium under fluoroscopic guidance. Energy is delivered through the catheter to ablate, or destroy, reentrant circuits in the pulmonary veins responsible for propagating AF. The most common energy source for catheter ablation is radiofrequency energy, though cryoablation is sometimes used as an alternative. Catheter ablation is often reserved for patients in whom symptomatic AF is refractory to, or the patient is intolerant of, at least one antiarrhythmic agent. However, some patients prefer catheter ablation to avoid antiarrhythmic drug adverse effects. Compared to antiarrhythmic drugs, catheter ablation does not reduce the risk of death, disabling stroke, serious bleeding, or cardiac arrest but does reduce AF recurrence.[25,26]

Prevention of Stroke and Systemic Embolism Most patients with paroxysmal, persistent, or permanent AF should receive therapy for prevention of stroke and systemic embolism unless compelling contraindications exist. The CHA_2DS_2-VASc score

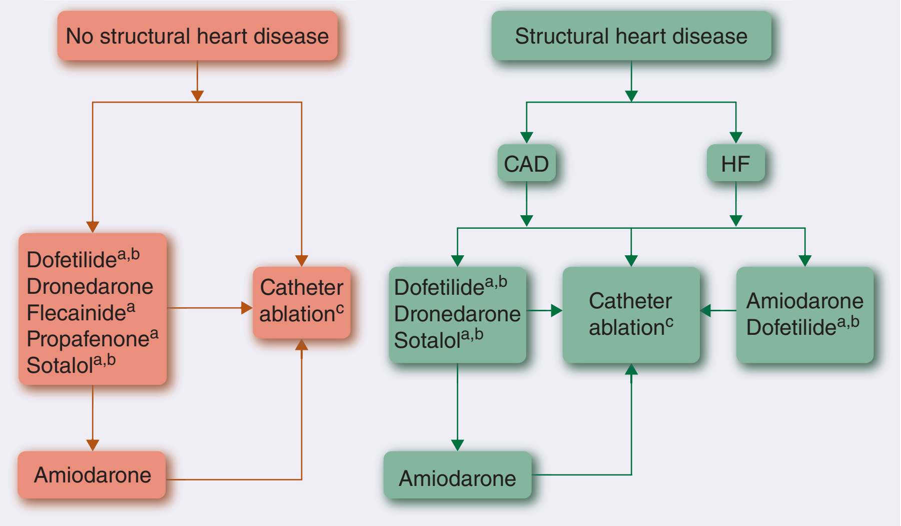
No structural heart disease
Structural heart disease
CAD
HF
Dofetilide[a,b] Dronedarone Flecainide[a] Propafenone[a] Sotalol[a,b]
Catheter ablation[c]
Amiodarone
Dofetilide[a,b] Dronedarone Sotalol[a,b]
Catheter ablation[c]
Amiodarone Dofetilide[a,b]
Amiodarone

FIGURE 10–6. Decision algorithm for maintenance of sinus rhythm/reduction in the frequency of episodes of atrial fibrillation (AF) for patients with symptomatic paroxysmal or persistent AF despite rate control therapy. In boxes where multiple medications are listed, drugs are listed alphabetically, not in order of preference. [a]Not recommended in patients with severe left ventricular hypertrophy. [b]Should be used cautiously in patients at risk for torsades de pointes. [c]Catheter ablation is only recommended as first-line therapy in patients with paroxysmal AF and is recommended depending on patient preference when performed at experienced centers. (CAD, coronary artery disease; HF, heart failure.) (Adapted with permission from January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. J Am Coll Cardiol. 2014;64:e1–e76.)

is used to assess stroke risk in patients with atrial fibrillation.[10,17] Oral anticoagulation is recommended in men and women with CHA_2DS_2-VASc scores greater than or equal to 2 or 3, respectively. A decision strategy for assigning patients to receive anticoagulation for prevention of stroke or systemic embolism in AF is presented in Table 10–10.[17]

The landscape of anticoagulation for stroke prevention in AF has changed with the availability of the DOACs. Dabigatran, approved by the Food and Drug Administration (FDA) in 2010, is a direct thrombin inhibitor for reducing the risk of stroke and systemic embolism in patients with nonvalvular AF. Dabigatran is associated with lower rates of stroke and systemic embolism than warfarin in patients with AF, with a similar incidence of major bleeding.[27] Dabigatran should not be used in patients with end-stage kidney disease (creatinine clearance [CrCl] under 15 mL/min [0.25 mL/s]) or advanced liver disease (impaired baseline clotting function). The recommended dabigatran dose is 150 mg twice daily except for patients with severe kidney disease (CrCl: 15–30 mL/min [0.25–0.50 mL/s]), for whom the recommended dose is 75 mg twice daily.

Advantages of dabigatran include INR monitoring is not required and the drug's onset of action is rapid, eliminating the need for bridging with unfractionated or low-molecular-weight heparins. In addition, there is a lower likelihood of drug interactions with dabigatran than with warfarin. However, dabigatran is a P-glycoprotein (P-gp) substrate, and therefore concomitant administration with P-gp inhibitors such as amiodarone, dronedarone, and verapamil may result in increases in plasma dabigatran concentrations.[28] Adjustments in the dose of dabigatran, or avoidance altogether, are recommended with specific decrements of CrCl in the presence of these P-gp inhibitors. Similarly, concomitant administration of dabigatran with combined P-gp and strong cytochrome P450 (CYP) 3A inducers (eg, phenytoin, carbamazepine, primidone, rifampin, phenobarbital, St. John's wort) should be avoided based on reduction in plasma dabigatran concentrations.[28] In patients with life-threatening or uncontrolled bleeding on dabigatran, a humanized monoclonal antibody fragment (idarucizumab) is FDA approved to rapidly reverse its anticoagulant effects.[29] Finally, while none of the DOACs are recommended for administration to patients with AF that has occurred as a result of valvular heart disease (defined as AF with moderate-to-severe mitral stenosis or a mechanical heart valve),[17] dabigatran is specifically contraindicated in patients with mechanical heart valves due to higher rates of stroke, MI, and thrombus formation on the mechanical valve compared with warfarin.

Rivaroxaban, an oral factor Xa inhibitor, was FDA approved in 2011 for reducing the risk of stroke and systemic embolism in patients with nonvalvular AF. Rivaroxaban was noninferior to warfarin for preventing stroke or systemic embolism in patients with AF and had a lower risk of intracranial and fatal bleeding.[30] Rivaroxaban is contraindicated in patients with end-stage renal disease (CrCl < 15 mL/min [0.25 mL/s]). The recommended rivaroxaban dose is 20 mg once daily

Table 10–10

American Heart Association/American College of Cardiology/Heart Rhythm Society Recommendations for Prevention of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation (AF)[a,17]

CHA_2DS_2-VASc Score	Recommended Stroke Prevention Strategy
0 in men or 1 in women	May omit anticoagulation
1 in men or 2 in women	Oral anticoagulation may be considered
≥ 2 in men or ≥ 3 in women	Oral anticoagulation recommended. Options include: Warfarin (INR: 2–3) Dabigatran Rivaroxaban Apixaban Edoxaban DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in DOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) Warfarin or apixaban are reasonable in patients with end-stage CKD (CrCl < 15 mL/min [0.25 mL/s]) or who are on dialysis

CHA_2DS_2-VASc score calculated as follows:[10]

	Score	CHA_2DS_2-VASc score	Adjusted stroke rate (% per year)
Congestive heart failure	1 point	0	0
Hypertension	1 point	1	1.3
Age ≥ 75 years	2 points	2	2.2
Diabetes mellitus	1 point	3	3.2
History of **s**troke, TIA, or thromboembolism	2 points	4	4.0
Vascular disease (prior MI, PAD, or aortic plaque)	1 point	5	6.7
Age 65–74 years	1 point	6	9.8
Female **s**ex	1 point	7	9.6
Maximum score	9 points	8	6.7
		9	15.2

[a] Patients with AF who have mechanical heart valves should receive warfarin titrated to an INR of 2–3 or 2.5–3.5 depending on the type and location of the prosthetic heart valve.

CKD, chronic kidney disease; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; INR, international normalized ratio; MI, myocardial infarction; PAD, peripheral arterial disease; TIA, transient ischemic attack.

with the evening meal. For patients with CrCl 15 to 50 mL/min (0.25–0.83 mL/s), the dose should be reduced to 15 mg once daily with the evening meal. Similar to dabigatran, rivaroxaban should be avoided in patients receiving combined P-gp and strong CYP3A inducers. Rivaroxaban should also be avoided if the CrCl is less than 80 mL/min (1.33 mL/s) in patients receiving concomitant dronedarone, amiodarone, verapamil, or diltiazem.[28] In patients with life-threatening or uncontrolled bleeding, a modified recombinant inactive form of human factor Xa (andexanet alfa) is FDA approved to rapidly reverse rivaroxaban's anticoagulant effects.[31]

Apixaban, an oral factor Xa inhibitor, was FDA approved in 2012 for reducing the risk of stroke and systemic embolism in patients with nonvalvular AF. Apixaban is superior to warfarin for preventing stroke or systemic embolism in patients with AF, with lower bleeding risk.[32] The recommended dose of apixaban is 5 mg orally twice daily. Apixaban dose should be reduced to 2.5 mg orally twice daily when any two of the following characteristics are present: serum creatinine greater than 1.5 mg/dL (133 μmol/L), 80 years of age or older, and body weight less than or equal to 60 kg (132 lb). Apixaban should not be administered to patients with severe liver disease. While patients with CrCl less than 25 mL/min (0.42 mL/s) were excluded from the landmark AF trial, an observational study found a lower risk of major bleeding with apixaban versus warfarin in patients with end-stage renal disease on dialysis.[33] Consequently, the current AF guidelines recommend either apixaban or warfarin as reasonable options for patients with end-stage chronic kidney disease (CKD; CrCl < 15 mL/min [0.25 mL/s] or on dialysis).[17] Similar to rivaroxaban, apixaban should be avoided in patients receiving combined P-gp and strong CYP3A inducers.[28] Andexanet alfa is also FDA approved to treat life-threatening or uncontrolled bleeding in patients receiving apixaban.[31]

Edoxaban, another oral factor Xa inhibitor, was FDA approved in 2015 for reduction in risk of stroke and systemic embolism in patients with nonvalvular AF. Edoxaban is noninferior to warfarin for preventing stroke or systemic embolism in these patients, with a lower bleeding risk.[34] The recommended edoxaban dose is 60 mg orally once daily in patients with CrCl 50 to 95 mL/min (0.83–1.58 mL/s). In patients with kidney disease (CrCl 15–50 mL/min [0.25–0.83 mL/s]), the dose should be reduced to 30 mg orally once daily. There are no data or dosage recommendations for patients with CrCl less than 15 mL/min (0.25 mL/s). Edoxaban should not be used in patients with CrCl greater than 95 mL/min (1.58 mL/s), as these patients have an increased risk of ischemic stroke with edoxaban 60 mg once daily compared to warfarin-treated patients. The most likely reason for this finding is increased renal edoxaban clearance leading to reduced anticoagulant effect in patients with CrCl greater than 95 mL/min (1.58 mL/s). Like other factor Xa inhibitors, edoxaban should be avoided in patients receiving combined P-gp and strong CYP3A inducers. The edoxaban dose should also be decreased by 50% in patients receiving concomitant dronedarone.[28]

For patients not DOAC eligible (eg, patients with moderate-to-severe mitral stenosis, mechanical heart valve, or with end-stage CKD not otherwise suitable for apixaban), warfarin adjusted to an INR of 2 to 3 (target 2.5) is recommended.[17] A standard empirical dosing approach can be used, such as initiating warfarin at 5 mg once daily, and titrating based on daily INR measurements until a stable therapeutic INR is achieved. Another approach is to use a clinical dosing algorithm, such as those available at warfarindosing.org, to determine the initial warfarin dose[35]; dose titration based on daily INR measurements is still required if this approach is employed. In some situations, pharmacogenomic data may be available to help guide initial warfarin dosing. These tests assess single-nucleotide polymorphisms for the gene that encodes *CYP2C9*, the primary hepatic enzyme responsible for warfarin metabolism, and the gene *VKORC1*, which encodes vitamin K epoxide reductase complex subunit 1, the enzyme that is inhibited by warfarin as its mechanism of anticoagulation.[35] Patients with specific polymorphisms of one or both of these genes may require adjustment of the initial warfarin dose to achieve adequate anticoagulation or avoid over-anticoagulation and toxicity; guidelines for pharmacogenetics-guided warfarin dosing have been published.[35] Genetic testing to guide the initiation of warfarin therapy is not yet standard practice, and some question the efficacy and cost-effectiveness of routine genetic testing with warfarin therapy. Clinical trials evaluating anticoagulation control with pharmacogenomic guidance versus standard dosing have led to mixed results.[35] The role of routine genetic testing in selecting initial warfarin doses continues to evolve. However, in patients for whom *VKORC1* and/or *CYP2C9* genotype information is available, the pharmacogenetics-guided warfarin dosing guidelines are useful for guiding initial warfarin dose selection.[35]

Patient Encounter Part 3: Creating a Care Plan

Based on the information presented, create a care plan for the patient's acute AF episode and for long-term management of his AF.

Your plan should include (a) a statement of the drug-related needs and/or problems, (b) the goals of therapy, (c) a patient-specific detailed therapeutic plan, and (d) a follow-up plan to determine whether the goals have been achieved and adverse effects avoided.

▶ *Outcome Evaluation*

- Monitor the patient to determine whether the ventricular rate control goal is met. A target heart rate less than 80 beats/min is recommended for symptomatic patients and those with HFrEF. A target heart rate of less than 110 beats/min may be reasonable for asymptomatic patients with preserved LV systolic function.[10]
- Monitor ECG to assess continued presence of AF and determine whether conversion to sinus rhythm has occurred.
- In patients receiving warfarin, monitor INR approximately monthly to make sure it is therapeutic (target: 2.5; range: 2–3).
- Monitor for adverse effects of specific drug therapy (see Table 10–7). Monitor patients receiving oral anticoagulation for signs and symptoms of bruising or bleeding.

Paroxysmal Supraventricular Tachycardia

Paroxysmal supraventricular tachycardia (PSVT) refers to a number of arrhythmias that originate above the ventricles and require atrial or AV nodal tissue for initiation and maintenance.[36] The most common form of PSVT is AV nodal reentrant tachycardia caused by a reentrant circuit that involves the AV node or tissue adjacent to the AV node. Other types of PSVT include the relatively uncommon Wolff-Parkinson-White syndrome, which is caused by reentry through an accessory extra-AV nodal pathway. For the purposes of this section, the term *PSVT* refers to AV nodal reentrant tachycardia.

Clinical Presentation and Diagnosis of PSVT

Symptoms

- Symptoms include palpitations, "neck-pounding," dizziness, light-headedness, shortness of breath, polyuria, chest pain (if underlying CAD is present), near-syncope, and syncope. Patients commonly complain of palpitations; often the complaint is "I can feel my heart beating fast" or "I can feel my heart fluttering" or "It feels like my heart is going to beat out of my chest"
- Other symptoms depend on the degree to which cardiac output is diminished, which in turn depends on heart rate and extent to which stroke volume is reduced by the rapidly beating heart

Diagnosis

- Because the symptoms of all tachyarrhythmias depend primarily on heart rate and are therefore similar, diagnosis depends on the presence of PSVT on the ECG, characterized by narrow QRS complexes (< 0.12 seconds). P waves are usually visible but may be difficult to discern if the heart rate is extremely rapid
- PSVT is a regular rhythm and occurs at rates of 100 to 250 beats/min

▶ *Epidemiology and Etiology*

Approximately 570,000 persons in the United States have PSVT, with an estimated prevalence of 2.29 per 1000 individuals.[6,36] The incidence of PSVT is 35 per 100,000 person-years,[6] and there are roughly 89,000 new cases annually.[36] The average age of onset of PSVT is 57 years. PSVT occurs more commonly in women than men, and individuals older than 65 years have five times the risk of developing PSVT compared to younger people.[6,36] Although PSVT can occur in patients experiencing myocardial ischemia or MI, it sometimes occurs in individuals with no history of cardiac disease.

▶ *Pathophysiology*

PSVT is caused by reentry that includes the AV node as a part of the reentrant circuit. Typically, electrical impulses travel forward (antegrade, from atria to ventricles) down the AV node and then travel back up the AV node (retrograde, from ventricles to atria) in a repetitive circuit. In some patients, the retrograde conduction pathway of the reentrant circuit may exist in extra-AV nodal tissue adjacent to the AV node. One of these pathways usually conducts impulses rapidly while the other usually conducts impulses slowly. Most commonly, during PSVT the impulse conducts antegrade through the slow pathway and retrograde through the faster pathway; in approximately 5% to 10% of patients the reentrant circuit is reversed.[36]

▶ *Treatment*

Desired Outcomes The desired outcomes for treatment are to terminate the arrhythmia, restore sinus rhythm, and prevent recurrence. Drug therapy is used to terminate the arrhythmia and restore sinus rhythm; nonpharmacologic measures are generally preferred to prevent recurrence, though some patients prefer drug therapy.

Termination of PSVT KEY CONCEPT The primary method to terminate PSVT is inhibition of impulse conduction and/or prolongation of the refractory period within the AV node. Because PSVT is propagated via a reentrant circuit involving the AV node, inhibition of conduction within the AV node interrupts and terminates the reentrant circuit.

KEY CONCEPT Prior to initiation of drug therapy to terminate PSVT, some simple nonpharmacologic methods known as vagal maneuvers may be attempted.[16,36] Vagal maneuvers stimulate the activity of the parasympathetic nervous system, which inhibits AV nodal conduction, facilitating arrhythmia termination. Vagal maneuvers alone may terminate PSVT in up to 28% of cases.[36] The simplest vagal maneuver to perform is cough, which stimulates the vagus nerve. Instructing the patient to cough two or three times may successfully terminate PSVT. Carotid sinus massage is another useful vagal maneuver; one of the carotid sinuses, located in the neck in the vicinity of the carotid arteries, may be gently massaged for 5 to 10 seconds, stimulating vagal activity. Carotid sinus massage should not be performed in patients with a history of stroke or transient ischemic attack or in those in whom carotid bruits are heard on auscultation. The Valsalva maneuver, during which patients bear down against a closed glottis for 10 to 30 seconds, may also be attempted. The Valsalva maneuver is more effective than carotid sinus massage.[36] If one vagal maneuver is unsuccessful, switching to another maneuver may successfully terminate PSVT.[36]

If vagal maneuvers are unsuccessful, IV drug therapy should be initiated.[16,36] Drugs used for termination of hemodynamically stable PSVT are presented in Table 10–11.[16,36] A decision strategy for pharmacologic termination of PSVT is presented in Figure 10–7.[36]

KEY CONCEPT Adenosine is the drug of choice for pharmacologic termination of PSVT and is successful in 95% of patients. Adenosine inhibits conduction transiently and is associated with adverse effects (Table 10–7) including flushing, transient sinus bradycardia or AV block, and bronchospasm in susceptible patients. Adenosine may also cause chest pain that mimics myocardial ischemia but is not actually associated with ischemia. The adenosine half-life is approximately 10 seconds; therefore, in most patients, adverse effects are of short duration.

If adenosine does not terminate PSVT, subsequent choices of therapy depend on whether the patient is hemodynamically stable or not. If the patient is hemodynamically unstable, synchronized DCC should be administered, using an initial energy level of 50 to 100 J; if the initial DCC attempt is unsuccessful, the shock energy should be increased in a stepwise fashion.[16] If the patient is hemodynamically stable, IV β-blockers, diltiazem or verapamil may be administered. β-Blockers are preferred if the patient has underlying HFrEF.

Prevention of Recurrence A decision strategy for prevention of recurrent PSVT is presented in Figure 10–8. If the patient's episodes of PSVT are asymptomatic or minimally symptomatic, long-term treatment may not be necessary. However, for patients with symptomatic episodes of PSVT, catheter ablation is a nonpharmacologic treatment option. During this procedure, a catheter is introduced transvenously and directed to the right atrium under fluoroscopic guidance. The catheter is advanced to the AV node and energy is delivered through the catheter to ablate, or destroy, the extranodal pathway of the reentrant circuit. This procedure usually achieves a complete cure of PSVT and obviates the need for long-term antiarrhythmic drug therapy. The complication rate associated with catheter ablation of PSVT is low (< 1%) and includes complete AV block (via inadvertent ablation of the AV node), perforation, pseudoaneurysm, bleeding at the site of catheter insertion in the groin, and pulmonary edema.

Despite the success rates with catheter ablation and the relatively low risk of complications, some patients prefer not to

Table 10–11

Drugs for Termination of Paroxysmal Supraventricular Tachycardia[8,36]

Drug	Mechanism of Action	Dose
Adenosine	Direct AV node inhibition	6 mg IV rapid push followed by rapid saline flush. If no response in 1–2 minutes, 12 mg IV rapid push followed by rapid saline flush. If no response in 1–2 minutes, administer second 12 mg IV rapid push, followed by rapid saline flush
Diltiazem	Direct AV node inhibition	0.25 mg/kg IV over 2 minutes, followed by continuous IV infusion of 5–10 mg/hour, up to 15 mg/hour
Verapamil	Direct AV node inhibition	5–10 mg (0.75–0.15 mg/kg) IV over 2 minutes If no response, administer an additional 10 mg (0.15 mg/kg) IV, then continuous infusion of 0.005 mg/kg/min
β-Blockers	Direct AV node inhibition	Esmolol 500 mcg/kg IV over 1 minute Then 50 mcg/kg/min continuous infusion. If inadequate response, give second loading dose of 500 mcg/kg and increase maintenance infusion to 100 mcg/kg/min. Increment 50 mcg/kg/min dose increases in this manner as necessary to maximum infusion rate of 300 mcg/kg/min Propranolol 1 mg IV over 1 minute; if necessary, repeat 1 mg IV doses at 2-minute intervals, up to 3 doses Metoprolol 2.5–5 mg IV over 2 minutes; if necessary, repeat 2.5–5 mg IV bolus in 10 minutes, up to 3 doses
Digoxin	Vagal stimulation, direct AV node inhibition	0.25–0.5 mg IV bolus; if necessary, repeat 0.25 mg IV bolus every 6–8 hours, to a maximum dose of 1 mg (8–12 mcg/kg) over 24 hours

AV, atrioventricular; IV, intravenous.

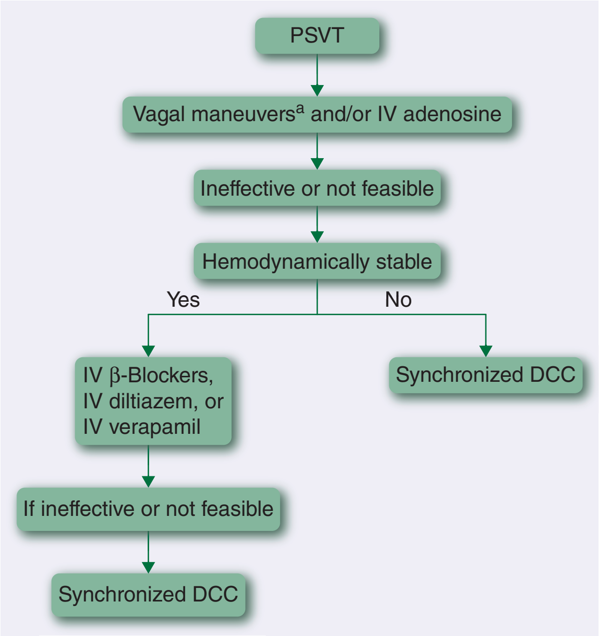
PSVT
Vagal maneuvers[a] and/or IV adenosine
Ineffective or not feasible
Hemodynamically stable
Yes
No
IV β-Blockers, IV diltiazem, or IV verapamil
Synchronized DCC
If ineffective or not feasible
Synchronized DCC

FIGURE 10–7. Decision algorithm for termination of PSVT. [a]Cough, carotid sinus massage (do not perform in patients with carotid bruits), Valsalva maneuver. (DCC, direct current cardioversion; IV, intravenous; PSVT, paroxysmal supraventricular tachycardia.) (Adapted with permission from Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2016;67:e27–e115.)

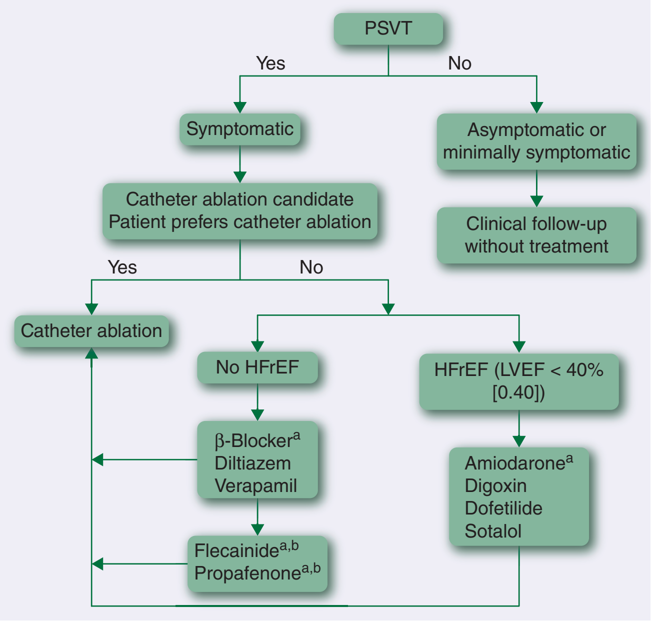
PSVT
Yes
No
Symptomatic
Asymptomatic or minimally symptomatic
Catheter ablation candidate
Patient prefers catheter ablation
Clinical follow-up without treatment
Yes
No
Catheter ablation
No HFrEF
HFrEF (LVEF < 40% [0.40])
β-Blocker[a]
Diltiazem
Verapamil
Amiodarone[a]
Digoxin
Dofetilide
Sotalol
Flecainide[a,b]
Propafenone[a,b]

FIGURE 10–8. Decision algorithm for prevention of recurrence of PSVT. Drug doses as in Tables 10–6 and 10–9. [a]Drugs are listed alphabetically, not in order of preference. [b]Neither flecainide nor propafenone should be used in patients with known ischemic heart disease. (HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; PSVT, paroxysmal supraventricular tachycardia.) (Adapted with permission from Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2016;67:e27–e115.)

undergo the procedure or are not suitable candidates. For these patients, drug therapy may be administered to prevent recurrence of PSVT or at least reduce the frequency of recurrent episodes. For patients with normal LV function, oral β-blockers, diltiazem, or verapamil are preferred. In patients for whom a trial of one or more of those drugs provides an unsatisfactory response, oral flecainide or propafenone may be administered; however, flecainide and propafenone are contraindicated in patients with a history of MI or any known underlying CAD, due to an increased risk of death associated with those drugs in that population. For patients with HFrEF, diltiazem, verapamil, flecainide, and propafenone are contraindicated due to negative inotropic effects and the potential to exacerbate HF. In this patient population, oral amiodarone, digoxin, dofetilide, or sotalol may be used.

▶ *Outcome Evaluation*

- Monitor for termination of PSVT and restoration of normal sinus rhythm.
- Monitor for adverse effects of adenosine or any other antiarrhythmic agents administered (Table 10–7).
- In patients taking drug therapy for long-term prevention of recurrence of PSVT, monitor for recurrence of and frequency of symptoms, as well as for adverse drug effects (Table 10–7).

VENTRICULAR ARRHYTHMIAS

Premature Ventricular Complexes

PVCs are ectopic electrical impulses originating in ventricular tissue, resulting in wide, misshapen, abnormal QRS complexes. PVCs have also been known by other terms, ventricular premature beats (VPBs), ventricular premature contractions (VPCs), and ventricular premature depolarizations (VPDs).

▶ *Epidemiology, Etiology, and Pathophysiology*

PVCs occur with variable frequency, depending on age, underlying comorbid conditions, and duration of rhythm monitoring.[37] In a population of healthy individuals, prevalence of PVCs was 0.8%.[6] In another study in which individuals without HF underwent ambulatory ECG monitoring (median duration 22 hours), 0.011% of all heartbeats were PVCs.[6] Prevalence of PVCs increases with age and is approximately 0.5% in individuals less than 20 years of age and 2.7% in people older than 50 years of age.[6,38] Older age, hypertension, concomitant heart disease, and smoking are all associated with increased PVC frequency.[37]

The mechanism(s) responsible for PVCs remains uncertain but are thought to be due to abnormal ventricular automaticity and/or reentry related to enhanced sympathetic nervous system activity and altered electrophysiological characteristics of the heart during myocardial ischemia and following MI.[37] Patients with a low PVC burden and no underlying heart disease are usually not at increased risk of life-threatening cardiovascular events.[37,38] Complex or frequent PVCs, especially in patients with CAD or LV dysfunction, are associated with increased mortality due to sudden cardiac death.[37,38]

▶ *Treatment*

Desired Outcomes Desired outcomes are to alleviate patient symptoms and reduce the risk of PVC-induced cardiomyopathy in patients with very frequent PVCs.

Pharmacologic Therapy **KEY CONCEPT** Asymptomatic PVCs should not be treated with antiarrhythmic drug therapy. Given that complex or frequent PVCs are associated with increased risk of sudden cardiac death in patients with a history of MI, the Cardiac Arrhythmia Suppression Trials (CAST and CAST II) tested the hypothesis that suppression of asymptomatic PVCs with the drugs flecainide, encainide, or moricizine in patients with a recent history of MI would decrease the incidence of sudden cardiac death.[39,40] However, results showed that not only did antiarrhythmic agents not reduce risk of sudden cardiac death, there was a significant *increase* in risk of death in patients who received therapy with encainide or flecainide compared to placebo.[39] During the continuation of the study with moricizine (CAST II), there was a significantly higher incidence of death in the moricizine group compared to the placebo group during the first 2 weeks of therapy.[40] Additional evidence suggests that other Vaughan Williams class I agents, including quinidine, procainamide, and disopyramide, also increase risk of death in patients with complex PVCs following MI.[37,38]

Clinical Presentation and Diagnosis of PVCs

- PVCs are usually categorized as simple or frequent/repetitive: simple PVCs occur as infrequent, isolated single abnormal beats; frequent/repetitive PVCs occur frequently (at least one PVC on a 12-lead ECG or ≥ 30 per hour) and/or in specific patterns. Very frequent PVCs are defined as greater than 10,000 to 20,000 per day
- Two consecutive PVCs are referred to as a couplet. The term *bigeminy* refers to a PVC occurring with every other beat; *trigeminy* means a PVC occurring with every third beat; *quadrigeminy* means a PVC occurring every fourth beat

Symptoms

- Most patients with simple or complex PVCs are asymptomatic. Occasionally, patients with complex or frequent PVCs may experience palpitations, lightheadedness, or dizziness. Patients with very frequent PVCs can develop reversible PVC-induced cardiomyopathy (a form of LV dysfunction associated with symptoms of HF)

KEY CONCEPT In patients with symptomatic PVCs with no structural heart disease, treatment with β-blockers or nondihydropyridine CCBs is recommended to reduce PVC frequency and improve symptoms.[38] If β-blockers or nondihydropyridine CCBs are ineffective or poorly tolerated, these patients can be treated with antiarrhythmic drugs (eg, flecainide, propafenone, sotalol, amiodarone) or catheter ablation.[37,38]

For patients with symptomatic PVCs and underlying structural heart disease, treatment with β-blockers is recommended.[37,38] β-blockers reduce mortality in this population and effectively suppress PVCs.[37,38] Patients with frequent symptomatic PVCs who do not respond adequately to β-blockers, nondihydropyridine CCBs, or antiarrhythmic drugs, or who do not tolerate those medications, can undergo catheter ablation. For patients with PVC-induced cardiomyopathy, drug therapy with β-blockers or amiodarone or catheter ablation are recommended to reduce PVC frequency and improve symptoms and LV function.

▶ *Outcome Evaluation*

- Monitor patients for PVC frequency and symptom relief.
- Monitor for adverse effects of β-blockers: bradycardia, hypotension, fatigue, masking symptoms of hypoglycemia, glucose intolerance (in diabetic patients), wheezing or shortness of breath (in patients with severe asthma or chronic obstructive pulmonary disease [COPD]).

Table 10–12

Etiologies of Ventricular Tachycardia and Ventricular Fibrillation

Coronary artery disease
Myocardial infarction
Heart failure
Electrolyte abnormalities: hypokalemia, hypomagnesemia
Drugs:
  Adenosine
  Amiodarone
  Chlorpromazine
  Cocaine and amphetamines
  Digoxin
  Disopyramide
  Flecainide
  Ibutilide
  Procainamide
  Propafenone
  Sotalol
  Terbutaline
  Thioridazine
  Trazodone
  Venlafaxine

Ventricular Tachycardia

VT is a series of three or more consecutive PVCs at a rate greater than 100 beats/min. VT is defined as nonsustained if it lasts greater than or equal to 3 beats and terminates spontaneously; sustained VT lasts greater than 30 seconds or requires termination because of hemodynamic instability in less than 30 seconds.[5] VT is usually monomorphic, meaning each QRS complex displays the same shape, axis, and amplitude. VT may occasionally be polymorphic, with QRS complexes displaying various shapes, axes, and amplitudes.

▶ *Epidemiology, Etiology, and Pathophysiology*

Prevalence of monomorphic VT in the general population is unknown.[6] In populations at risk, the VT incidence is variable, depending on underlying etiologies and comorbidities. Etiologies of VT are presented in Table 10–12. VT is common in patients with ischemic heart disease, occurring in 5% to 10% of patients hospitalized for acute MI.[38] Nonsustained VT occurs in 20% to 80% of patients with HF.[41] Other VT etiologies include electrolyte abnormalities such as hypokalemia, hypoxia, and drugs. VT occurring in the absence of structural heart disease is referred to as “idiopathic” VT. Some patients with idiopathic VT have verapamil-sensitive VT, while others have outflow tract VT, indicating the VT originates in the outflow tract of the right or left ventricle.[38] VT is usually initiated by a precisely timed PVC, occurring during the relative refractory period, which provokes reentry within ventricular tissue. Sustained VT requires immediate intervention, because if untreated, the rhythm may cause sudden cardiac death via hemodynamic instability and absence of a pulse (pulseless VT) or via degeneration of VT into VF.

▶ *Treatment*

Desired Outcomes Desired outcomes are to terminate the arrhythmia, restore sinus rhythm, and prevent sudden cardiac death.

Pharmacologic Therapy Hemodynamically unstable VT should be terminated immediately using synchronized DCC.[38,42] In the event VT is present but the patient does not have a palpable pulse (and therefore no blood pressure), asynchronous defibrillation should be performed at 360 J for monophasic waveforms and starting at 120 to 200 J for biphasic waveforms.[42]

Drugs used to terminate hemodynamically stable VT are presented in Table 10–13.[38] A decision algorithm for management of hemodynamically stable VT is presented in Figure 10–9.[38] For patients with structural heart disease who develop VT, DCC is the preferred therapy as it is considered to be more effective than drug therapy. For patients in whom DCC is undesirable (eg, if

Table 10–13

Drugs for Termination of Ventricular Tachycardia[38]

Drug	Loading Dose	Maintenance Dose
Procainamide	20–50 mg/min continuous IV infusion until maximum dose of 10–17 mg/kg is reached	Continuous IV infusion 1–4 mg/min
Amiodarone	150 mg IV over 10 minutes	1 mg/min continuous infusion for 6 hours, then 0.5 mg/min for 18 hours
Sotalol	75 mg IV every 12 hours	—
Verapamil	2.5–5 mg/kg IV bolus every 15–30 minutes	
β-Blockers	Esmolol—see Table 10–6	See Table 10–6
	Metoprolol—see Table 10–6	See Table 10–6
	Propranolol—see Table 10–6	See Table 10–6

IV, intravenous.

Clinical Presentation and Diagnosis of VT

Symptoms

- Symptoms depend primarily on heart rate and include palpitations, dizziness, light-headedness, shortness of breath, chest pain (if underlying CAD is present), near-syncope, and syncope
- Patients with nonsustained VT may be asymptomatic if the arrhythmia duration is sufficiently short. However, if the rate is rapid, patients with nonsustained VT may experience symptoms
- Patients with sustained VT are usually symptomatic, provided the rate is fast enough to provoke symptoms. Patients with rapid sustained VT may be hemodynamically unstable
- In some patients, sustained VT results in the absence of a pulse or may deteriorate to VF, resulting in sudden cardiac death

Diagnosis

- Diagnosis of VT requires ECG confirmation
- VT is characterized by wide, misshapen QRS complexes, with the rate varying from 140 to 250 beats/min
- In most patients with VT, shape and appearance of the QRS complexes are consistent and similar, referred to as monomorphic VT. However, some patients experience polymorphic VT, in which shape and appearance of the QRS complexes vary

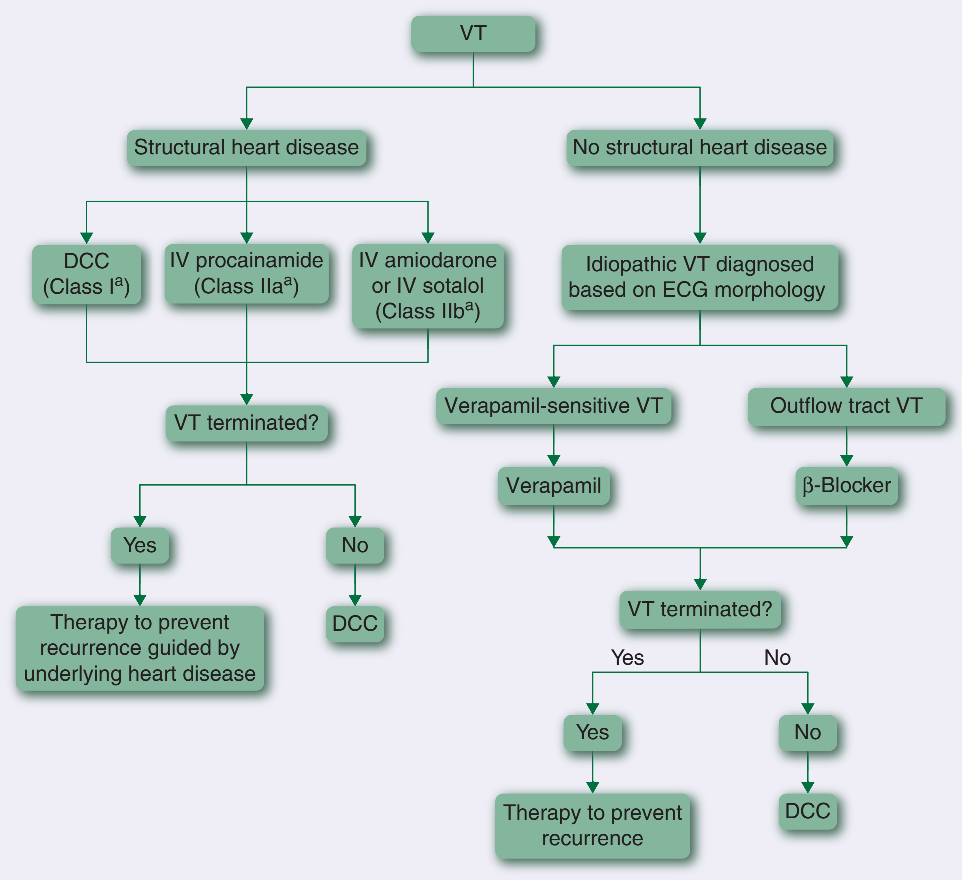
VT
Structural heart disease
No structural heart disease
DCC (Class I[a])
IV procainamide (Class IIa[a])
IV amiodarone or IV sotalol (Class IIb[a])
Idiopathic VT diagnosed based on ECG morphology
Verapamil-sensitive VT
Outflow tract VT
VT terminated?
Verapamil
β-Blocker
Yes
No
Therapy to prevent recurrence guided by underlying heart disease
DCC
VT terminated?
Yes
No
Yes
No
Therapy to prevent recurrence
DCC

FIGURE 10–9. Decision algorithm for termination of hemodynamically stable ventricular tachycardia. [a]Class I recommendations represent strong level of evidence; Class IIa recommendations represent moderate level of evidence; and Class IIb recommendations represent weak level of evidence. (DCC, direct current cardioversion; ECG, electrocardiogram; IV, intravenous; VT, ventricular tachycardia.)

patients have eaten a meal that day and cannot be safely sedated for DCC), IV procainamide is the drug of choice. IV amiodarone or sotalol are recommended for patients in whom VT is unresponsive to procainamide.[38]

For patients with idiopathic VT for which the arrhythmia is verapamil-sensitive, verapamil should be administered (Figure 10–9). For patients with outflow tract VT, IV β-blockers are preferred agents.[38]

Nonpharmacologic Therapy: Prevention of Sudden Cardiac Death KEY CONCEPT In patients who have experienced VT and are at risk for sudden cardiac death from recurrent ventricular arrhythmias, an implantable cardioverter-defibrillator (ICD) is the treatment of choice.[38] An ICD is a device that provides internal electrical cardioversion of VT or defibrillation of VF. The ICD does not prevent the patient from developing the arrhythmia, but it reduces the risk that the patient will die of sudden cardiac death as a result of the arrhythmia. Early versions of ICDs required a thoracotomy for implantation; now ICDs are implanted transvenously, similar to pacemakers, markedly reducing incidence of complications. ICDs are indicated for patients who are survivors of sudden cardiac death due to hemodynamically unstable VT or VF.[38]

Patients with ischemic heart disease and LVEF less than or equal to 30% to 35% (0.3–0.35) are at increased risk of sudden cardiac death. ICDs are significantly more effective than antiarrhythmic drugs such as amiodarone or sotalol for reducing risk of sudden cardiac death in these patients and therefore are preferred therapy.[38,43] In addition to the ICD, guideline-directed medical therapy (eg, β-blockers, angiotensin-converting enzyme [ACE] inhibitors/angiotensin receptor blockers/sacubitril/valsartan, and mineralocorticoid receptor antagonists) should also be optimized.[38] However, many patients with ICDs receive concurrent antiarrhythmic drug therapy to reduce the frequency with which patients experience the discomfort of shocks and to prolong battery life of the devices. Combined pharmacotherapy with amiodarone and a β-blocker is more effective than monotherapy with sotalol or β-blockers for reducing frequency of ICD shocks.[44]

▶ *Outcome Evaluation*

- Monitor patients for termination of VT and restoration of normal sinus rhythm.
- Monitor patients for adverse effects of antiarrhythmic drugs (see Table 10–7).

Ventricular Fibrillation

VF is irregular, disorganized, chaotic electrical activity in the ventricles resulting in the absence of ventricular depolarizations and, consequently, lack of pulse, cardiac output, and blood pressure.

▶ *Epidemiology and Etiology*

Annual incidence of out-of-hospital cardiac arrest in the United States is estimated to be 74 to 141 individuals per 100,000

Clinical Presentation and Diagnosis of VF

Symptoms

- VF results in immediate loss of pulse and blood pressure. Patients who are in the standing position at the onset of VF suddenly and immediately collapse to the ground

Diagnosis

- Absence of a pulse does not guarantee VF because pulse may also be absent in patients with asystole, VT, or pulseless electrical activity
- Confirmation of diagnosis with an ECG is necessary to determine appropriate treatment. ECG reveals no organized, recognizable QRS complexes. If treatment is not initiated within a few minutes, death will occur, or at best, resuscitation of the patient with permanent anoxic brain injury

population, or roughly 180,000 to 350,000 people.[6] Only 10% of patients treated for out-of-hospital cardiac arrest by emergency medical services (EMS) survive to hospital discharge.[6] Although some of these deaths are due to asystole, the majority occur as a result of primary VF or VT that degenerates into VF. Etiologies of VF are presented in Table 10–12 and are similar to those of VT.

▶ Treatment

Desired Outcomes Desired outcomes are to (a) terminate VF, (b) achieve return of spontaneous circulation, (c) achieve patient survival to hospital admission (in those with out-of-hospital cardiac arrest) and to hospital discharge, and (d) improve neurologic outcomes.

Pharmacologic and Nonpharmacologic Therapy VF is by definition hemodynamically unstable, due to the absence of a pulse and blood pressure. Initial management includes provision of basic life support, including calling for help and initiation of cardiopulmonary resuscitation (CPR).[42] Oxygen should be administered as soon as it is available. Most importantly, defibrillation should be performed as soon as possible. It is critically important to understand the only means of successfully terminating VF and restoring sinus rhythm is electrical defibrillation. Defibrillation should be attempted using 360 J for monophasic defibrillators, and 120 to 200 J for biphasic shocks, after which CPR should be resumed immediately while the defibrillator charges. If the first shock was unsuccessful, subsequent defibrillation attempts should be performed at equivalent or higher energy doses.[42]

If VF persists following two defibrillation shocks, drug therapy may be administered. KEY CONCEPT The purpose of drug administration for treatment of VF is to facilitate successful defibrillation. Drug therapy alone will not terminate VF. Drugs used for facilitation of defibrillation in patients with VF are presented in Table 10–14.[42] Drug administration should occur during CPR, before or after delivery of a defibrillation shock. The vasopressor agent epinephrine is administered initially because it has been shown that a critical factor in successful defibrillation is maintenance of coronary perfusion pressure, which is achieved via the vasoconstricting effects of this agent. A treatment algorithm for VF is presented in Figure 10–10. Although the vasopressor agent vasopressin can be considered in cardiac arrest, it offers no advantage over epinephrine and is not generally recommended.[42,45] Additionally, the combination of vasopressin and epinephrine offers no advantages over epinephrine alone.[42,45] Thus, epinephrine alone is the vasopressor of choice for use in cardiac arrest as it simplifies the cardiac arrest treatment algorithm.[42,45] Administration of amiodarone and lidocaine leads to improved survival to hospital admission in patients with pulseless VT or VF.[46] Note that amiodarone doses recommended for administration during a resuscitation attempt for VF (see Table 10–14) are different than those used for termination of VT (see Table 10–13).

Table 10–14

Drugs for Facilitation of Defibrillation in Patients With Ventricular Fibrillation[42,46]

Drug	Dose
Epinephrine	1 mg IV/IO every 3–5 minutes
Amiodarone	300 mg IV/IO. One subsequent dose of 150 mg IV/IO may be administered
Lidocaine	1–1.5 mg/kg IV/IO. One subsequent dose of 0.5–0.75 mg/kg may be administered

IO, Intraosseous; IV, intravenous.

▶ Outcome Evaluation

- Monitor the patient for return of pulse and blood pressure and for termination of VF and restoration of normal sinus rhythm.
- After successful resuscitation, monitor the patient for adverse effects of drugs administered (Table 10–7).

Torsades de Pointes

TdP is a specific polymorphic VT associated with prolongation of the QTc interval in the sinus beats that precede the arrhythmia.[1,47]

▶ Epidemiology and Etiology

Incidence of TdP in the population at large is unknown although estimates suggest approximately 6% of patients develop QT prolongation when receiving drugs that lengthen the QT interval and roughly 0.3% experience TdP.[6] Incidence of TdP associated with specific drugs ranges from less than 1% to as high as 8% to 10%, depending on dose and plasma concentration of the drug and presence of other TdP risk factors.[47]

TdP may be inherited or acquired. Patients with specific genetic mutations in cardiac potassium channels may have an inherited long QT syndrome, in which the QTc interval is prolonged, and these patients are at risk for TdP.[1,47] Acquired TdP may be caused by numerous drugs (Table 10–15); the list of drugs known to cause TdP continues to expand.[47,48]

▶ Pathophysiology

TdP is caused by circumstances, often drugs, that lead to prolongation in the repolarization phase of the ventricular action potential (Figure 10–2) manifested on the ECG by prolongation of the QTc interval. A common feature of drugs causing QTc prolongation and TdP is blockade of the I_{Kr} (the rapid component of the delayed rectifier potassium current) potassium channel resulting in prolonged ventricular repolarization and QTc interval lengthening. Prolongation of ventricular repolarization promotes development of early ventricular afterdepolarizations during the relative refractory period, which may provoke reentry leading to TdP.[47]

KEY CONCEPT Drug-induced TdP rarely occurs in patients without specific risk factors for the arrhythmia (Table 10–16).[47,48] In most

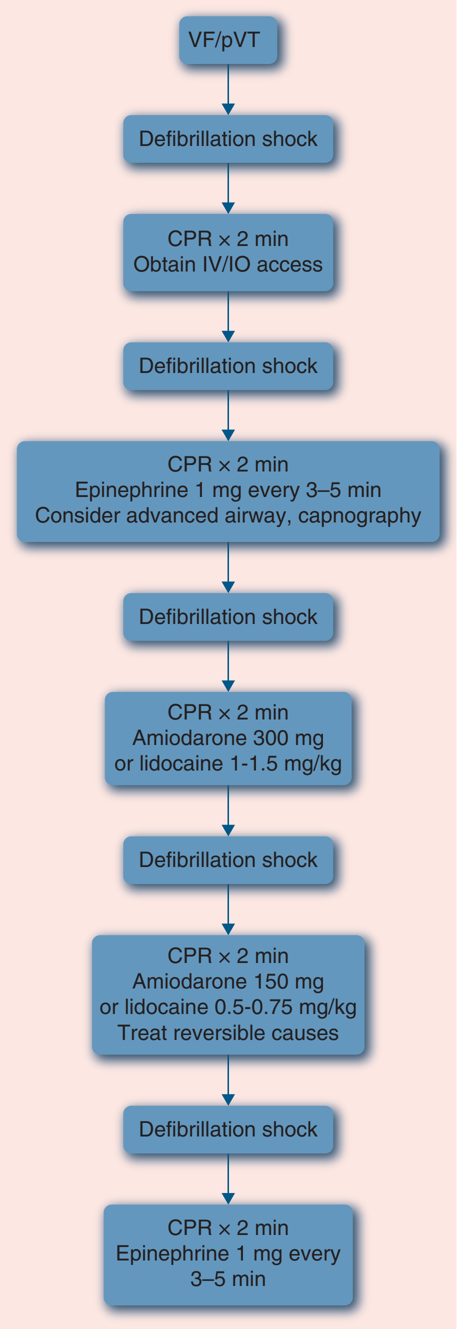
VF/pVT
Defibrillation shock
CPR × 2 min
Obtain IV/IO access
Defibrillation shock
CPR × 2 min
Epinephrine 1 mg every 3–5 min
Consider advanced airway, capnography
Defibrillation shock
CPR × 2 min
Amiodarone 300 mg
or lidocaine 1-1.5 mg/kg
Defibrillation shock
CPR × 2 min
Amiodarone 150 mg
or lidocaine 0.5-0.75 mg/kg
Treat reversible causes
Defibrillation shock
CPR × 2 min
Epinephrine 1 mg every
3–5 min

FIGURE 10–10. Decision algorithm for resuscitation of VF or pulseless VT. (CPR, cardiopulmonary resuscitation; IO, intraosseous; IV, intravenous; pVT, pulseless ventricular tachycardia; VF, ventricular fibrillation.) (Data from Panchal AR, Berg KM, Kudenchuk PJ, et al. 2018 American Heart Association focused update on advanced cardiovascular life support use of antiarrhythmic drugs during and immediately after cardiac arrest: an update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2018;138:e740–e749.)

cases, administration of a drug known to cause TdP is unlikely to trigger the arrhythmia; however, likelihood of the arrhythmia increases in patients with concomitant risk factors. Clinical decision support systems are available to assist in identifying patients at risk for and reduce incidence of QTc prolongation.[49,50]

Table 10–15

Some Drugs[a] Known to Cause Torsades de Pointes[1,47,48]

Amiodarone (rare)
Arsenic trioxide
Azithromycin
Chloroquine/hydroxychloroquine
Chlorpromazine
Ciprofloxacin
Citalopram
Clarithromycin
Cocaine
Disopyramide
Dofetilide
Donepezil
Dronedarone
Droperidol
Erythromycin
Escitalopram
Flecainide
Fluconazole
Haloperidol
Ibutilide
Levofloxacin
Methadone
Moxifloxacin
Ondansetron
Oxaliplatin
Pentamidine
Pimozide
Procainamide
Propofol
Quinidine
Sevoflurane
Sotalol
Thioridazine
Vandetanib

[a] This table does not provide an exhaustive list of drugs that may increase the risk of torsades de pointes. For an exhaustive list, please consult reference 48.

Onset of TdP associated with oral drug therapy is somewhat variable and in some cases may be delayed; often, a patient can be taking a drug known to cause TdP for months or longer without problem until another risk factor for the arrhythmia becomes present, which then may trigger the arrhythmia.

In some patients, TdP may be of short duration and may terminate spontaneously. However, TdP may not terminate on its own, and if left untreated, may degenerate into VF and sudden cardiac death.[1,47] Several drugs, including terfenadine, astemizole, cisapride, and grepafloxacin, have been withdrawn from the US market as a result of causing deaths due to TdP.

Table 10–16

Risk Factors for Drug-Induced Torsades de Pointes (TdP)[1,47,48]

QTc interval > 500 ms
Increase in QTc interval by > 60 ms compared with the pretreatment value
Female sex
Age > 65 years
Heart failure
Electrolyte abnormalities: hypokalemia, hypomagnesemia, hypocalcemia
Bradycardia
Elevated plasma concentrations of QTc interval-prolonging drugs due to drug interactions or absence of dose adjustment for organ dysfunction
Rapid IV infusion of TdP-inducing drugs
Concomitant administration of more than one agent known to cause QTc interval prolongation/TdP
Concomitant administration of potassium-wasting diuretics (eg, loops or thiazides)
Genetic predisposition—congenital long QT syndrome
Sepsis
Previous history of drug-induced TdP
Vomiting/diarrhea leading to electrolyte disturbances

IV, intravenous; ms, milliseconds; QTc, corrected QT interval.

Clinical Presentation and Diagnosis of TdP

Symptoms

- Symptoms associated with TdP depend primarily on heart rate and arrhythmia duration and include palpitations, dizziness, light-headedness, shortness of breath, chest pain (if underlying CAD is present), near-syncope, and syncope
- TdP may be hemodynamically unstable if the rate is sufficiently rapid
- Like sustained monomorphic VT, TdP may result in the absence of a pulse or may rapidly degenerate into VF, resulting in sudden cardiac death

Diagnosis

- Diagnosis of TdP requires examination of the arrhythmia on ECG
- TdP, or "twisting of the points," appears on ECG as apparent twisting of the wide QRS complexes around the isoelectric baseline
- Associated with heart rates from 140 to 280 beats/min
- Characteristic feature: a "long-short" initiating sequence that occurs as a result of a PVC followed by a compensatory pause followed by the first beat of the TdP
- Episodes of TdP may self-terminate, with frequent recurrence

▶ *Treatment*

Desired Outcomes Desired outcomes include (a) prevention of TdP, (b) termination of TdP, (c) prevention of recurrence, and (d) prevention of sudden cardiac death.

Pharmacologic and Nonpharmacologic Therapy KEY CONCEPT In patients with risk factors for TdP, drugs with the potential to cause QTc interval prolongation and TdP should be avoided or used with extreme caution, and diligent QTc interval monitoring performed. A decision algorithm for management of TdP is presented in Figure 10–11. Management of drug-induced TdP includes discontinuation of the potential causative agent. Patients with hemodynamically unstable TdP should undergo immediate defibrillation, rather than synchronized DCC, because polymorphic arrhythmias are usually not responsive to DCC. In patients with hemodynamically stable TdP, electrolyte abnormalities such as hypokalemia, hypomagnesemia, or hypocalcemia should be corrected. Hemodynamically stable TdP should be treated with IV magnesium sulfate, irrespective of whether the patient is hypomagnesemic; magnesium has been shown to terminate TdP in normomagnesemic patients.[38,42] Magnesium sulfate should be administered IV in doses of 1 to 2 g, diluted in 50 to 100 mL 5% dextrose in water (D_5W), administered over 15 minutes; doses may be repeated to a total of 6 g.[38] Alternatively, a continuous magnesium infusion (0.5–1 g/hour) may be initiated after the first bolus. In addition, electrolyte repletion with potassium to greater than or equal to 4 mEq/L (mmol/L) and magnesium to greater than or equal to 2 mEq/L (1 mmol/L) is recommended.[38]

For hemodynamically stable TdP that is unresponsive to IV magnesium sulfate and is accompanied by bradycardia or

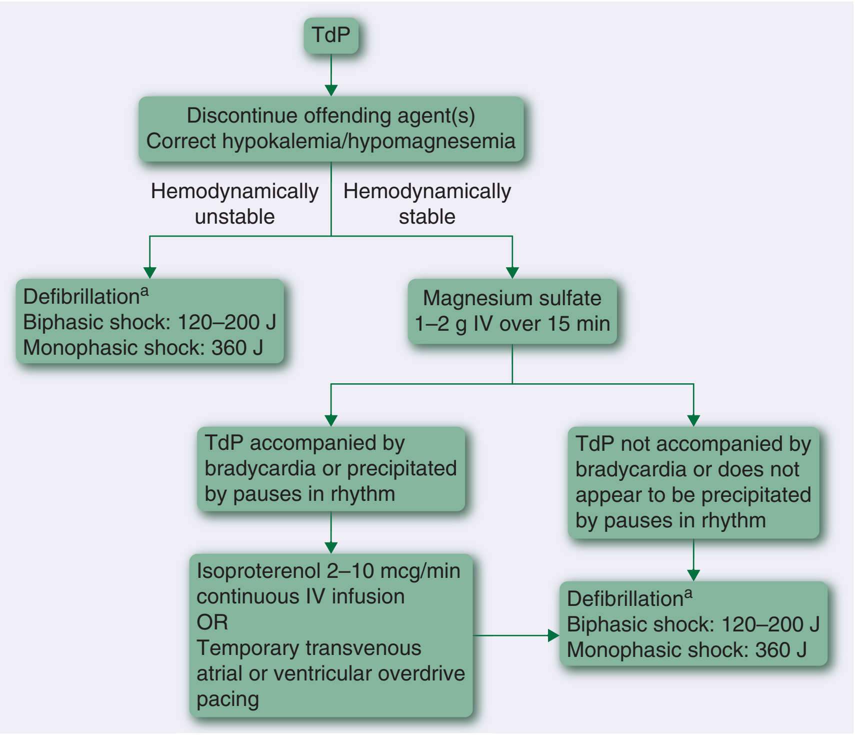
TdP
Discontinue offending agent(s)
Correct hypokalemia/hypomagnesemia
Hemodynamically unstable
Hemodynamically stable
Defibrillation^a
Biphasic shock: 120–200 J
Monophasic shock: 360 J
Magnesium sulfate
1–2 g IV over 15 min
TdP accompanied by bradycardia or precipitated by pauses in rhythm
TdP not accompanied by bradycardia or does not appear to be precipitated by pauses in rhythm
Isoproterenol 2–10 mcg/min continuous IV infusion
OR
Temporary transvenous atrial or ventricular overdrive pacing
Defibrillation^a
Biphasic shock: 120–200 J
Monophasic shock: 360 J

FIGURE 10–11. Decision algorithm for management of torsades de pointes. [a]As polymorphic arrhythmias do not permit synchronization, defibrillation is recommended, rather than synchronized direct current cardioversion. Administer sedation when possible. (IV, intravenous; J, Joules; TdP, torsades de pointes.) (Reprinted with permission from Erstad B, ed. Critical Care Pharmacotherapy. Lenexa, KS; American College of Clinical Pharmacy: 2016;730.)

Patient Care Process

Collect Information:

- Perform a thorough medication history to determine whether the patient is receiving prescription or nonprescription drugs that may cause or contribute to development of an arrhythmia. See Tables 10–2, 10–3, 10–4, 10–12, and 10–15.
- Determine the patient's serum electrolyte concentrations to determine presence of hypokalemia, hyperkalemia, hypomagnesemia, hypermagnesemia, or hypocalcemia.
- Consider heart rate, blood pressure, and symptoms to determine whether the patient is hemodynamically stable or unstable, and the degree to which symptoms are limiting function and quality of life.
- Review the patients' ECG(s) and/or ECG rhythm strips.

Assess the Information:

- Evaluate the patient for presence of drug-induced diseases, drug allergies, drug interactions, and impaired organ function that can alter drug clearance.
- For patients with preexisting arrhythmias, assess the current drug therapy regimen for efficacy, side effects, and adherence.
- In patients with AF receiving anticoagulation for stroke prevention, evaluate for appropriateness, adverse effects, drug–drug and drug–food interactions, and INR in patients receiving warfarin.
- Assess adherence to current drug therapy regimens.
- Assess the patient's 12-lead ECG or single rhythm strips to determine if an arrhythmia is present, and identify the specific arrhythmia, and evaluate and monitor symptoms.
- Assess information from the chest X-ray, transthoracic echocardiograms or TEEs, laboratory tests, and other physical examination and diagnostic information pertinent to arrhythmias.

Develop a Care Plan:

- Develop drug therapy treatment plans for management of the pertinent arrhythmia: sinus bradycardia, AV block, AF, PSVT, PVCs, VT (including TdP), or VF. See Figures 10–4 through 10–11 and Tables 10–6, 10–7, 10–8, 10–9, 10–10, 10–11, 10–13, and 10–14.

Implement the Care Plan:

- Educate the patient about drug therapy changes, medication administration, potential new adverse effects, and how to manage adverse effects.
- Address patient concerns about arrhythmias and their management.
- Discuss importance of medication adherence and risk factor modification for management of arrhythmias.
- Determine whether the patient has prescription coverage and/or whether recommended agents are included on the institution's formulary.

Follow-up: Monitor and Evaluate:

- Develop specific drug therapy monitoring plans, including assessment of symptoms, ECG, adverse effects of drugs, and potential drug interactions.
- Monitor QTc interval in patients receiving QTc interval-prolonging drugs.
- Provide information regarding safe and effective oral anticoagulation:
    - Notify clinicians in the event of severe bruising, blood in urine or stool, **melena**, **hemoptysis**, **hematemesis**, or frequent **epistaxis**.
    - Patients taking warfarin should avoid radical changes in diet.
    - Avoid alcohol.
    - Do not take nonprescription medications or herbal/alternative/complementary medicines without notifying physician, pharmacist, and/or healthcare team members.
- Provide patient education regarding disease state and drug therapy.

triggered by pauses in rhythm, isoproterenol administered via continuous IV infusion 2 to 10 mcg/min may be administered, or temporary transvenous atrial or ventricular pacing may be employed to increase the heart rate.[38]

▶ *Outcome Evaluation*

- Monitor vital signs (heart rate and blood pressure).
- Monitor the ECG to determine the QTc interval (maintain < 470 ms in males and 480 ms in females) and for the presence of TdP.[1]
- Monitor serum potassium, magnesium, and calcium concentrations. Maintain serum potassium concentrations *greater than or equal to* 4 mEq/L (mmol/L) and magnesium *greater than or equal to* 2 mEq/L (1 mmol/L).
- Monitor for symptoms of tachycardia.
- Monitor for other patient-specific risk factors for QTc prolongation and TdP (eg, drug interactions, impaired organ function).

Abbreviations Introduced in This Chapter

1°	First-degree
2°	Second-degree
3°	Third-degree
ACE	Angiotensin-converting enzyme
ADHF	Acute decompensated heart failure
AF	Atrial fibrillation
aPTT	Activated partial thromboplastin time
ATPase	Adenosine triphosphatase
AV	Atrioventricular
Ca	Calcium
CAD	Coronary artery disease
CAST	Cardiac Arrhythmia Suppression Trial
CCB	Calcium channel blocker
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CPR	Cardiopulmonary resuscitation
CrCl	Creatinine clearance

CYP	Cytochrome P450
DCC	Direct current cardioversion
DOAC	Direct oral anticoagulant
D_5W	5% Dextrose in water
ECG	Electrocardiogram
ED	Emergency department
EMS	Emergency medical services
FDA	Food and Drug Administration
GI	Gastrointestinal
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
ICD	Implantable cardioverter-defibrillator
INR	International normalized ratio
IO	Intraosseous
IV	Intravenous
J	Joule
K	Potassium
LV	Left ventricle/ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
ms	Milliseconds
Na	Sodium
NYHA	New York Heart Association
P-gp	P-glycoprotein
PAD	Peripheral arterial disease
PSVT	Paroxysmal supraventricular tachycardia
PVC	Premature ventricular complex
QTc	Corrected QT interval
SA	Sinoatrial
TdP	Torsades de pointes
TEE	Transesophageal echocardiogram
TIA	Transient ischemic attack
VF	Ventricular fibrillation
VPB	Ventricular premature beat
VPC	Ventricular premature contraction
VPD	Ventricular premature depolarization
VT	Ventricular tachycardia

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11

Venous Thromboembolism

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Identify risk factors and signs and symptoms of deep vein thrombosis (DVT) and pulmonary embolism (PE).
2. Describe the processes of hemostasis and thrombosis.
3. Determine a patient's risk of developing venous thrombosis.
4. Formulate an appropriate prevention strategy for a patient at risk for DVT.
5. Select and interpret laboratory test(s) to monitor antithrombotic medications for safety and efficacy.
6. Identify factors that place a patient at high risk of bleeding while receiving antithrombotic medications.
7. State at least two potential advantages of newer anticoagulants (ie, low-molecular-weight heparins [LMWHs], fondaparinux, oral direct thrombin inhibitors [DTIs], and oral direct factor Xa inhibitors) over traditional anticoagulants (ie, unfractionated heparin and warfarin).
8. Manage a patient with toxicity secondary to an anticoagulant with or without bleeding.
9. Identify relevant factors such as drug–drug and drug–food interactions to optimize anticoagulant medication selection.
10. Formulate an appropriate treatment plan, including duration and monitoring, for a patient who develops a DVT or PE.

INTRODUCTION

Venous thromboembolism (VTE) is one of the most common cardiovascular disorders in the United States. VTE is manifested as deep vein thrombosis (DVT; ie, thrombus causing obstruction of a deep vein in the leg, pelvis, or abdomen) and pulmonary embolism (PE; ie, thrombus causing obstruction of a pulmonary artery or one of its branches and resulting in pulmonary infarction) (Figure 11–1).[1,2] A thrombus is a blood clot attached to the vessel wall composed of platelets, fibrin, and clotting factors that may partially or completely occlude the lumen of a blood vessel and compromise blood flow and oxygen delivery to distal tissue. It is often provoked by prolonged immobility or vascular injury and most frequently seen in patients hospitalized for a serious medical illness, trauma, or major surgery. VTE can also occur with little or no provocation in patients who have an underlying hypercoagulable disorder.

Although VTE may initially cause few or no symptoms, the first overt manifestation of the disease may be sudden death from PE which can occur within minutes, before effective treatment can be given.[2,3] A history of VTE is a significant risk factor for recurrent thromboembolic events.[4-7] Postthrombotic syndrome (PTS) is a complication of VTE that occurs due to damage to the vein caused by a blood clot and leads to development of symptomatic venous insufficiency such as chronic lower extremity swelling, pain, tenderness, skin discoloration, and ulceration.[2]

The treatment of VTE is fraught with substantial risks.[8] KEY CONCEPT Antithrombotic therapies (thrombolytics and anticoagulants) require precise dosing and meticulous monitoring, as well as ongoing patient assessment and education.[4,9,10] Well-organized anticoagulation management services improve quality of care and reduce overall cost. A systematic approach to drug therapy management reduces risks, but bleeding remains a common and serious complication.[10,11] Therefore, preventing VTE is paramount to improving outcomes. When VTE is suspected, a rapid and accurate diagnosis is critical to making appropriate treatment decisions. The optimal use of antithrombotic drugs requires not only an in-depth knowledge of their pharmacology and pharmacokinetic properties but also a comprehensive approach to patient management.[3,12]

EPIDEMIOLOGY AND ETIOLOGY

The true incidence of VTE in the general population is unknown because many patients, perhaps more than 50%, have no overt symptoms or go undiagnosed.[1,12,13] An estimated 2 million people in the United States develop VTE each year, of whom 600,000 are hospitalized and 60,000 die. The estimated annual direct medical costs of managing the disease are well over $1 billion. The incidence of VTE nearly doubles in each decade of life older than 50 years of age and is slightly higher in men. As the population ages, the total number of DVT and PE cases continues to rise.[1,2,13,14]

KEY CONCEPT The risk of VTE is related to several factors including age, history of VTE, major surgery (particularly orthopedic procedures of the lower extremities), trauma, malignancy, pregnancy, estrogen use, and hypercoagulable states (Table 11–1).[5-7] VTE risk factors can be categorized into one of the three elements of Virchow triad: stasis in blood flow, vascular endothelial injury,

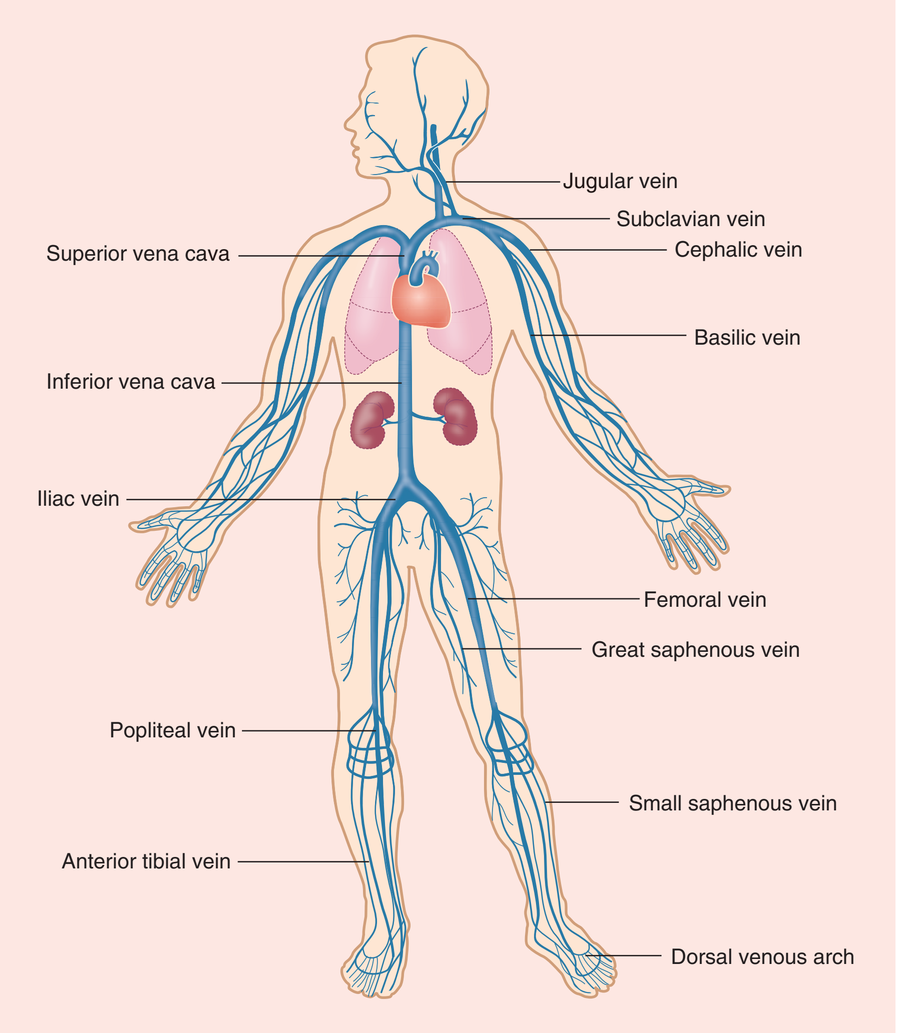


FIGURE 11–1. Venous circulation. (From Witt DM, Clark NP, Vazquez SR. Venous thromboembolism. In: DiPiro JT, Yee GC, Posey LM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill. Available from: https://accesspharmacy.mhmedical.com/content.aspx?bookid=2577&sectionid=219316417. Accessed July 15, 2020.)

and inherited or acquired changes in blood constituents resulting in hypercoagulable states.[15-17] These risk factors are additive, and some can be easily identified in clinical practice.[1,3] A prior history of venous thrombosis (in which blood changes from a liquid to a solid state and produces a blood clot) is perhaps the strongest risk factor for recurrent VTE, presumably because of damage to venous valves and obstruction of blood flow caused by the initial event.[5-7] Rapid blood flow (as in arteries) has an inhibitory effect on thrombus formation, but a slow rate of blood flow (as in veins) reduces the clearance of activated clotting factors in the zone of injury and slows the influx of regulatory substances. Stasis tips the delicate balance of procoagulation and anticoagulation in favor of thrombogenesis. The rate of blood flow in the venous circulation, particularly in the deep veins of the lower extremities, is relatively slow. Valves in the deep veins of the legs, as well as contraction of the calf and thigh muscles, facilitate the flow of blood back to the heart and lungs. Damage to the venous valves and periods of prolonged immobility result in venous stasis. Vessel obstruction, either from a thrombus or external compression, promotes clot propagation. Numerous medical conditions and surgical procedures are associated with reduced venous blood flow and increase the risk of VTE. Greater than normal blood viscosity, seen in myeloproliferative disorders like polycythemia vera, may also contribute to slowed blood flow and thrombus formation.[5-7,16,17]

While a normal endothelium is antithrombotic, damage to the endothelium creates a substrate for platelet binding and activation that ultimately leads to clot formation. Major surgery, trauma, and indwelling central catheters can cause endothelial damage. Smoking and hypertension can also lead to endothelial dysfunction by shifting the balance between clot formation and clot breakdown toward thrombosis.[5-7,16,17]

A growing list of hereditary deficiencies, gene mutations, and acquired diseases has been linked to hypercoagulability (Table 11–1).[18,19] Some patients may have multiple genetic defects. Hereditary deficiencies include activated protein C resistance also known as factor V Leiden, the prothrombin G20210A gene mutation, deficiencies of the natural anticoagulants protein C, protein S, and antithrombin (AT), and high concentrations of factors VIII, IX, and XI. Acquired disorders of hypercoagulability include malignancy, antiphospholipid antibodies, obesity, estrogen use, and pregnancy.[20,21] Estrogen-containing contraceptives, estrogen replacement therapy, and many of the selective estrogen receptor modulators (SERMs) increase the risk of venous thrombosis.[20,22] Although the mechanisms are not clearly understood, estrogens increase serum clotting factor concentrations and induce

Table 11–1

Risk Factors for Venous Thromboembolism (VTE)

Risk Factor	Considerations and Examples
Age	Risk doubles with each decade after age 50
History of VTE	Strongest known risk factor
Venous stasis	Major medical illness (eg, heart failure, acute myocardial infarction, ischemic stroke, acute infection)
	Major surgery (eg, general anesthesia for > 30 minutes)
	Paralysis (eg, due to stroke or spinal cord injury)
	Polycythemia vera
	Obesity
	Varicose veins
	Immobility (eg, bed rest for ≥ 3 days during hospital admission)
Vascular injury	Major orthopedic surgery (eg, knee and hip replacement)
	Trauma (especially fractures of the pelvis, hip, or leg)
	Indwelling venous catheters
Hypercoagulable states	Malignancy, diagnosed or occult
	Activated protein C resistance/factor V Leiden
	Prothrombin G20210A gene mutation
	Protein C deficiency
	Protein S deficiency
	Antithrombin deficiency
	Factor VIII excess (> 90th percentile)
	Factor XI excess (> 90th percentile)
	Antiphospholipid antibodies
	Dysfibrinogenemia
	Plasminogen activator inhibitor-1 (PAI-1) excess
	Pregnancy/postpartum
Drug therapy	Estrogen-containing oral contraceptive pills
	Estrogen replacement therapy
	Selective estrogen receptor modulators (SERMs)
	Heparin
	Chemotherapy

activated protein C resistance. Increased serum estrogen concentrations may explain, in part, the increased risk of VTE during pregnancy and the postpartum period.[22]

PATHOPHYSIOLOGY

Hemostasis, the arrest of bleeding following vascular injury, is essential to life.[23] Within the vascular system, blood remains in a fluid state, transporting oxygen, nutrients, plasma proteins, and waste. When a vessel is injured, a dynamic interplay between thrombogenic (activating) and antithrombotic (inhibiting) forces results in the local formation of a hemostatic plug that seals the vessel wall and prevents further blood loss (Figures 11–2 and 11–3). A disruption of this delicate system of checks and balances may lead to inappropriate clot formation within the blood vessel that can obstruct blood flow or embolize to a distant vascular bed.

Under normal circumstances, endothelial cells lining the inside of blood vessels maintain blood flow by producing a number of substances that inhibit platelet adherence, prevent activation of the coagulation cascade, and facilitate fibrinolysis.[16,17,23] Vascular injury exposes the subendothelium. Platelets adhere to the subendothelium with their glycoprotein (GP) Ib surface receptors and facilitated by von Willebrand factor (vWF). This causes platelets to become activated, releasing a number of procoagulant substances that stimulate circulating platelets to expose GP IIb and IIIa surface receptors subsequently allowing platelets to adhere to one another, resulting in platelet aggregation (Figure 11–2). The damaged vascular tissue releases tissue factor that activates the extrinsic pathway of the coagulation cascade (Figure 11–3).[23]

The clotting cascade is a stepwise series of enzymatic reactions that results in the formation of a fibrin mesh.[12] Clotting factors circulate in the blood in inactive forms. Once a precursor is activated by specific stimuli, it activates the next clotting factor in the sequence. The final steps in the cascade are the conversion of prothrombin (factor II) to thrombin (factor IIa) and fibrinogen to fibrin. Thrombin plays a key role in the coagulation cascade; it is responsible not only for the activation of fibrin but also for the activation of factors V and VIII, creating a positive feedback loop that greatly accelerates the entire cascade. Thrombin also enhances platelet aggregation.

Traditionally, the coagulation cascade has been divided into three distinct parts: the intrinsic, the extrinsic, and the common pathways. This artificial division is misleading because there are numerous interactions between the three pathways.[16,17,23] A number of tempering mechanisms modulate coagulation (Figure 11–2).[23,24] Without effective self-regulation, the coagulation cascade would proceed unabated until all clotting factors and platelets are consumed.

CLINICAL PRESENTATION AND DIAGNOSIS

Although a thrombus can form in any part of the venous circulation, most begin in the lower extremities. Once formed, a venous thrombus may (a) remain asymptomatic, (b) spontaneously lyse, (c) obstruct the venous circulation, (d) propagate into more proximal veins, (e) embolize, and/or (f) slowly incorporate into the endothelial layer of the vessel.[1,3,16] Most patients with VTE never develop symptoms.[3,25] However, even those who initially experience no symptoms may suffer long-term consequences, such as PTS and recurrent VTE.

Given that VTE can be debilitating or fatal, it is important to treat it quickly and aggressively.[1,2,12] However, because major bleeding induced by antithrombotic drugs can be equally harmful, it is also important to avoid treatment when the diagnosis is not reasonably certain. Assessment should focus on patient-specific risk factors during the medical history (Table 11–1).[1,2,12] Venous thrombosis is uncommon in the absence of risk factors, and the effects of these risk factors are additive. If a patient has multiple risk factors, VTE should be strongly suspected even when the symptoms are very subtle.

KEY CONCEPT The symptoms of DVT or PE are nonspecific, and it is extremely difficult to distinguish VTE from other disorders on clinical symptoms alone.[1-3,25] Therefore, objective tests are required to confirm or rule out the diagnosis. Patients with DVT frequently present with unilateral leg pain on the affected leg, swelling that can persist after a night's sleep, and cyanosis of the skin in the affected leg (Table 11–2). Similarly, PTS, a long-term complication of DVT caused by damage to the venous valves, produces chronic lower extremity swelling, pain, and tenderness that lead to skin discoloration and ulceration. To distinguish acute DVT from PTS and other possible diagnoses, a clinical prediction rule that incorporates signs, symptoms, and risk factors can be used to categorize the patient as at low, intermediate, or high probability of having acute DVT. This model, known as the Wells criteria, is summarized in Table 11–2.[2,3,12] If the clinical probability of DVT is low, the D-dimer test can be used to confirm the

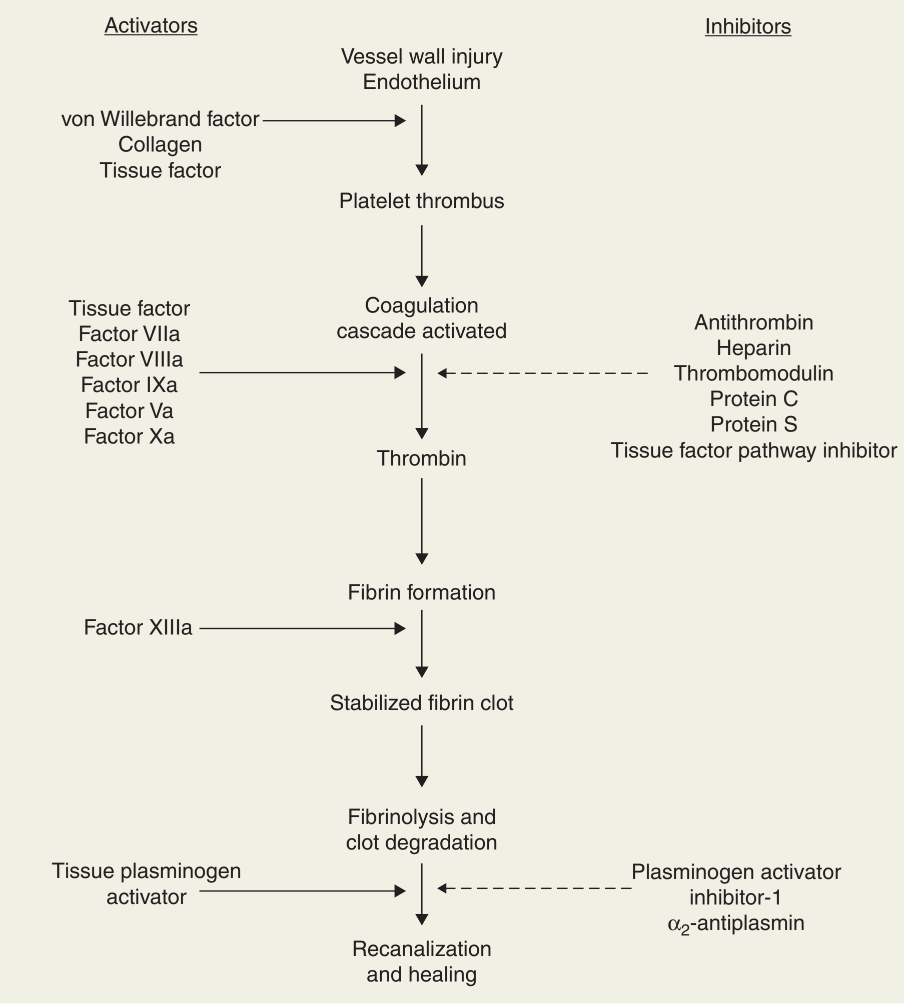

Activators
Inhibitors
Vessel wall injury
Endothelium
von Willebrand factor
Collagen
Tissue factor
Platelet thrombus
Tissue factor
Factor VIIa
Factor VIIIa
Factor IXa
Factor Va
Factor Xa
Coagulation cascade activated
Antithrombin
Heparin
Thrombomodulin
Protein C
Protein S
Tissue factor pathway inhibitor
Thrombin
Fibrin formation
Factor XIIIa
Stabilized fibrin clot
Fibrinolysis and clot degradation
Tissue plasminogen activator
Plasminogen activator inhibitor-1
α_2-antiplasmin
Recanalization and healing

FIGURE 11–2. Hemostasis and thrombosis. (From Witt DM, Clark NP, Vazquez SR. Venous thromboembolism. In: DiPiro JT, Yee GC, Posey LM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill. Available from: https://accesspharmacy.mhmedical.com/content.aspx?bookid=2577&sectionid=21931641. Accessed July 15, 2020.)

patient does not have DVT. The D-dimer test is a quantitative measure of fibrin breakdown in the serum and a marker of acute thrombotic activity. D-dimer assays are sensitive but not specific markers for VTE, so a negative D-dimer test can be used to rule out the diagnosis of DVT.

If the D-dimer test is positive in a low-probability patient, or if the patient has a moderate or high probability of DVT, then an objective radiographic test is used to confirm the diagnosis of DVT. Contrast venography allows visualization of the entire venous system in the lower extremities. This radiographic contrast study is the most accurate and reliable method for diagnosis of DVT and considered the gold standard in clinical trials.[3,25,26] However, venography is an expensive, invasive procedure that is technically difficult to perform and evaluate. Severely ill patients may be unable to tolerate the procedure, and many develop hypotension and cardiac arrhythmias. Furthermore, the contrast material is irritating to vessel walls and toxic to the kidneys. For these reasons, noninvasive testing using duplex ultrasonography is preferred.

Like DVT, the nonspecific nature of the signs and symptoms of PE requires further evaluation. Table 11–3 describes the Wells criteria, a validated prediction model that can be used to stratify patients into high, moderate, and low probability of PE.[3,25-27] In patients with a low clinical probability of PE, diagnosis of PE can be ruled out if D-dimer testing is negative. If D-dimer testing is positive, or if the patient has a moderate or high clinical probability of PE, diagnostic imaging studies should be performed. Pulmonary angiography allows visualization of the pulmonary arteries and is the gold standard for diagnosing PE but is an extremely invasive procedure. Diagnosis of VTE can be made if there is a persistent intraluminal filling defect observed on multiple X-ray films. However, as with DVT, a noninvasive test is preferred, such as computed tomographic pulmonary angiography, magnetic resonance imaging (MRI), and ventilation/perfusion (V/Q) scans.

PREVENTION

Given that VTE is often clinically silent and potentially fatal, prevention strategies have the greatest potential to improve patient outcomes.[5-7] The goal of an effective VTE prophylaxis program is to identify all patients at risk, determine each patient's level of risk, and select and implement regimens that provide sufficient protection for the level of risk.[5-7] **KEY CONCEPT** At the time of hospital admission, transition of care, and prior to discharge, all patients should be evaluated for risk of VTE, and appropriate prophylaxis strategies should be routinely used. Prophylaxis should be continued throughout the period of risk.

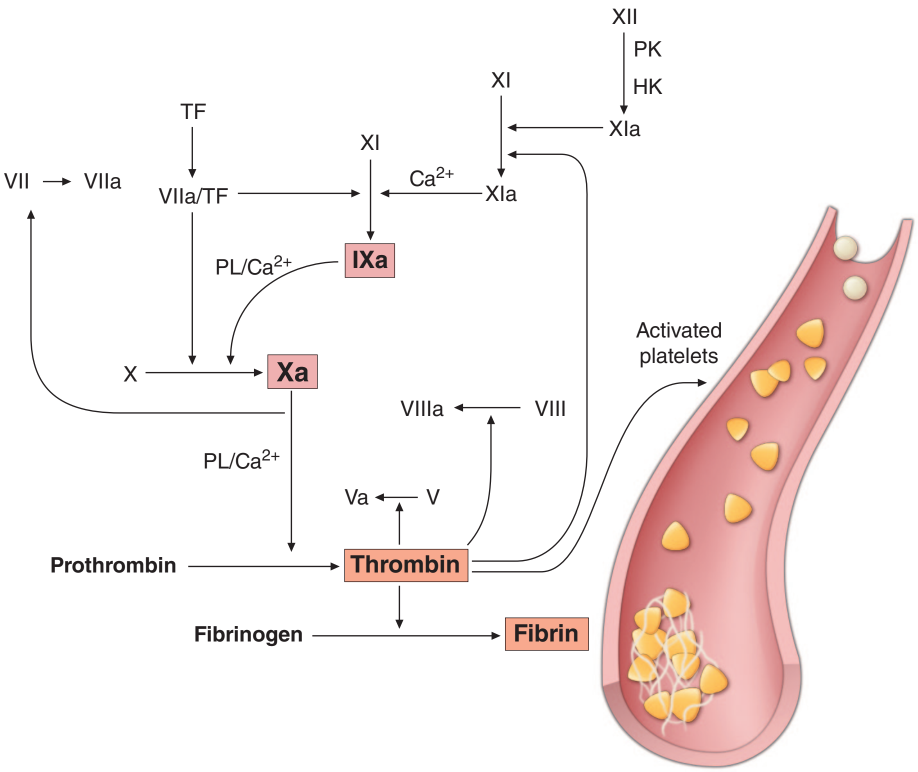


FIGURE 11–3. Summary of coagulation pathways. Specific coagulation factors ("a" indicates activated form) are responsible for the conversion of soluble plasma fibrinogen into insoluble fibrin. This process occurs via a series of linked reactions in which the enzymatically active product subsequently converts the downstream inactive protein into an active serine protease. The activation of thrombin leads to additional stimulation of platelets. (Ca^{2+}, calcium; HK, high-molecular-weight kininogen; PK, prekallikrein; PL, phospholipid surface; TF, tissue factor.) (From Freedman JE, Loscalzo J. Arterial and venous thrombosis. In: Longo DL, Fauci AS, Kasper DL, et al., eds. Harrison's Principles of Internal Medicine, 20th ed. New York, NY: McGraw-Hill; 2018.)

Table 11–2

Clinical Model/Modified Wells Criteria for Evaluating the Pretest Probability of Deep Vein Thrombosis (DVT)

Clinical Characteristic	Score
Active cancer (cancer treatment within previous 6 months or currently on palliative treatment)	+1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	+1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia	+1
Localized tenderness along the distribution of the deep venous system	+1
Entire leg swollen	+1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	+1
Pitting edema confined to the symptomatic leg	+1
Collateral superficial veins (nonvaricose)	+1
Previously documented DVT	+1
Alternative diagnosis at least as likely as DVT	–2

Assess the patient for the presence of any of the 9 clinical characteristics listed above
Assign a score of "+1" for each characteristic that is present.
Tally the total score.
If an alternative diagnosis is at least as likely as DVT, then subtract 2 points from the total points tallied above.
In patients with symptoms in both legs, the more symptomatic leg is used.

Risk Score Interpretation

Total Risk Score	Clinical Probability of DVT
0	Low
1	Moderate
2	Moderate
3 or higher	High

Clinical Presentation and Diagnosis of DVT

General

Most commonly develops in patients with identifiable risk factors (Table 11–1) during or following a hospitalization. Many patients have asymptomatic disease.

Symptoms

Patient may complain of persistent unilateral leg swelling, pain, warmth, and/or skin discoloration. Symptoms are nonspecific, and objective testing must be performed to establish the diagnosis.

Signs

- Superficial veins may be dilated, and a "**palpable cord**" may be felt in the affected leg.
- May experience unilateral leg edema with measurable difference in leg circumference compared to the unaffected leg, erythema, increase in warmth, and tenderness with palpation of calf muscles.
- May experience pain in the popliteal or calf region in the affected leg when the examiner dorsiflexes the foot while the knee is flexed/slightly bent (Homans sign).
- Note: Physical examination signs can be unreliable. Homans sign can also be unreliable.

Clinical Probability

Apply the Wells criteria to determine the probability that the patient's signs, symptoms, and risk factors are the result of DVT (Table 11–2).

Laboratory Tests

- Initial laboratory evaluation should include complete blood count (CBC) with differential, coagulation studies (such as **prothrombin time** [PT]/**international normalized ratio** [INR], activated partial thromboplastin time [aPTT]), serum chemistries with renal and liver function, and urinalysis.
- Serum concentrations of D-dimer, a by-product of thrombin generation, will be elevated in an acute event. A negative D-dimer in a patient with low clinical probability of DVT can be used to rule out DVT.
- Patient may have an elevated erythrocyte sedimentation rate (ESR) and white blood cell (WBC) count.

Diagnostic Tests

- Duplex ultrasonography is the most commonly used test to diagnose DVT. It is a noninvasive test that can measure the rate and direction of blood flow and visualize clot formation in proximal veins of the legs. It cannot reliably detect small blood clots in distal veins. Coupled with a careful clinical assessment, it can confirm or rule out (exclude) the diagnosis in most cases. Repeat testing may be necessary if the first test is negative and the patient is still symptomatic.
- Venography (also known as phlebography) is the gold standard for diagnosis of DVT. However, it is an invasive test that involves injection of radiopaque contrast dye into a foot vein. It is expensive and can cause anaphylaxis and nephrotoxicity.

There are several risk assessment models available for estimating VTE risk specific to hospitalized medical and surgical patients.[5-7,12] While none of these models have been extensively validated, the Padua prediction score is recommended for assessment of medical patients (Table 11–4), and the Caprini score is recommended for assessment of general surgical patients (Table 11–5). Bleeding risk should also be assessed to help identify patients in whom the risk of bleeding may outweigh benefits of pharmacologic prophylaxis.[5-7] Table 11–6 lists general and

Table 11–3

Clinical Model/Wells Criteria for Evaluating the Pretest Probability of Pulmonary Embolism (PE)

Clinical Characteristic	Score
Cancer	+1
Hemoptysis	+1
Previous PE or DVT	+1.5
Heart rate > 100 beats/min	+1.5
Recent surgery or immobilization	+1.5
Clinical signs of DVT	+3
Alternative diagnosis less likely than PE	+3

Risk Score Interpretation

Total Risk Score	Clinical Probability of PE
0–1	Low
2–6	Moderate
7 or higher	High

DVT, deep vein thrombosis.

Table 11–4

Risk Factors for Predicting Venous Thromboembolism (VTE) in Hospitalized Medical Patients (Padua Prediction Score)

Risk Factor	Points
Active cancer[a]	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility[b]	3
Already known thrombophilic condition[c]	3
Recent (≤ 1 month) trauma and/or surgery	2
Elderly age (≥ 70 years)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (body mass index ≥ 30)	1
Ongoing hormonal treatment	1
Cumulative score of ≥ 4 points indicates high risk of VTE	

[a] Patients with local or distant metastases and/or in whom chemotherapy or radiotherapy had been performed in the previous 6 months.

[b] Anticipated bed rest with bathroom privileges (either because of patient's limitations or on physician's order) for at least 3 days.

[c] Carriage of defects of antithrombin, protein C or S, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome.

Adapted with permission from Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl):e195S–e226S.

Clinical Presentation and Diagnosis of PE

General

Most commonly develops in patients with risk factors for VTE (Table 11–1) during or following a hospitalization. Although many patients will have symptoms of DVT prior to developing a PE, many will not, and some patients can be asymptomatic. Patients may die suddenly before effective treatment can be initiated.

Symptoms

- May complain of cough, pleuritic chest pain, chest tightness, shortness of breath with or without exertion, wheezing, orthopnea, or palpitations.
- May present with hemoptysis (spit or cough up blood).
- May complain of dizziness or experience syncope.
- May be misdiagnosed as a myocardial infarction (MI) or pneumonia, and objective testing must be performed to establish the diagnosis.

Signs

- May have tachypnea (increased respiratory rate) and tachycardia (increased heart rate).
- May appear diaphoretic (sweaty) and may have fever.
- Neck veins (external jugular veins) may be distended reflecting increased jugular venous pressure and increased heart pressure.
- The examiner may see use of accessory respiratory muscles and may hear diminished breath sounds, crackles, wheezes, or pleural friction rub during auscultation of the lungs. A parasternal lift or right ventricular S_3, S_4 may be found on the heart examination.
- In massive PE, the patient may appear cyanotic and hypotensive and may appear to have signs of right-sided heart failure. In such cases, oxygen saturation by pulse oximetry or arterial blood gas will likely indicate the patient is hypoxic.
- In the worst cases, the patient may go into circulatory shock and die within minutes.

Clinical Probability

Apply the Wells criteria to determine the probability that the patient's signs, symptoms, and risk factors are the result of PE (Table 11–3).

Laboratory Tests

- Serum concentrations of D-dimer, a by-product of thrombin generation, will be elevated. A negative D-dimer in a patient with low clinical probability of PE can be used to rule out PE.
- In patients with a low probability for PE, the PE rule-out criterion ("PERC rule") is an alternative to D-dimer testing. In patients who meet all following eight criteria, the likelihood of PE is low, and no further testing is required: age less than 50 years; heart rate less than 100 beats/min; oxyhemoglobin saturation at or above 95% (0.95); no hemoptysis; no estrogen use; no prior DVT or PE; no unilateral leg swelling; and no surgery/trauma requiring hospitalization within the prior 4 weeks.
- May have an elevated ESR and WBC count.
- May have elevated serum lactate dehydrogenase (LDH) or aspartate aminotransferase (AST; serum glutamic-oxaloacetic transaminase [SGOT]) with normal bilirubin.
- Serum troponin I, troponin T, and B-type natriuretic peptide can be elevated in a large PE. These typically resolve within 40 hours if due to PE but persist longer after acute MI.
- Electrocardiogram may show nonspecific ST-segment and T-wave changes and tachycardia. Arterial blood gases may show acute respiratory alkalosis from hyperventilation.

Diagnostic Imaging Tests

- A computed tomography (CT) pulmonary angiography with radiocontrast is the most commonly used test to diagnose PE, but some institutions still use a V/Q scan. Spiral (or helical) CT scans can detect emboli in the proximal pulmonary arteries. A V/Q scan measures the distribution of blood and air flow in the lungs. When there is a large mismatch between blood and air flow in one area of the lung, there is a high probability the patient has a PE.
- Pulmonary angiography is the gold standard for diagnosis of PE. However, it is an invasive test that involves injection of radiopaque contrast dye into the pulmonary artery. The test is expensive and associated with significant risk of mortality.

procedure-specific risk factors for major bleeding complications. Patients with moderate to high risk of VTE should receive pharmacologic prophylaxis. If pharmacologic prophylaxis is contraindicated, such as in patients actively bleeding or at high risk of bleeding, nonpharmacologic prophylaxis should be used (Table 11–7).

Several pharmacologic and nonpharmacologic methods are effective for preventing VTE, and these can be used alone or in combination (Table 11–7).[5-7] Nonpharmacologic methods improve venous blood flow by mechanical means; drug therapy prevents thrombus formation by inhibiting the coagulation cascade.

Nonpharmacologic Therapy

Ambulation as soon as possible following surgery lowers the incidence of VTE in low-risk patients.[5-7] Walking increases venous blood flow and promotes the flow of natural antithrombotic factors into the lower extremities. All hospitalized patients should be encouraged to ambulate as early as possible, and as frequently as possible.

Graduated compression stockings (GCS) are specialized hosiery that provide graduated pressure on the lower legs and feet to help prevent thrombosis. Compared with anticoagulant drugs, GCS are relatively inexpensive and safe; however, they are less effective and not recommended in moderate-to-higher-risk patients.[2] They offer an alternate in low-to moderate-risk patients when pharmacologic interventions are contraindicated. When combined with pharmacologic interventions, GCS have an additive effect. However, some patients are unable to wear compression stockings because of the size or shape of their legs, and some patients may find them hot, confining, and very difficult to put on and remove.

Table 11–5

Risk Factors for Predicting Venous Thromboembolism (VTE) in General Surgical Patients (Modified Caprini Risk Assessment Model for VTE in General Surgical Patients)

Risk Score

1 Point	2 Points	3 Points	5 Points
Age 41–60 years Minor surgery BMI > 25 kg/m^2 Swollen legs Varicose veins Pregnancy or postpartum History of unexplained or recurrent spontaneous abortion Oral contraceptives or hormone replacement Sepsis (< 1 month) Serious lung disease, including pneumonia (< 1 month) Abnormal pulmonary function Acute myocardial infarction Heart failure (< 1 month) History of inflammatory bowel disease Medical patient at bed rest	Age 61–74 years Arthroscopic surgery Major open surgery (> 45 minutes) Laparoscopic surgery (> 45 minutes) Malignancy Confined to bed (> 72 hours) Immobilizing plaster cast Central venous access	Age ≥ 75 years History of VTE Family history of VTE Factor V Leiden Prothrombin G20210A Lupus anticoagulant Anticardiolipin antibodies Elevated serum homocysteine Heparin-induced thrombocytopenia Other congenital or acquired thrombophilia	Stroke (< 1 month) Elective arthroplasty Acute spinal cord injury (< 1 month)

Risk Score Interpretation

Total Risk Score	Risk of VTE
0	Very low (< 0.5%)
1–2	Low (1.5%)
3–4	Moderate (3%)
≥ 5	High (6%)

BMI, body mass index.

Adapted with permission from Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl):e227S–e277S.

Table 11–6

Risk Factors for Major Bleeding Complications

General Risk Factors	Procedure-Specific Risk Factors	Procedures in Which Bleeding Complications May Have Especially Severe Consequences
Active bleeding Previous major bleeding Known, untreated bleeding disorder Severe renal or hepatic failure Thrombocytopenia Acute stroke Uncontrolled systemic hypertension Lumbar puncture, epidural, or spinal anesthesia within previous 4 hours or next 12 hours Concomitant use of anticoagulants, antiplatelet therapy, or thrombolytic drugs	**Abdominal Surgery** Male sex, preoperative hemoglobin level < 13 g/dL (130 g/L; 8.07 mmol/L), malignancy, and complex surgery defined as two or more procedures, difficult dissection, or more than one anastomosis **Pancreaticoduodenectomy** Sepsis, pancreatic leak, sentinel bleed **Hepatic Resection** Number of segments, concomitant extrahepatic organ resection, primary liver malignancy, lower preoperative hemoglobin level, and platelet counts **Cardiac Surgery** Use of aspirin, use of clopidogrel within 3 days before surgery BMI > 25 kg/m^2, nonelective surgery, placement of five or more grafts, older age, renal insufficiency, operation other than CABG, longer bypass time **Thoracic Surgery** Pneumonectomy or extended resection	Craniotomy Spinal surgery Spinal trauma Reconstructive procedures involving free flap

BMI, body mass index; CABG, coronary artery bypass graft.

Adapted with permission from Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl):e227S–e277S.

Table 11–7

Thrombosis Risk Classification and Recommended Venous Thromboembolism Prevention Strategies[5-7]

Indication and Level of Risk	Prevention Strategies
Hospitalized Medical Patients	
Low thrombosis risk	Early ambulation
High thrombosis risk[a] (Padua score > 4)	LMWH, LDUH, fondaparinux, betrixaban
Critically Ill Patients	
High thrombosis risk[a]	LMWH, LDUH
General Surgical Patients	
Very low thrombosis risk (Caprini Score 0)	Early ambulation
Low thrombosis risk (Caprini Score 1–2)	IPC
Moderate thrombosis risk[b] (Caprini Score 3–4)	LMWH, LDUH, IPC
High thrombosis risk[b] (Caprini Score ≥ 5)	LMWH, LDUH, plus GCS or IPC
Cancer Surgery	LMWH, rivaroxaban, apixaban
Major Orthopedic Surgery	
Hip fracture surgery[b]	LMWH, fondaparinux, LDUH, adjusted dose warfarin, aspirin
Hip and knee arthroplasty[b]	LMWH, fondaparinux, LDUH, warfarin, aspirin, apixaban, dabigatran, rivaroxaban

[a] Mechanical methods of prophylaxis with IPC or GCS should be used in patients actively bleeding or those at high risk of bleeding complications (see **Table 11–6** for risk factors for major bleeding).

[b] Mechanical methods of prophylaxis with IPC should be used in patients actively bleeding or those at high risk of bleeding complications (see **Table 11–6** for risk factors for major bleeding).

GCS, graduated compression stockings; IPC, intermittent pneumatic compression; LDUH, low-dose unfractionated heparin; LMWH, low-molecular-weight heparin.

Similar to GCS, intermittent pneumatic compression (IPC) devices increase the velocity of blood flow in the lower extremities.[5-7] These devices sequentially inflate a series of cuffs wrapped around the patient's legs from the ankles to the thighs and then deflate in 1- to 2-minute cycles. Although IPC has been shown to reduce the risk of VTE in surgical patients, most studies failed to define the type of device used. IPC was frequently used in combination with other prophylaxis methods, making it difficult to quantify their efficacy. Although IPC is safe to use in patients who have contraindications to pharmacologic therapies, it does have a few drawbacks: it is more expensive than GCS; it is a relatively cumbersome technique; some patients may have difficulty sleeping while using it, and some patients find the devices hot and uncomfortable. To be effective, IPC needs to be used throughout the day. In practice, this is difficult to achieve, and special efforts should be made to ensure the devices are worn and operational for most of the day.

Inferior vena cava (IVC) filters, also known as Greenfield filters, provide short-term protection against PE in very high-risk patients by preventing the embolization of a thrombus formed in the lower extremities into the pulmonary circulation.[5-7] Insertion of a filter into the IVC is a minimally invasive procedure. Despite the widespread use of IVC filters, there are very limited data regarding their effectiveness and long-term safety. The evidence suggests that IVC filters, particularly in the absence of effective antithrombotic therapy, are thrombogenic themselves and increase the long-term risk of recurrent DVT and of filter thrombosis. Although IVC filters can reduce the short-term risk of PE in patients at highest risk, they should be reserved for patients in whom other prophylactic strategies cannot be used. To further reduce the long-term risk of VTE in association with IVC filters, pharmacologic prophylaxis is necessary in patients with IVC filters in place, and warfarin therapy should begin as soon as the patient is able to tolerate it.[2] If used, retrievable filters are preferred, which can be removed once pharmacologic prophylaxis can be safely administered or once the patient is no longer at risk for VTE.

Pharmacologic Therapy

Appropriately selected drug therapies can dramatically reduce the incidence of VTE in medical and surgical patients (Table 11–7). Choice of medication and dose to use for VTE prevention must be based on the patient's level of risk for thrombosis and bleeding risk, as well as the cost and availability of an adequate drug therapy monitoring system.[5-7]

The most extensively studied drugs for the prevention of VTE are unfractionated heparin (UFH), the low-molecular-weight heparins (LMWHs; dalteparin and enoxaparin), fondaparinux, and warfarin.[5-7] Generally, the LMWHs provide improved protection against VTE when compared with low-dose UFH in most medical and surgical patients and when compared to low-dose UFH and warfarin in major orthopedic surgery patients. Fondaparinux is more effective than LMWH in patients undergoing high-risk orthopedic surgery, but it has a heightened risk of bleeding.

For hospitalized general surgical and medical patients, the available evidence supports the use of UFH 5000 units subcutaneously (SC) every 8 to 12 hours, enoxaparin 40 mg SC daily, dalteparin 2500 to 5000 units SC daily, or fondaparinux 2.5 mg SC daily. Betrixaban is also approved for extended VTE prophylaxis in hospitalized adult patients with acute medical illnesses and was found noninferior to prophylactic-dose enoxaparin with no differences in major bleeding. Betrixaban is given as an initial 160-mg dose followed by 80 mg daily, with the dose halved in the setting of severe renal impairment (creatinine clearance [CrCl] 15–30 mL/min [0.25–0.5 mL/s]) or concomitant use of P-glycoprotein (P-gp) inhibitors.[28]

For the prevention of VTE following major orthopedic surgery, current evidence supports the use of UFH, LMWH, fondaparinux, adjusted dose warfarin, aspirin, and the direct oral anticoagulants (DOACs; apixaban, dabigatran, edoxaban, and rivaroxaban). The role of aspirin for VTE prevention is controversial as it produces a very modest reduction in VTE following orthopedic surgeries of the lower extremities.[5]

The effectiveness of UFH, aspirin, and warfarin is lower than LMWH, and long-term safety data are lacking for apixaban, dabigatran, and rivaroxaban; thus the American College of Chest Physicians (ACCP) guidelines recommend the use of LMWH or fondaparinux preferentially over other pharmacologic options in major orthopedic surgery patients.[5] The appropriate prophylactic dose for each LMWH product in orthopedic surgery is indication specific; however, enoxaparin 30 mg SC twice daily or 40 mg SC daily, and dalteparin 5000 units SC daily are the most commonly used regimens. The dose of fondaparinux is 2.5 mg SC daily.

The dose of warfarin, another commonly used option for prevention of VTE following orthopedic surgery, must be adjusted to maintain an INR between 2 and 3.[5] Oral administration and low drug acquisition cost give warfarin some advantages over the LMWHs and fondaparinux. However, warfarin does not achieve its full antithrombotic effect for several days and requires frequent monitoring and periodic dosage adjustments, making therapy cumbersome. Warfarin should only be used when a systematic patient monitoring system is available.

The oral factor Xa inhibitors rivaroxaban and apixaban are also options for VTE prevention following hip and knee replacement surgery and in high-risk cancer patients and offer a convenient alternative to traditional anticoagulants.[5,29-31] Both agents have shown superior efficacy compared to LMWH with a similar rate of bleeding complications in orthopedic surgery patients. Rivaroxaban is given at a fixed dose of 10 mg once daily, and apixaban is given at a fixed dose of 2.5 mg twice daily. Both are given without the need for routine laboratory monitoring and dosing adjustments (as with warfarin) and without the inconvenience of administration by injection (as with LMWH and fondaparinux).

The oral direct thrombin inhibitor (DTI) dabigatran is another option for VTE prevention following orthopedic surgery but is only approved for use following hip replacement surgery. Dabigatran is given as an initial 110-mg dose, followed by 220 mg once daily. Dabigatran should not be used in those with CrCl less than 30 mL/min (0.50 mL/s) or concomitantly with P-gp inhibitors.

Optimal duration for VTE prophylaxis is not well established but should be given throughout the period of risk. For patients who have undergone total knee replacement, total hip replacement, or hip fracture repair, prophylaxis is recommended for a minimum of 10 to 14 days; however, extending it up to 35 days is recommended due to continued VTE risk up to 1 month postsurgery.[5-7]

Patient Encounter 1

A 32-year-old woman (BMI 23 kg/m^2) with a recent history of 3-day hospitalization due to traumatic injuries sustained from a motor vehicle crash is readmitted to the hospital with increasing left leg pain and redness, fever, and fatigue. She is diagnosed with osteomyelitis and started on antibiotic therapy.

PMH: Left leg type II fracture status post reduction and immobilization.

FH: Father died at 55 years due to PE; mother died at 63 years due to breast cancer; sister with history of DVT at 37 years.

SH: Occasional alcohol use. Employed in county government. Lives at home with spouse and pets.

Home Meds: Norethindrone/ethinyl estradiol 0.5 m/0.035 mg daily, hydrocodone-acetaminophen 10 mg/325 mg every 4 hours as needed, ibuprofen 600 mg twice daily as needed.

Allergies: amoxicillin (anaphylaxis)

VS: BP 135/70 mm Hg, HR 72 beats/min, RR 16 breaths/min, T 38.7°C (101.7°F), Wt 67 kg (147 lb).

Labs: WBC 22.4 × 10^3/mm^3 (22.4 × 10^9/L); estimated glomerular filtration rate (eGFR) 80 mL/min/1.73 m^2; CrCl 78 mL/min (1.30 mL/s).

Hospital Treatment: cefazolin 2 g IV every 7 hours, hydrocodone-acetaminophen 10/325 mg PO every 4 to 6 hours as needed, ibuprofen 400 mg PO every 4 to 6 hours as needed.

Which risk factor(s) predispose this patient to VTE?

What is her estimated risk for developing VTE?

Given her presentation and history, create an appropriate VTE prophylaxis plan including the pharmacologic agent, dose, route and frequency of administration, duration of therapy, and monitoring parameters.

TREATMENT

Desired Therapeutic Outcomes

The goal of VTE treatment is to prevent short- and long-term complications of the disease. The aim of initial therapy is to prevent propagation or local extension of the clot, embolization, hemodynamic collapse, and death. The goal of long-term and extended therapy is to prevent complications such as PTS, pulmonary hypertension, and recurrent VTE.[2,12]

General Treatment Principles

Anticoagulant drugs are considered the mainstay of therapy for patients with VTE, and the therapeutic strategies for DVT and PE are similar.[2,12] Management decisions are guided by balancing the risks and benefits of various treatment options. Treatment of VTE can be divided into three phases: acute (first 5–10 days), long term (first 3 months), and extended (beyond 3 months).[12] The acute treatment phase of VTE is typically accomplished by administering a fast-acting parenteral anticoagulant or a DOAC (Table 11–8). The long-term and extended phase treatments of VTE are usually accomplished using oral anticoagulant agents such as warfarin, or one of the DOACs.[2,12] In certain populations, such as patients with cancer and women who are pregnant, the LMWHs are the preferred agents during long-term and extended treatment phases due to better safety or efficacy.[2,31] The etiology of VTE will guide the duration of therapy. VTE can be provoked (by transient or persistent risk factors), unprovoked (or idiopathic), and cancer associated. Patients with unprovoked or cancer-associated VTE have a significantly higher risk of recurrence compared to patients with provoked VTE.[2,12,31]

KEY CONCEPT In the absence of contraindications, treatment of VTE should initially include a rapidly acting DOAC (eg, apixaban, rivaroxaban, edoxaban) or a rapid-acting injectable anticoagulant (eg, UFH, LMWH, fondaparinux). If warfarin is used for oral anticoagulation, it should be initiated on the same day as the parenteral anticoagulant, and the parenteral agent should be overlapped for a minimum of 5 days and until the INR is greater than or equal to 2 for at least 24 to 48 hours. If dabigatran or edoxaban is used for oral anticoagulation, they should be initiated after 5 to 10 days of initial treatment with a parenteral

Table 11–8

Pharmacologic Options for the Acute Phase Treatment of Venous Thromboembolism (VTE)

Parenteral Anticoagulants

UFH

IV administration:[a] use weight-based dosing nomogram (**Table 11–10**)

Or

SC administration: 17,500 units (250 units/kg) given every 12 hours (an initial 5000-unit IV bolus dose is recommended to obtain rapid anticoagulation)

Adjust subsequent doses to attain a goal aPTT based on the institution-specific therapeutic range

Or

SC administration: 333 units/kg followed by 250 units/kg given every 12 hours (fixed-dose unmonitored dosing regimen)

LMWHs

Dalteparin: 200 units/kg SC once daily *or* 100 units/kg SC twice daily

Enoxaparin: 1.5 mg/kg SC once daily *or* 1 mg/kg SC twice daily; if CrCl < 30 mL/min (0.50 mL/s): 1 mg/kg SC once daily

Factor Xa Inhibitor

Fondaparinux[b]:

For body weight ≤ 50 kg (110 lb), use 5 mg SC once daily
For body weight 50–100 kg (110–220 lb), use 7.5 mg SC once daily
For body weight ≥ 100 kg (220 lb), use 10 mg SC once daily

Direct Oral Anticoagulants (DOACs)

Apixaban: 10 mg PO twice daily for the initial 7 days, then 5 mg PO twice daily[c]

Dabigatran: 150 mg PO twice daily after 5–10 days of parenteral anticoagulation[d]

Edoxaban: 60 mg PO once daily or 30 mg[e] PO once daily after 5–10 days of parenteral anticoagulation

Rivaroxaban: 15 mg PO twice daily for the initial 21 days, then 20 mg PO daily[d,f]

[a] IV administration preferred due to improved dosing precision.

[b] Contraindicated in patients with CrCl < 30 mL/min (0.50 mL/s).

[c] After the initial 6 months of therapy, the dose is reduced to 2.5 mg PO twice daily.

[d] Avoid in patients with CrCl < 30 mL/min (0.50 mL/s).

[e] Reduced dose for CrCl 15–50 mL/min (0.25–0.83 mL/s), body weight ≤ 60 kg (132 lb), or concomitant use of P-glycoprotein inhibitors.

[f] In cancer patients, rivaroxaban and edoxaban are the only DOACs recommended for VTE treatment. Rivaroxaban is recommended for both initial and long-term treatment. Edoxaban is recommended only for long-term treatment.

aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; IV, intravenous; LMWHs, low-molecular-weight heparins; SC, subcutaneous; UFH, unfractionated heparin.

anticoagulant. Anticoagulation therapy should be continued for a minimum of 3 months. However, duration of anticoagulation therapy should be based on the patient's risk of VTE recurrence and major bleeding.[2,12]

Pharmacologic Therapy

▸ *Thrombolytics*

The role of thrombolysis in the treatment of VTE is controversial.[2,12,32] Compared with anticoagulants, thrombolytics restore venous patency more quickly; however, the bleeding risk associated with their use is significantly higher. In patients with DVT, thrombolytics decrease short-term pain and swelling and prevent destruction of the venous valves. While they may decrease the incidence and severity of PTS, clinical trials have failed to show reduction in recurrent DVT, PE, or death[32]; therefore, their use in most patients is not recommended.[2,12] In a select group of high-risk patients with massive iliofemoral DVT who are at risk of venous gangrene and limb loss, thrombolysis may be considered. See Table 11–9.

In patients with acute PE, use of thrombolytics provides short-term benefits such as restoring pulmonary artery patency and hemodynamic stability.[2,12,32] However, systemic thrombolysis does not reduce mortality and is associated with a greater risk of major bleeding.[12] Given the relative lack of data to support their routine use, thrombolytics should be reserved for select high-risk circumstances. Candidates for thrombolytic therapy are patients with acute massive embolism who are hemodynamically

Table 11–9

Thrombolysis for the Treatment of Venous Thromboembolism

- Thrombolytic therapy should be reserved for patients who present with PE with shock, hypotension, or massive DVT with limb gangrene
- Diagnosis must be objectively confirmed before initiating thrombolytic therapy
- Thrombolytic therapy is most effective when administered as soon as possible after PE diagnosis, but benefit may extend up to 14 days after symptom onset

FDA-Approved PE Thrombolytic Regimens

- Streptokinase 250,000 units IV bolus over 30 minutes followed by 100,000 units/hour for 12–24 hours[a]
- Urokinase 4400 units/kg IV bolus over 10 minutes followed by 4400 units/kg/hour for 12–24 hours[a]
- Alteplase (rt-PA) 100 mg IV over 2 hours

Non–FDA-Approved Thrombolytic Regimens

- Reteplase two 10-unit IV boluses given 30 minutes apart
- Tenecteplase weight-adjusted IV bolus over 5 seconds (30–50 mg with a 5-mg step every 10 kg from < 60 to > 90 kg)

- Factors that increase the risk of bleeding must be evaluated before thrombolytic therapy is initiated (ie, recent surgery, trauma or internal bleeding, uncontrolled hypertension, recent stroke, or intracranial hemorrhage)
- Baseline laboratories should include CBC and blood typing in case transfusion is needed
- IV UFH should not be used during IV thrombolytic therapy. Neither the aPTT nor any other anticoagulation parameter should be monitored during the thrombolytic infusion
- aPTT should be measured following the completion of thrombolytic therapy:
  - If aPTT < 2.5 times the control value, UFH infusion should be started and adjusted to maintain aPTT in therapeutic range
  - If aPTT > 2.5 times the control value, remeasure every 2–4 hours and start UFH infusion when aPTT is < 2.5
- Avoid phlebotomy, arterial puncture, and other invasive procedures during thrombolytic therapy to minimize the risk of bleeding

[a] Two-hour infusions of streptokinase and urokinase are as effective and safe as alteplase; 2-hour infusion times are preferred over longer infusion times.

aPTT, activated partial thromboplastin time; CBC, complete blood count; DVT, deep vein thrombosis; FDA, Food and Drug Administration; IV, intravenous; PE, pulmonary embolism; rt-PA, recombinant tissue plasminogen activator; UFH, unfractionated heparin.

Patient Encounter 2

A 62-year-old woman with a new diagnosis of ovarian cancer is admitted to the hospital for debulking surgery.

PMH: Depression × 19 years; obesity × 25 years, ulcerative colitis × 35 years, history of hip fracture 8 years ago with subsequent lower left extremity DVT, treated with LMWH and warfarin for 3 months.

FH: Mother died at 72 years due to ovarian cancer; brother 55 years old with type 2 diabetes; maternal grandmother died at 65 years due to breast cancer.

SH: Smoked half a pack per day for 25 years, quit 15 years ago; occasional alcohol use. Lives alone and expects to be discharged to a rehabilitation facility postoperatively before returning home.

Home Meds: Sertraline 100 mg by mouth daily; oxycodone 5–10 mg by mouth every 5 hours as needed for pain; St. John's wort 2 capsules daily.

Allergies: NKDA

VS: BP 110/60 mm Hg, HR 55 beats/min, RR 18 breaths/min, T 37.0°C (98.6°F), Wt 127 kg (280 lb), BMI 41 kg/m^2.

Labs: Hemoglobin, hematocrit, platelets, and liver function tests (LFTs) within normal limits; eGFR 96 mL/min/1.73 m^2; CrCl 94 mL/min (1.57 mL/s).

Which risk factor(s) predispose this patient to VTE?

How should postoperative VTE be prevented?

How long should she receive VTE prophylaxis?

What education about VTE prophylaxis should she receive?

unstable (systolic blood pressure [SBP] < 90 mm Hg) and at low risk for bleeding. Current guidelines recommend a short infusion time (2 hours) over a prolonged infusion time (24 hours) and administration through a peripheral vein over a pulmonary artery catheter.[2,12]

▶ *Unfractionated Heparin*

UFH has traditionally been the drug of choice for indications requiring rapid anticoagulation including the acute treatment of VTE. Unlike thrombolytics, UFH and other anticoagulants will not dissolve a formed clot but prevent its propagation and growth.[2,9] Heparin exerts its anticoagulant effect by augmenting the natural anticoagulant, AT. See Figure 11–4.

UFH can be administered via the intravenous (IV) or subcutaneous (SC) route.[2,9] See Table 11–8. When rapid anticoagulation is required, UFH should be administered IV, and an initial bolus dose should be given. For the treatment of VTE, UFH is generally given as a continuous IV infusion. The half-life of UFH is dose dependent and ranges from 30 to 90 minutes but may be significantly longer, up to 150 minutes, with high doses. UFH is eliminated by two mechanisms: (a) enzymatic degradation via a saturable zero-order process, and (b) renally via a first-order process. Lower UFH doses are primarily cleared via enzymatic processes, whereas higher doses are primarily renally eliminated. Clearance of UFH can be impaired in patients with renal and hepatic dysfunction. Patients with active thrombosis may require higher UFH doses due to a more rapid elimination or variations in the plasma concentrations of heparin-binding proteins.

Certain patient-specific situations may require UFH higher doses to achieve a therapeutic anticoagulant effect. AT deficiency and elevated factor VIII levels are common in pregnant patients. AT deficiency has been linked to higher UFH dose requirements. The requirement of these higher UFH doses is termed *heparin resistance*. Factor VIII elevations can result in altered activated partial thromboplastin time (aPTT) response to UFH, and monitoring with antifactor Xa levels is recommended.[2,9,10]

The dose of UFH required to achieve a therapeutic anticoagulant response is correlated to the patient's weight.[2,9] Weight-based dosing regimens should be used to exceed the therapeutic threshold in the first 24 hours after initiating treatment.[9,10] Achieving a therapeutic aPTT in the first 24 hours after initiating UFH is critical because it has been shown to lower the risk of recurrent VTE. For nonobese patients, the actual body weight should be used to calculate the initial UFH dose (Table 11–10). For obese patients, using the actual body weight to calculate the initial dose is also generally recommended; however, data are limited in morbidly obese patients, that is, weight more than 150 kg (330 lb). Some experts recommend using an adjusted body weight (ABW) in these patients instead. The infusion rate is then adjusted based on laboratory monitoring of the patient's response.[9,10] (See Table 11–10.)

KEY CONCEPT Due to significant interpatient variability and changes in patient response over time, UFH requires close monitoring and periodic dose adjustment. The response to UFH can be monitored using a variety of laboratory tests including the aPTT, whole blood clotting time, activated clotting time (ACT), antifactor Xa activity, and plasma heparin concentration.[9,10] Although it has several limitations, the aPTT is the most widely used test in clinical practice to monitor UFH. Traditionally, therapeutic aPTT range is defined as 1.5 to 2.5 times the control aPTT value. However, due to variations in reagents and instruments used to measure the aPTT in different laboratories, each institution should establish a therapeutic range for UFH. The institution-specific therapy range should correlate with a plasma heparin concentration of 0.2 to 0.4 units/mL (kU/L) by protamine titration or 0.3 to 0.7 units/mL (kU/L) by an amidolytic antifactor Xa assay.[4,27] An aPTT should be obtained at baseline, 6 hours after initiating the heparin infusion, and 6 hours after each dose change because this is the time required to reach steady state. UFH dose is then adjusted based on the aPTT measurement and institutional-specific therapeutic range (Table 11–10). In patients with heparin resistance, antifactor Xa concentrations may be a more accurate method of monitoring the patient's response.[9,10]

Side effects associated with UFH include bleeding, thrombocytopenia, hypersensitivity reactions, and with prolonged use, alopecia, hyperkalemia, and osteoporosis.[9,10] **KEY CONCEPT** Bleeding is the most common adverse effect associated with antithrombotic drugs including UFH therapy.[8] A patient's risk of major hemorrhage is related to the intensity and stability of therapy, age, concurrent drug use, history of gastrointestinal bleeding, risk of falls or trauma, and recent surgery. Several risk factors can increase the risk of UFH-induced bleeding (Table 11–11). The risk of bleeding is related to intensity of anticoagulation. Higher aPTT values are associated with an increased risk of bleeding. The risk of major bleeding is 1% to 5% during the first few days of treatment.[2,9,10] In addition to the aPTT, hemoglobin, hematocrit, and blood pressure should be monitored. Concurrent use of UFH with other antithrombotic agents, such as thrombolytics and antiplatelet agents, also increases bleeding risk. Patients receiving UFH therapy should be closely monitored for signs and symptoms of bleeding, including epistaxis, hemoptysis, hematuria, hematemesis, **hematochezia**, **melena**, severe headache, and joint pain. If major bleeding occurs, UFH should be stopped immediately and the source of bleeding treated.[9,10] If necessary, use protamine

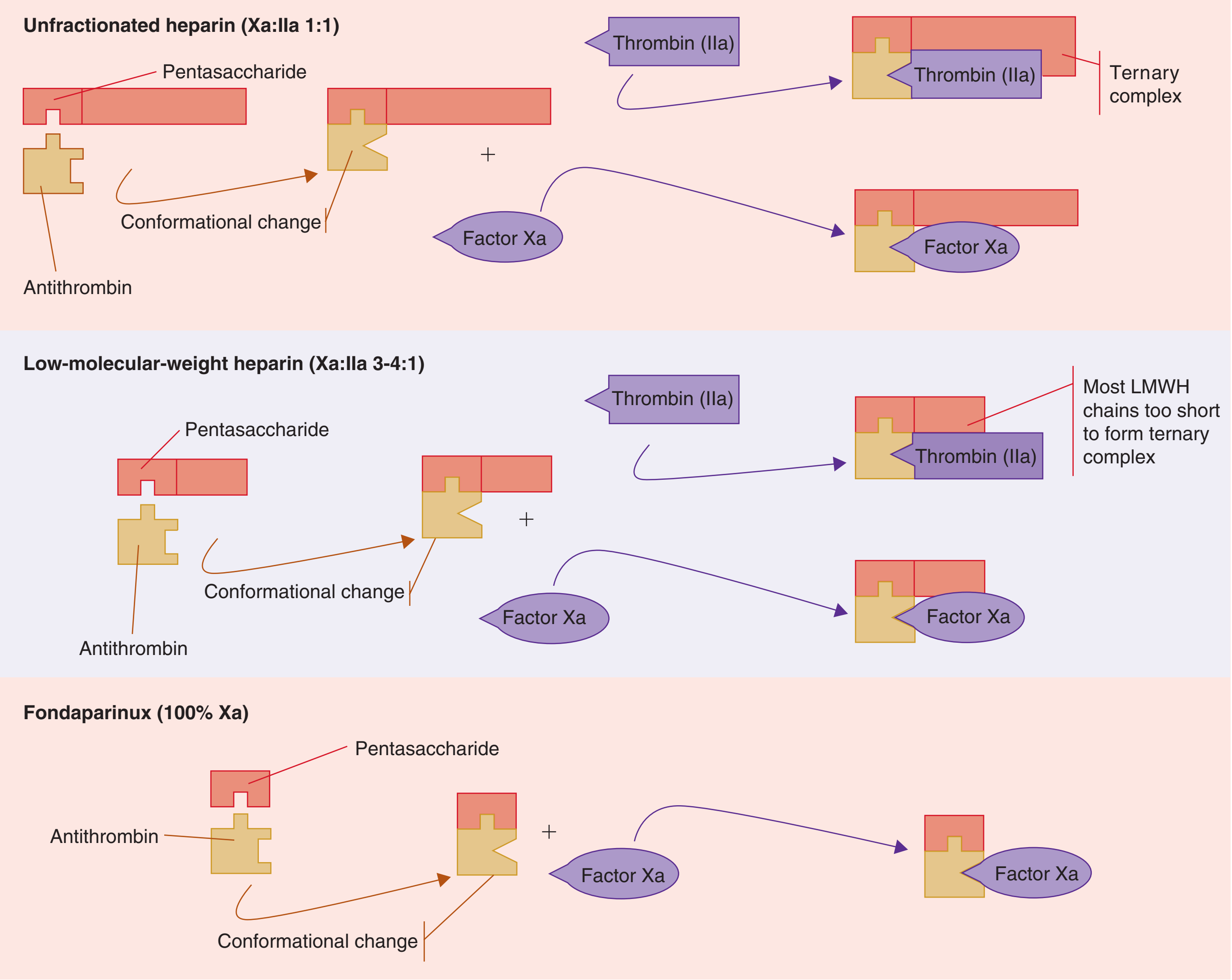

Unfractionated heparin (Xa:IIa 1:1)
Pentasaccharide
Antithrombin
Conformational change
Thrombin (IIa)
Factor Xa
+
Thrombin (IIa)
Ternary complex
Factor Xa
Low-molecular-weight heparin (Xa:IIa 3-4:1)
Pentasaccharide
Antithrombin
Conformational change
Thrombin (IIa)
Factor Xa
+
Thrombin (IIa)
Most LMWH chains too short to form ternary complex
Factor Xa
Fondaparinux (100% Xa)
Pentasaccharide
Antithrombin
Conformational change
+
Factor Xa
Factor Xa

FIGURE 11–4. Mechanism of action of unfractionated heparin, low-molecular-weight heparin (LMWH), and fondaparinux. (From Witt DM, Clark NP. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill; 2014:266.)

sulfate as an antidote to reverse the effects of UFH. The usual dose is 1 mg protamine sulfate per 100 units of UFH, up to a maximum of 50 mg, given as a slow IV infusion over 10 minutes. The effects of UFH are neutralized in 5 minutes, and the effects of protamine persist for 2 hours. If bleeding is not controlled or the anticoagulant effect rebounds, repeated doses of protamine may be administered.[9,10]

Heparin-induced thrombocytopenia (HIT) is a very serious adverse effect associated with UFH use. Platelet counts should be monitored at baseline and every 2 to 3 days throughout the course of UFH therapy.[9,10] HIT should be suspected if the platelet count drops by more than 50% from baseline or to below 150 × $10^3/\text{mm}^3$ (150 × 10^9/L). HIT should also be suspected if thrombosis occurs despite UFH use. Immediate discontinuation of all heparin-containing products including the use of LMWHs and heparin-based flushes is required. Alternative anticoagulation with parenteral DTIs should be initiated. In patients with contraindications to anticoagulation therapy, UFH should not be administered (Table 11–12).

UFH may be used to treat VTE during pregnancy. UFH should be used with caution in the peripartum period due to risk of maternal hemorrhage. UFH is not secreted into breast milk and is safe for use by women who wish to breast-feed.[2,9,10,20] For treatment of VTE in children, the UFH dose is 50 units/kg bolus followed by an infusion of 20,000 units/m^2 per 24 hours. Alternatively, a loading dose of 75 units/kg followed by an infusion of 28 units/kg/hour if younger than 12 months and 20 units/kg/hour if older than 1 year may be considered.[33]

▶ *Low-Molecular-Weight Heparins*

Compared with UFH, LMWHs have improved pharmacodynamic and pharmacokinetic properties.[9,10,12] They exhibit less binding to plasma and cellular proteins, resulting in a more predictable anticoagulant response. Consequently, routine monitoring of anticoagulation activity and dose adjustments are not required in most patients. LMWHs have longer plasma half-lives, allowing once- or twice-daily administration, improved SC bioavailability, and dose-independent renal clearance. In addition, LMWHs have a more favorable side effect profile than UFH. They are also associated with a lower incidence of HIT, osteopenia, and osteoporosis. Two LMWHs are currently available in the United States: dalteparin and enoxaparin.

Table 11–10

Weight-Based[a] Dosing for UFH Administered by Continuous IV Infusion for Venous Thromboembolism

Initial Loading Dose	Initial Infusion Rate
80 units/kg (maximum = 10,000 units)	18 units/kg/hour (maximum = 2300 units/hour)
	Maintenance Infusion Rate
aPTT (seconds)	*Dose Adjustment*
< 37 (or < 12 seconds below institution-specific therapeutic range)	80 units/kg bolus then increase infusion by 4 units/kg/hour
37–47 (or 1–12 seconds below institution-specific therapeutic range)	40 units/kg bolus then increase infusion by 2 units/kg/hour
48–71 (within institution-specific therapeutic range)	No change
72–93 (or 1–22 seconds above institution-specific therapeutic range)	Decrease infusion by 2 units/kg/hour
> 93 (or > 22 seconds above institution-specific therapeutic range)	Hold infusion for 1 hour then decrease by 3 units/kg/hour

[a] Use actual body weight for all calculations. Adjusted body weight (ABW) may be used for morbidly obese patients (> 130% of ideal body weight [IBW]).

ABW = IBW + (Actual body weight − IBW) × 0.7

aPTT, activated partial thromboplastin time; IV, intravenous; UFH, unfractionated heparin.

Like UFH, LMWHs prevent the propagation and growth of formed thrombi.[9] The anticoagulant effect is mediated through a specific pentasaccharide sequence that binds to AT. The primary difference in the pharmacologic activity of UFH and LMWH is their relative inhibition of thrombin (factor IIa) and factor Xa. Smaller heparin fragments (as in LMWHs) cannot bind AT and thrombin simultaneously (Figure 11–4). The SC bioavailability of the LMWHs is greater than 90%. Peak anticoagulant effect of the LMWHs is reached 3 to 5 hours after a SC dose. The elimination half-life is 3 to 6 hours and is agent-specific. In patients with renal impairment, the half-life of LMWHs is prolonged.[9,10,12]

Table 11–11

Risk Factors for Major Bleeding While on Anticoagulation

Increased anticoagulation intensity (eg, INR > 5, aPTT > 120 seconds)
Initiation of therapy (first few days and weeks)
Unstable anticoagulation response (eg, variable INR response)
Age older than 65 years
Concurrent antiplatelet drug use
Concurrent NSAID or aspirin use
History of gastrointestinal bleeding
Recent surgery or trauma
High risk for fall/trauma (eg, elderly, sedentary/bedbound, high-risk medications)
Heavy alcohol use
Renal failure
Cerebrovascular disease
Active malignancy

aPTT, activated partial thromboplastin time; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug.

Table 11–12

Contraindications to Anticoagulation Therapy

General
- Active bleeding
- Hemophilia or other hemorrhagic tendencies
- Severe liver disease with elevated baseline PT/INR
- Severe thrombocytopenia (platelet count $< 20 \times 10^3/\text{mm}^3$ [$20 \times 10^9/\text{L}$])
- Malignant hypertension
- Inability to meticulously supervise and monitor treatment

Drug-Specific Contraindications

UFH
- Hypersensitivity to UFH
- History of HIT

LMWHs
- Hypersensitivity to LMWH, UFH, pork products, methylparaben, or propylparaben
- History of HIT or suspected HIT

Fondaparinux
- Hypersensitivity to fondaparinux
- Severe renal insufficiency (CrCl < 30 mL/min [0.50 mL/s])
- Body weight < 50 kg (110 lb) for prophylaxis
- Bacterial endocarditis
- Thrombocytopenia with a positive in vitro test for antiplatelet antibodies in the presence of fondaparinux

Lepirudin
- Hypersensitivity to hirudins

Argatroban
- Hypersensitivity to argatroban

Warfarin
- Hypersensitivity to warfarin
- Pregnancy
- History of warfarin-induced skin necrosis
- Inability to obtain follow-up PT/INR measurements
- Inappropriate medication use or lifestyle behaviors

Dabigatran
- Mechanical prosthetic heart valves
- Hypersensitivity to dabigatran

Apixaban
- Hypersensitivity to apixaban

Rivaroxaban
- Hypersensitivity to rivaroxaban

CrCl, creatinine clearance; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; LMWHs, low-molecular-weight heparins; PT, prothrombin time; UFH, unfractionated heparin.

Dose of LMWHs for the treatment of VTE is determined based on the patient's weight and is administered SC once or twice daily (Table 11–8). Due to their predictable anticoagulant effect, routine monitoring is not necessary in most patients.[9] LMWHs have been evaluated in many randomized trials and have been shown to be at least as safe and effective as UFH for the treatment of VTE.[2,12] Indeed, the rate of mortality was lower in patients treated with an LMWH in clinical trials. This mortality benefit was primarily seen in patients with cancer.[34]

Prior to initiating treatment with an LMWH, baseline laboratory tests should include PT/INR, aPTT, CBC, and serum creatinine (SCr). Monitor the CBC with platelet count every 3 to 5 days during the first 2 weeks of therapy, and every 2 to 4 weeks with extended use.[9,10] Use LMWHs cautiously in patients with renal impairment due to the potential of drug accumulation and risk of bleeding. Specific dosing recommendations for patients with a CrCl less than 30 mL/min (0.50 mL/s) are currently available for enoxaparin but are lacking for other LMWH agents (Table 11–8).

Current guidelines recommend the use of UFH over LMWH in patients with severe renal dysfunction (CrCl < 30 mL/min [0.50 mL/s]).[2]

KEY CONCEPT Most patients with an uncomplicated DVT and PE can be managed safely at home.[2] LMWHs can be easily administered in the outpatient setting, thus enabling treatment of VTE at home. Several large clinical trials have demonstrated the efficacy and safety of LMWHs for outpatient treatment of DVT and PE, and this approach is commonly utilized in clinical practice.[2,34] Patients with DVT with normal vital signs, low bleeding risk, no other comorbid conditions requiring hospitalization, and who are stable may have anticoagulant initiated at home. Although the treatment of patients with PE in the outpatient setting is more controversial, patients with submassive PE who are hemodynamically stable can be safely treated in the outpatient setting as well.[12] Patients considered for outpatient therapy must be reliable or have adequate caregiver support and must be able to strictly adhere to the prescribed treatment regimen and recommended follow-up visits. Close patient follow-up is critical to the success of any outpatient DVT treatment program. Home DVT treatment results in cost savings and improved patient satisfaction and quality of life.[2,12,34]

Laboratory methods of measuring a patient's response to LMWH may be warranted in certain situations.[9,35] Although controversial, measurement of antifactor Xa activity has been the most widely used method in clinical practice. Monitoring of antifactor Xa activity may be considered in adult patients who are morbidly obese (weight > 150 kg [330 lb] or body mass index [BMI] > 50 kg/m^2), weigh less than 50 kg (110 lb), or have significant renal impairment (CrCl < 30 mL/min [0.50 mL/s]). Laboratory monitoring may also be useful in children, pregnant women, and those on long-term therapy.[35]

As with UFH, bleeding is the major complication associated with LMWHs. The incidence of major bleeding reported in clinical trials is less than 3%.[8,9] Minor bleeding, especially bruising at the injection site, occurs frequently. Protamine sulfate will partially reverse the anticoagulant effects of the LMWHs and should be administered in the event of major bleeding. Due to its limited binding to LMWH chains, protamine only neutralizes 60% of their antithrombotic activity. If the LMWH was administered within the previous 8 hours, give 1 mg protamine sulfate per 1 mg of enoxaparin or 100 antifactor Xa units of dalteparin. If bleeding is not controlled, give another 0.5 mg of protamine sulfate for every antifactor Xa 100 units of LMWH. Give smaller protamine doses if more than 8 hours have lapsed since the last LMWH dose.

The incidence of HIT is lower with LMWHs than with UFH.[9,10] However, LMWHs cross-react with heparin antibodies in vitro and should not be given as an alternative anticoagulant in patients with a diagnosis or history of HIT. Monitor platelet counts every few days during the first 2 weeks and periodically thereafter.

In patients undergoing spinal and epidural anesthesia or spinal puncture, spinal and epidural hematomas have been linked to the use of LMWHs. In patients with indwelling epidural catheters, concurrent use of LMWHs and all other agents that impact hemostasis should be avoided. When inserting and removing the indwelling epidural catheters, the timing of LMWH administration around catheter manipulation should be carefully coordinated. Catheter manipulation should only occur at minimal or trough anticoagulant levels.[9,10]

LMWHs are a convenient alternative to UFH for the treatment of VTE in pregnant women.[9,20] The LMWHs do not cross the placenta. Because the pharmacokinetics of LMWHs may change during pregnancy, monitoring of antifactor Xa activity every 4 to 6 weeks to make dose adjustments is recommended.[35] LMWHs have also been used to treat VTE in pediatric patients. Children younger than 1 year require higher doses (eg, enoxaparin 1.5 mg/kg SC every 12 hours). Monitor antifactor Xa activity to guide dosing in children.[33]

▶ *Factor Xa Inhibitors*

Parenteral Fondaparinux is an indirect inhibitor of factor Xa and exerts its anticoagulant activity by accelerating AT.[9,36] Due to its small size, fondaparinux exerts inhibitory activity specifically against factor Xa and has no effect on thrombin (Figure 11–4). After SC administration, fondaparinux is completely absorbed, and peak plasma concentrations are reached within 2 to 3 hours.[9,36] It has a half-life of 17 to 21 hours, permitting once-daily administration, but the anticoagulant effects of fondaparinux will persist for 2 to 4 days after stopping the drug. In patients with renal impairment, fondaparinux clearance is reduced, and the anticoagulant effect persists even longer. Fondaparinux does not require routine coagulation monitoring or dose adjustments.

Fondaparinux is not metabolized in the liver and therefore has few drug interactions.[9,36] However, concurrent use with other antithrombotic agents increases the risk of bleeding. Unlike the heparins, factor Xa inhibitors do not affect platelet function and do not react with the heparin platelet factor (PF)-4 antibodies seen in patients with HIT. Thus, they have a theoretical role in treatment and prevention of HIT. A few small observational studies report fondaparinux use in the management of patients with HIT. Based on these data some centers use fondaparinux in patients with subacute HIT or a history of HIT who require anticoagulation therapy.[9]

Fondaparinux is as safe and effective as IV UFH for the treatment of PE and SC LMWH for the treatment of DVT.[9,35] The recommended dose for fondaparinux in the treatment of VTE is based on the patient's weight (Table 11–8). Fondaparinux is renally eliminated, and accumulation can occur in patients with renal dysfunction. Due to the lack of specific dosing guidelines, fondaparinux is contraindicated in patients with severe renal impairment (CrCl < 30 mL/min [0.50 mL/s]). Baseline renal function should be measured and monitored closely throughout therapy. Based on limited data, monitoring antifactor Xa activity to guide fondaparinux dosing is not recommended.[9,36]

As with other anticoagulants, the major side effect associated with fondaparinux is bleeding. Fondaparinux should be used cautiously in elderly patients because their risk of bleeding is higher. Patients receiving fondaparinux should be carefully monitored for signs and symptoms of bleeding. A CBC should be obtained at baseline and monitored periodically to detect the possibility of occult bleeding. In the event of major bleeding, fresh-frozen plasma and factor concentrates should be given. Fondaparinux is not reversed by protamine.[9,36] Data are limited regarding the use of fondaparinux during pregnancy, and its use in pediatric patients has not been studied.[36]

Oral Apixaban, rivaroxaban, edoxaban, and betrixaban are direct inhibitors of factor Xa, part of a newer generation of oral anticoagulants also referred to as direct-acting oral anticoagulants (DOACs).[29,30,37,38] Apixaban and rivaroxaban have been evaluated and approved by the Food and Drug Administration (FDA) for the treatment of VTE (DVT and PE) and reduction in the risk of recurrence of DVT and PE. Edoxaban is also approved for VTE treatment. Rivaroxaban had similar efficacy and safety when compared to traditional therapy with LMWH and a vitamin K

Table 11–13

Dosing of the Direct Oral Anticoagulants in the Treatment of Venous Thromboembolism (VTE) and Their Reversal Agents

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Acute VTE	150 mg BID after 5–10 days of parenteral anticoagulation	15 mg BID × 3 weeks then 20 mg once daily with food	10 mg BID for 7 days, then 5 mg BID	60 mg once daily
Prevention of VTE recurrence	150 mg BID	10 mg once daily with food (after 6 months of acute treatment)	2.5 mg BID (after 6 months of acute treatment)	n/a
Dosage adjustments and/or thresholds for avoidance	Any P-gp *inducer*: avoid concurrent use Any P-gp *inhibitor* with CrCl < 50 mL/min (0.83 mL/s): avoid concurrent use CrCl < 30 mL/min (0.50 mL/s): avoid use	CrCl 30–50 mL/min (0.50–0.83 mL/s): use with caution CrCl < 30 mL/min (0.50 mL/s): avoid use	Dual strong CYP3A4 and P-gp inhibitors: If dose > 2.5 mg BID, decrease by 50% If already taking 2.5 mg BID and dual strong CYP3A4 and P-gp inhibitor: avoid use No dose adjustment in renal impairment or end-stage renal disease required	CrCl 15–50 mL/min (0.25–0.83 mL/s) or body weight ≤ 60 kg (132 lb), or concurrent use with certain P-gp inhibitors: 30 mg once daily
FDA-approved reversal agent	Idarucizumab 5 g IV by infusion or bolus	Recombinant inactivated coagulation Factor Xa High dose: 800 mg IV bolus + 960 mg IV infusion Low dose: 400 mg IV bolus + 480 mg IV infusion	Recombinant inactivated coagulation Factor Xa High dose: 800 mg IV bolus + 960 mg IV infusion Low dose: 400 mg IV bolus + 480 mg IV infusion	n/a

CrCl, creatinine clearance; CYP, cytochrome P-450; FDA, Food and Drug Administration; IV, intravenous; P-gp, P-glycoprotein.

antagonist in the treatment of patients with VTE. One study suggests rivaroxaban may be inferior to warfarin in patients with triple positive antiphospholipid antibody syndrome.[39] Apixaban was noninferior in preventing recurrent VTE or VTE-related death but resulted in lower major bleeding events when compared to LMWH and warfarin therapy. Rivaroxaban and apixaban can be used as monotherapy without parenteral anticoagulation overlap, allowing for a single oral regimen approach for treating and preventing recurrent VTE. Edoxaban was noninferior to warfarin in recurrent VTE and associated with less major or clinically relevant nonmajor bleeding. Unlike the other oral factor Xa inhibitors, edoxaban is initiated after completing 5 to 10 days of initial treatment with a parenteral anticoagulant. See Table 11–13.

The DOACs inhibit a serine protease single target within the common pathway of the coagulation cascade during the final stages of clot formation. See Figure 11–5. This specificity provides a linear dose response and wider therapeutic index that allows for fixed dosing and precludes the need for routine coagulation monitoring.[4,12,29,30,37,38] Apixaban, rivaroxaban, edoxaban, and betrixaban are competitive, selective, and potent direct inhibitors of factor Xa that bind in a reversible manner to the active site of both free-floating factor Xa and factor Xa within the prothrombinase complex, thereby attenuating thrombin generation. These agents have intrinsic anticoagulant activity and do not require a cofactor to exert their effect as with UFH and the LMWHs.[4,12,29,30,37,38]

The pharmacokinetic and pharmacodynamic properties of DOACs are significantly different than those of warfarin. See

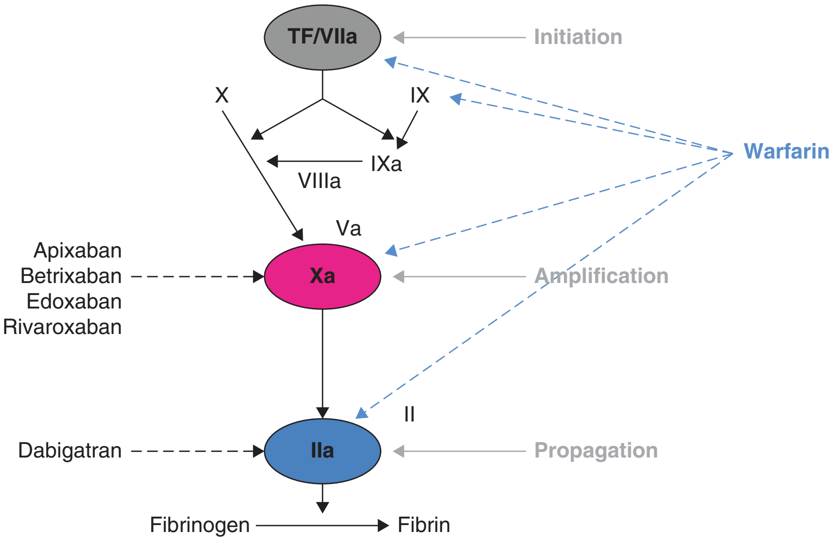


FIGURE 11–5. Mechanism of action of the oral anticoagulants and their targets of inhibition in relationship to other oral anticoagulants. (TF, tissue factor.) (Adapted from Weitz JI, Bates SM. New anticoagulants. J Thromb Haemost. 2005;3:1843–1853.)

Table 11–14. They have a more rapid onset and offset of action and shorter half-lives compared to warfarin. However, missed doses may be more prone to result in therapeutic complications than longer half-life therapies such as warfarin. DOACs are all eliminated renally to varying degrees (see Table 11–14), and dose adjustment or avoidance in patients with renal impairment may be needed.[4,12,29,30,37,38] See Table 11–13. All DOACs are substrates of the P-gp transport system, and the Xa inhibitors are also substrates of the hepatic cytochrome P-450 (CYP) isoenzyme system. Any inhibition or induction of these metabolic systems will alter their absorption.[29,30,37,38] There are currently no universally available standardized laboratory assays to measure the anticoagulant effect of DOACs. This can create challenges in situations where reversal of anticoagulation is required such as in cases of major bleeding or need for emergency surgery.[12,29,30,37-39] Fresh-frozen plasma, factor concentrates, or recombinant factor VIIa may be given in the event of a major life-threatening bleed.

Apixaban has dual pathways of elimination, with approximately 27% being cleared renally and the remainder eliminated via the fecal route. Elderly, low weight (< 50 kg [110 lb]), and patients with renal impairment can have increased exposure to apixaban, while gender and race do not appear to have clinically relevant influence. Pharmacokinetic modeling suggests apixaban does not accumulate significantly or require dose adjustment in patients with CrCl below 25 mL/min/1.73 m^2 (0.24 mL/s/m^2), but clinical data in this patient population are limited. Apixaban pharmacokinetics are not significantly altered in patients with mild- (Child-Pugh A) -to-moderate (Child-Pugh B) hepatic impairment. However, apixaban has not been studied in patients with severe hepatic impairment and is not recommended for

Table 11–14

Pharmacologic and Pharmacokinetic Characteristics of Direct Oral Anticoagulants

Property	Apixaban	Dabigatran	Rivaroxaban	Edoxaban	Betrixaban
Mechanism of action	Factor Xa inhibitor	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Bioavailability (%)	50%	3%–7%	80%–100% for 10-mg dose 66% for 20-mg dose[a]	62%	34%
T_{max} (hours)	1–3	1–3	2–4	1–2	3–4
Onset of effect	Within 3 hours	Within 3 hours	Within 4 hours	Within 2 hours	n/a
Half-life (hours)	8–15	12–17	5–13	10–14	19–27
Renal excretion	27%	80%	36%	50%	11%
CYP-mediated metabolism	25% CYP3A4/5, CYP2J2 (minor), CYP1A2 (minor)	No	30% CYP3A4/5, CYP2J2 (equal)	CYP3A4	Minor: CYP1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 3A4
Drug transporter	P-gp, BCRP	P-gp	P-gp, BCRP	P-gp	P-gp
Drug–drug interactions	Potent CYP3A4 and P-gp inhibitors; affecting absorption, metabolism, and excretion	Potent P-gp inhibitors; affecting absorption	Potent CYP3A4 and P-gp inhibitors; affecting absorption, metabolism, and excretion	P-gp inducers (eg, rifampin): affecting absorption	P-gp inhibitors: affecting absorption
Food effect	No effect reported	Delayed absorption with food but no influence on bioavailability	Delayed absorption with food with increased (+39%) bioavailability Take with largest meal of the day (usually dinner)	No effect reported	Reduced absorption by 61%–70% (low-fat meal) and 48%–50% (high-fat meal)
Age	Lower clearance as age increases	Lower clearance as age increases	No effect reported	No effect reported	No effect reported
Body weight	Higher exposure with low body weight (< 50 kg [110 lb])	No effect reported	No effect reported	13% higher exposure with median low body weight (55 kg [121 lb]) compared to high body weight (84 kg [185 lb])	n/a
Sex	Lower clearance in women	Lower clearance in women	No effect reported	No effect reported	No effect reported
Ethnicity	No effect reported	No effect reported	Lower dose in Japanese patients	No effect reported	n/a
Gastrointestinal tolerability	No effect reported	Dyspepsia 5%–10%	No effect reported	No effect reported	No effect reported
Coagulation measurement	Anti-FXa	ECT > dTT	Anti-Fxa	Anti-Fxa	Anti-Fxa

[a] Bioavailability is dependent on food intake for doses > 10 mg. Rivaroxaban doses > 10 mg should be administered with food.

BCRP, breast cancer resistance protein; CYP, cytochrome P-450; dTT, diluted thrombin time; ECT, ecarin clotting time; FXa, factor Xa; P-gp, P-glycoprotein; T_{max}, time to maximum plasma concentration.

Table 11–15

Drug Interactions and Monitoring Recommendations for Direct Oral Anticoagulants

	Apixaban	Rivaroxaban	Dabigatran	Edoxaban	Betrixaban
Drug interactions	Avoid concomitant use with strong dual inhibitors of CYP3A4 and P-gp (eg, ketoconazole, ritonavir, erythromycin) or reduce apixaban dose Avoid concomitant use with strong dual inducers of CYP3A4 and P-gp (eg, rifampin, phenytoin, carbamazepine) Concomitant use with antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID increases bleeding risk	Avoid concomitant use with strong dual inhibitors of CYP3A4 and P-gp (eg, ketoconazole, ritonavir, erythromycin) Avoid concomitant use with strong dual inducers of CYP3A4 and P-gp (eg, rifampin, phenytoin, carbamazepine) Avoid concomitant use with other anticoagulants	Avoid concomitant use with P-gp inducers (eg, rifampin) P-gp inhibitors and impaired renal function can lead to increased exposure to dabigatran: Avoid concomitant use with severe renal impairment (CrCl < 30 mL/min [0.50 mL/s]) For moderate renal impairment, reduce dose to 75 mg twice daily when used concomitantly with dronedarone or systemic ketoconazole or avoid concomitant use	Avoid concomitant use with P-gp inducers (eg, rifampin) Concomitant use with coagulants, antiplatelet drugs, and thrombolytics may increase the risk of bleeding	For concomitant use of P-gp inhibitors (eg, amiodarone, azithromycin, verapamil, ketoconazole, clarithromycin): reduce dose to 80 mg × 1 then 40 mg daily Concomitant use of anticoagulants, antiplatelet drugs, and thrombolytics may increase the risk of bleeding.
Monitoring	Baseline laboratory assessment: Hemoglobin/hematocrit, liver function, renal function, PT/INR At every visit: Adherence, signs/symptoms of bleeding or thromboembolism, side effects, concomitant medications (including over-the-counter) Annual laboratory assessment: Hemoglobin/hematocrit, renal function, liver function If CrCl 30–60 mL/min (0.50–1.0 mL/s), > 75 years, or fragile: renal function every 6 months If CrCl 15–30 mL/min (0.25–0.50 mL/s): renal function every 3 months If condition changes that might impact anticoagulation therapy: check renal and/or liver function				

CrCl, creatinine clearance; CYP, cytochrome P-450; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; P-gp, P-glycoprotein; PT, prothrombin time.

use in these patients. There are no adequate studies in pregnant women, and its use during pregnancy is likely to increase bleeding risk. Use in pediatric patients has not been studied.[29] Apixaban is a substrate of both the CYP 3A4/5 and P-gp systems, and it may be subject to a number of drug interactions (Table 11–15).[29] See Tables 11–13, 11–14, and 11–15 for pertinent drug interactions, monitoring, and dosing recommendations.

While routine anticoagulation monitoring is not required, there may be clinical scenarios where knowing the patient's degree of anticoagulation may be necessary.[40] A drug-specific chromogenic anti-Xa assay may be used to measure apixaban plasma concentrations; however, this assay is not readily available in most laboratories. Other tests such as the PT, aPTT, and INR are not recommended to assess the anticoagulant effects of apixaban.[29,40] Baseline and periodic patient assessment including adherence, side effects, and renal and liver function should be conducted (Table 11–15).[41]

Rivaroxaban's bioavailability is dose dependent.[30] At a dose of 10 mg, bioavailability is 80% to 100% and may be taken without regard for food. At higher doses, bioavailability is approximately 66% in the fasted state, which is increased to greater than 80% by food intake. Thus, rivaroxaban 15- and 20-mg tablets should be taken with the largest meal of the day. See Table 11–14. Like apixaban, rivaroxaban does not induce or inhibit CYP isoenzymes, but may be affected by medications that are substrates for this enzymatic pathway.[30] Rivaroxaban has a dual mode of elimination, with approximately 35% excreted unchanged in the urine and the remaining two-thirds (in the form of inactive metabolites) excreted fairly equally between the renal and hepatobiliary route.[30] Rivaroxaban is a P-gp substrate, not only at the level of gut absorption, but also at the level of elimination in the kidney. Medications that are substrates for the P-gp transport system may impact plasma concentrations of rivaroxaban.[30,41]

While patients with renal impairment can have increased exposure to rivaroxaban, gender, race, age, and extremes of weight (< 50 kg [110 lb] or > 120 kg [265 lb]) have not been shown to significantly impact its pharmacokinetics or pharmacodynamics. Rivaroxaban should be avoided in patients with CrCl less than 30 mL/min (0.50 mL/s) when used for VTE treatment.[30] See Table 11–13. Mild hepatic impairment has minimal impact on the pharmacokinetics and pharmacodynamics of rivaroxaban. Patients with moderate hepatic impairment (Child-Pugh B) have significantly increased exposure to rivaroxaban, and its use in patients with severe liver disease has not been studied.[30] There are no well-controlled studies in pregnant women and pediatric patients, and dosing of rivaroxaban in these patients has not been established.

Rivaroxaban should not be used concomitantly with medications that are dual P-gp and strong CYP3A4 inhibitors or inducers.[30,41] See Table 11–15. Use with weaker combined P-gp and CYP3A4 substrates should be undertaken with caution and only if benefit of use outweighs risk. Concomitant use of rivaroxaban with antiplatelet and nonsteroidal anti-inflammatory agents should be done with extreme caution due to the additive antithrombotic effects and heightened risk of bleeding. As with apixaban, a drug-specific chromogenic anti-Xa assay may be used to measure rivaroxaban activity. Rivaroxaban prolongs the aPTT and PT in a dose-dependent manner, but the PT is more sensitive to rivaroxaban than the aPTT.[29,40,41] Because it is widely available and has a low level of complexity, the PT may be used in a qualitative manner to quickly determine the presence of rivaroxaban. A normal result with most PT reagents would exclude clinically significant anticoagulant activity. The PT and INR are not suitable for measurement of rivaroxaban activity.

Edoxaban is 62% orally bioavailable and dose dependent and is 55% bound to plasma protein. Edoxaban undergoes minimal CYP3A4 metabolism, hydrolysis, and conjugation, although an active primary metabolite is formed via hydrolysis with renal elimination accounting for approximately half of edoxaban elimination. Edoxaban should not be used in those with moderate or severe hepatic impairment (Child-Pugh B and C). Individuals weighing 60 kg (132 lb) or less should receive a reduced dose of 30 mg daily. Similar to apixaban and rivaroxaban, chromogenic antifactor Xa can be considered to evaluate the presence of edoxaban. Edoxaban may affect PT and aPTT, but these measures should not be considered reliable measures of serum concentrations or anticoagulation intensity. Similar to other DOACs, concomitant use of edoxaban with P-gp inducers, particularly rifampin, should be avoided.[37,40,41]

Betrixaban is 34% orally bioavailable and, unlike rivaroxaban, administration with a low- or high-fat meal leads to reduced betrixaban exposure. Betrixaban should thus be administered with food. Betrixaban is mainly excreted through feces (85%), 11% through urine, and 1% metabolized via CYP1A1, 1A2, 2B6, 2C9, 2C19, 2D6, and 3A4. A reduced dose is recommended if severe renal impairment (CrCl 15–30 mL/min [0.25–0.50 mL/s]) or concomitant use of P-gp inhibitors is present. Betrixaban has not been evaluated in the setting of hepatic impairment, and its use in this patient population should be avoided. Recommended duration of treatment for betrixaban is 35 to 42 days.[38]

Inactivated recombinant coagulation factor Xa is a recombinant modified human factor Xa decoy protein that binds to the active site of factor Xa inhibitors with high affinity, thereby preventing DOAC-mediated factor Xa inhibition. This agent is administered intravenously and has been approved for reversal of rivaroxaban and apixaban.[42] A high or low dose is administered based on the DOAC used, DOAC dose taken, and time elapsed since last DOAC dose.

▶ *Direct Thrombin Inhibitors*

Given that thrombin is the central mediator of coagulation and amplifies its own production, it is a natural target for pharmacologic intervention.[9,43,44] DTIs bind thrombin and prevent interactions with their substrates (Figure 11–6).

Parenteral Parenteral DTIs are considered drugs of choice for the treatment of VTE in patients with a diagnosis or history of HIT.[9,43,44] Several injectable DTIs are approved for use in the United States including lepirudin, bivalirudin, argatroban, and desirudin. All have been used to treat thrombosis in patients with HIT, but only lepirudin and argatroban are FDA approved for this indication. However, as of 2012, lepirudin is no longer commercially available in the United States. Data with some DTIs (desirudin, bivalirudin) for the treatment of HIT are limited, and there are no high-quality studies that directly compare one DTI with another. DTIs differ in terms of their chemical structure, binding to the thrombin molecule, and pharmacokinetic profiles. See Table 11–16. Unlike heparins, DTIs do not require AT as a cofactor and do not bind to plasma proteins. Therefore, they produce a more predictable anticoagulant effect. DTIs have a targeted specificity for thrombin, the ability to inactivate clot-bound thrombin, and an absence of platelet interactions that can lead to HIT.[9,43,44]

Oral Small molecule DTIs have been structurally modified for oral administration.[43] One agent, dabigatran, is currently approved in the United States for treatment of VTE.[45] Dabigatran was found to be as effective and safe as warfarin in the treatment and prevention of recurrent VTE.[12,45] Like edoxaban, patients should be anticoagulated with UFH or LMWH for the initial 5 to 10 days of therapy and then transitioned to dabigatran for VTE treatment.[2,12,45] See Table 11–13. Similar to other DOACs, dabigatran can be given in fixed doses without the need for routine coagulation monitoring and has a fast onset and offset of action, offering more convenient anticoagulation options for patients and providers.[45]

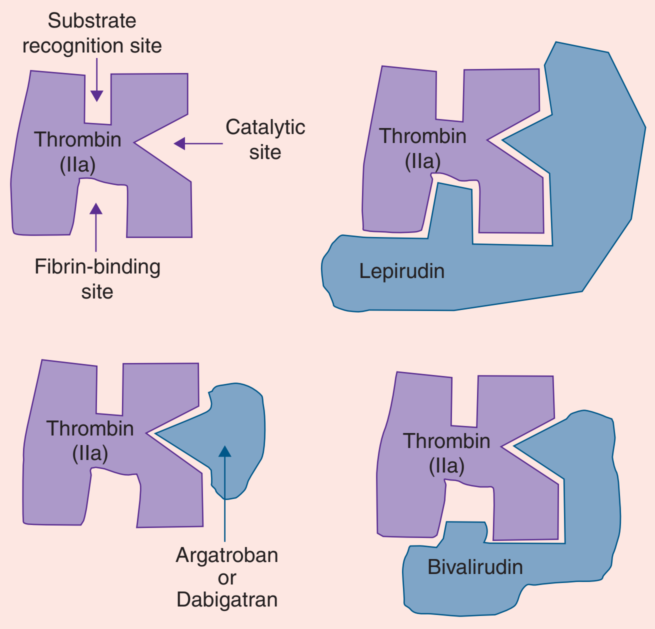


FIGURE 11–6. Mechanism of action of intravenous direct thrombin inhibitors, their binding sites, and relative inhibition of the thrombin catalytic and fibrin-binding sites. (From Witt DM, Nutescu EA, Haines S. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 8th ed. New York, NY: McGraw-Hill; 2011:326.)

Dabigatran is a direct reversible, competitive inhibitor of thrombin and an oral prodrug of dabigatran etexilate.[43-45] Dabigatran is converted to its active form dabigatran etexilate by serum esterases that are independent of CYP pathways. See Table 11–14. Dabigatran has an oral bioavailability of approximately 3% to 7% and requires an acidic environment for absorption. The prodrug is contained in small pellets coated with an acid core. These pellets are enclosed in a capsule shell. This specific capsule formulation improves the dissolution and absorption of the prodrug, independent of gastric pH. Therefore, the capsules should not be broken, chewed, or opened before administration. Dabigatran demonstrates 35% protein binding and is a substrate of the efflux transporter P-gp. Although the absence of CYP metabolism decreases potential for many drug interactions, coadministration with P-gp substrates, inhibitors, or inducers may affect the efficacy of dabigatran.[41,43] See Table 11–15.

Approximately 80% of dabigatran is eliminated in the urine, and its use is not recommended for VTE treatment in patients with a CrCl less than 30 mL/min (0.50 mL/s) due to increased risk of drug exposure and bleeding.[45] Subjects with severe liver disease were excluded from clinical trials of dabigatran. In those with moderate hepatic impairment (Child-Pugh B), the pharmacokinetic profile of dabigatran is not affected. Gender, age, race,

Table 11–16

Pharmacologic and Clinical Properties of Direct Thrombin Inhibitors Used in Treatment of Thrombosis in Patients with Heparin-Induced Thrombocytopenia (HIT)

	Lepirudin	Desirudin	Bivalirudin	Argatroban
Route of administration	IV	SC	IV	IV
FDA-approved indication	Treatment of thrombosis in patients with HIT	VTE prevention after total hip arthroplasty	Patients with unstable angina undergoing percutaneous transluminal coronary angioplasty; PCI with provisional use of glycoprotein IIb-IIIa inhibitor; patients with or at risk of HIT or HITTS undergoing PCI	Prophylaxis or treatment of thrombosis in adult patients with HIT; patients with or at risk of HIT undergoing PCI
Binding to thrombin	Irreversible Catalytic site and exosite-1	Irreversible Catalytic site and exosite-1	Partially reversible Catalytic site and exosite-1	Reversible Catalytic site
Half-life in healthy subjects	80 minutes	2–3 hours	25 minutes	40–50 minutes
Monitoring	aPTT (IV) SCr/CrCl	aPTT SCr/CrCl	aPTT/ACT SCr/CrCl	aPTT/ACT Liver function
Elimination	Renal	Renal	Enzymatic (80%) and renal (20%)	Hepatobiliary
Antibody development	Anti-hirudin antibodies in up to 40%–60% of patients	Not reported	May cross-react with anti-hirudin antibodies	No
Effect on INR	+	+	++	+++

+ minimal effect

++ moderate effect

+++ significant effect

ACT, activated clotting time; aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; FDA, Food and Drug Administration; HITTS, heparin-induced thrombocytopenia and thrombosis syndrome; INR, international normalized ratio; IV, intravenous; PCI, percutaneous coronary intervention; SC, subcutaneous; SCr, serum creatinine; VTE, venous thromboembolism.

or extremes of weight (< 50 kg [110 lb] or > 110 kg [243 lb]) do not significantly impact dabigatran pharmacology.

Dabigatran prolongs the aPTT, PT, thrombin time (TT), and ecarin clotting time (ECT) assays in a dose-dependent manner.[40,45] Peak values greater than 2.5 times control may indicate supratherapeutic levels. A normal aPTT would indicate a lack of clinically relevant anticoagulant activity. The aPTT may be used in a qualitative manner to determine the presence of anticoagulation with dabigatran. It should not be used to quantitate dabigatran plasma concentrations. The PT is relatively insensitive to dabigatran, and the INR is not suitable for measurement of dabigatran due to significant variability. The TT, diluted thrombin time (dTT), and ECT exhibit a linear dose-response with therapeutic dabigatran plasma concentrations. Unfortunately, none of these assays are widely available in practice. It is important to note that quantitative thresholds beyond which a patient would be at increased risk of clotting or bleeding have not been established for any of the DOACs.[40,43,45]

Contraindications to use of DTIs and risk factors for bleeding are similar to those of other antithrombotic agents (Tables 11–11 and 11–12). Bleeding is the most common side effect reported. Concurrent use of DTIs with thrombolytics or antiplatelet agents significantly increases bleeding complications.[46] Idarucizumab, a humanized monoclonal antibody fragment specific to dabigatran and its acyl glucuronide metabolites, binds free and thrombin-bound dabigatran with 350 times higher affinity compared to thrombin and is indicated for dabigatran reversal.[47] Idarucizumab is administered as two consecutive 2.5-g infusions or as a single bolus 5-g IV injection. Serious adverse reactions include thromboembolic risk accompanying dabigatran reversal, hypersensitivity reactions, and serious adverse events in those with hereditary fructose intolerance. Fresh-frozen plasma, factor concentrates, or recombinant factor VIIa may also be given in the event of a major life-threatening bleed; however, their efficacy for this use has not been established. DTIs can increase PT/INR and interfere with the accuracy of monitoring and dosing of warfarin therapy. Data on use of DTIs in pregnancy are very limited. Use of DTIs in pediatric patients has not been established.[45]

▶ *Warfarin*

KEY CONCEPT Warfarin had been the primary oral anticoagulant used in the United States when long-term or extended anticoagulation is required, but its use has decreased in favor of DOACs. Warfarin is FDA approved for prevention and treatment of VTE.[48] Although very effective, warfarin has a narrow therapeutic index, requiring frequent dose adjustments and careful patient monitoring.[4,10,11,48]

Warfarin exerts its anticoagulant effect by inhibiting production of the vitamin K–dependent coagulation factors II (prothrombin), VII, IX, and X, as well as the anticoagulant proteins C and S (Figure 11–7). Warfarin has no effect on circulating coagulation factors that have been previously formed, and its therapeutic antithrombotic activity is delayed for 5 to 7 days (potentially longer in slower metabolizers). This delay is related to half-lives of the clotting factors: 60 hours for factor II (prothrombin), 4 to 6 hours for factor VII, 24 hours for factor IX, and 48 to 72 hours for factor X. Proteins C and S, the natural anticoagulants, are inhibited more rapidly due to their shorter half-lives, 8 to 10 hours and 30 hours, respectively. Reductions in the concentration of natural anticoagulants before the clotting factors are depleted can lead to a paradoxical hypercoagulable state

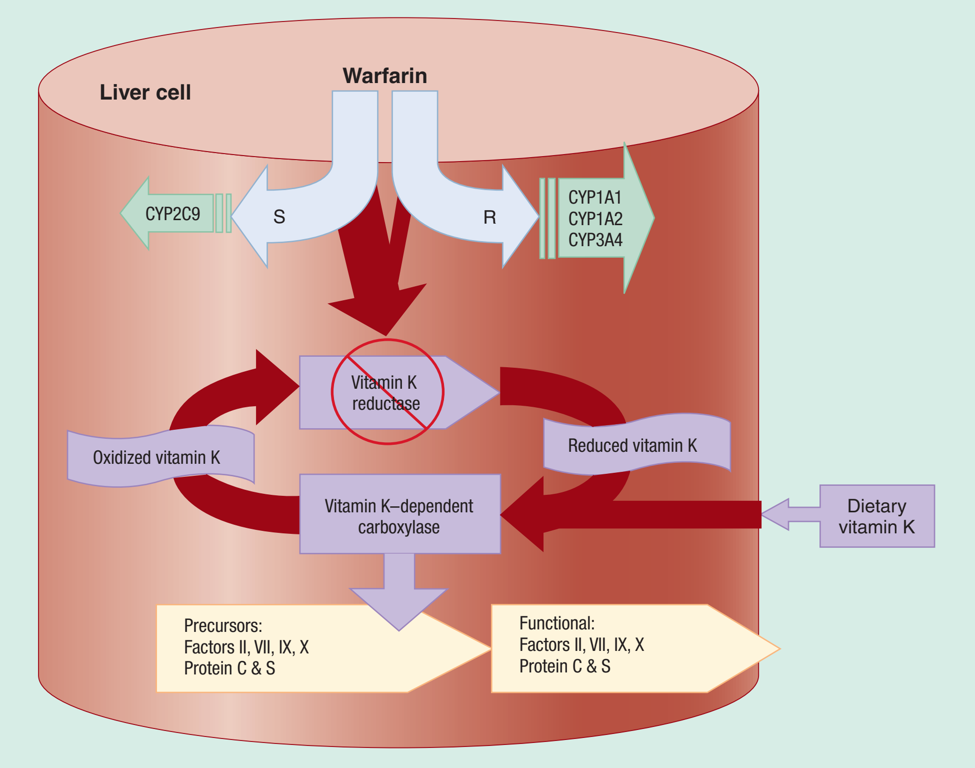


FIGURE 11–7. Pharmacologic activity and metabolism of warfarin and its downstream effects on the vitamin K cycle and clotting factor production. (CYP, cytochrome P-450 isoenzyme; S, S-warfarin; R, R-warfarin.) (From Witt DM, Nutescu EA, Haines S. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 8th ed. New York, NY: McGraw-Hill; 2011:328.)

during the first few days of warfarin therapy. It is for this reason that patients with acute thrombosis should receive a fast-acting anticoagulant (heparin, LMWH, or fondaparinux) while transitioning to warfarin therapy. Use of DOACs as bridging agents has not been well evaluated or approved.[4,10,11,48]

Warfarin is metabolized in the liver via several isoenzymes including CYP 1A2, 3A4, 2C9, 2C19, 2C8, and 2C18 (Figure 11–7).[4,10,11,48] Hepatic metabolism of warfarin varies greatly among patients, leading to large interpatient differences in dose requirements and genetic variations in these isoenzymes. Multiple studies have demonstrated that *VKORC1* and *CYP2C9* genotypes influence the interpatient variability in warfarin dose requirements, together explaining up to 45% of overall dose variance. Several algorithms that incorporate *CYP2C9* genotype and *VKORC1* haplotype with other patient characteristics to predict warfarin maintenance dosing requirements have been developed and showed efficacy in better predicting warfarin stable doses when compared to clinical algorithms. Based on these data, the FDA recommends incorporating patient's genotype information in guiding warfarin dosing when such information is available.[48] See Table 11–17.[48] Guidelines published by the Clinical Pharmacogenetics Implementation Consortium are available to guide, interpret, and apply genotype information to warfarin dosing.[49] Although randomized studies to date showed mixed results of pharmacogenomic-based warfarin dosing on clinical and health utilization outcomes, careful analyses of study design and single-nucleotide polymorphisms tested in relation to the study patient population are necessary to appropriately interpret the implications and validity of genotype-guided dosing study outcomes. Therefore, pharmacogenomic-based dosing has not yet been widely adopted in clinical practice, and some guidelines recommend against routine ordering of preemptive genetic testing.[2,4]

Warfarin displays nonlinear kinetics. Small-dose adjustments can lead to large changes in anticoagulant response.[4,10,11,48]

Table 11–17

Food and Drug Administration Recommended Warfarin Initial Daily Doses Based on *CYP2C9* and *VKORC1* Genotypes[48]

	CYP2C9					
VKORC1	***1/*1**	***1/*2**	***1/*3**	***2/*2**	***2/*3**	***3/*3**
GG	5–7 mg	5–7 mg	3–4 mg	3–4 mg	3–4 mg	0.5–2 mg
AG	5–7 mg	3–4 mg	3–4 mg	3–4 mg	0.5–2 mg	0.5–2 mg
AA	3–4 mg	3–4 mg	0.5–2 mg	0.5–2 mg	0.5–2 mg	0.5–2 mg

CYP, cytochrome P-450.

The dose of warfarin is determined by each patient's individual response to therapy and the desired intensity of anticoagulation. In addition to hepatic metabolism and genotype, warfarin dose requirements are influenced by diet, drug–drug interactions, and health status. Therefore, warfarin dose must be determined by frequent clinical and laboratory monitoring. Although there are conflicting data regarding the optimal warfarin induction regimen, when the patient's genotype is unknown, most patients can start with 5 mg daily, and subsequent doses are determined based on INR response (Figure 11–8). When initiating therapy, it is difficult to predict the precise warfarin maintenance dose a patient will require. Patients who are younger (< 55 years) and otherwise healthy can safely use higher warfarin "initiation" doses (eg, 7.5–10 mg). A more conservative "initiation" dose (eg, 4 mg or less) should be given to patients older than 75 years, patients with heart failure, liver disease, or poor nutritional status, and patients who are taking interacting medications or are at high risk of bleeding. Loading doses of warfarin (eg, 15–20 mg) are not

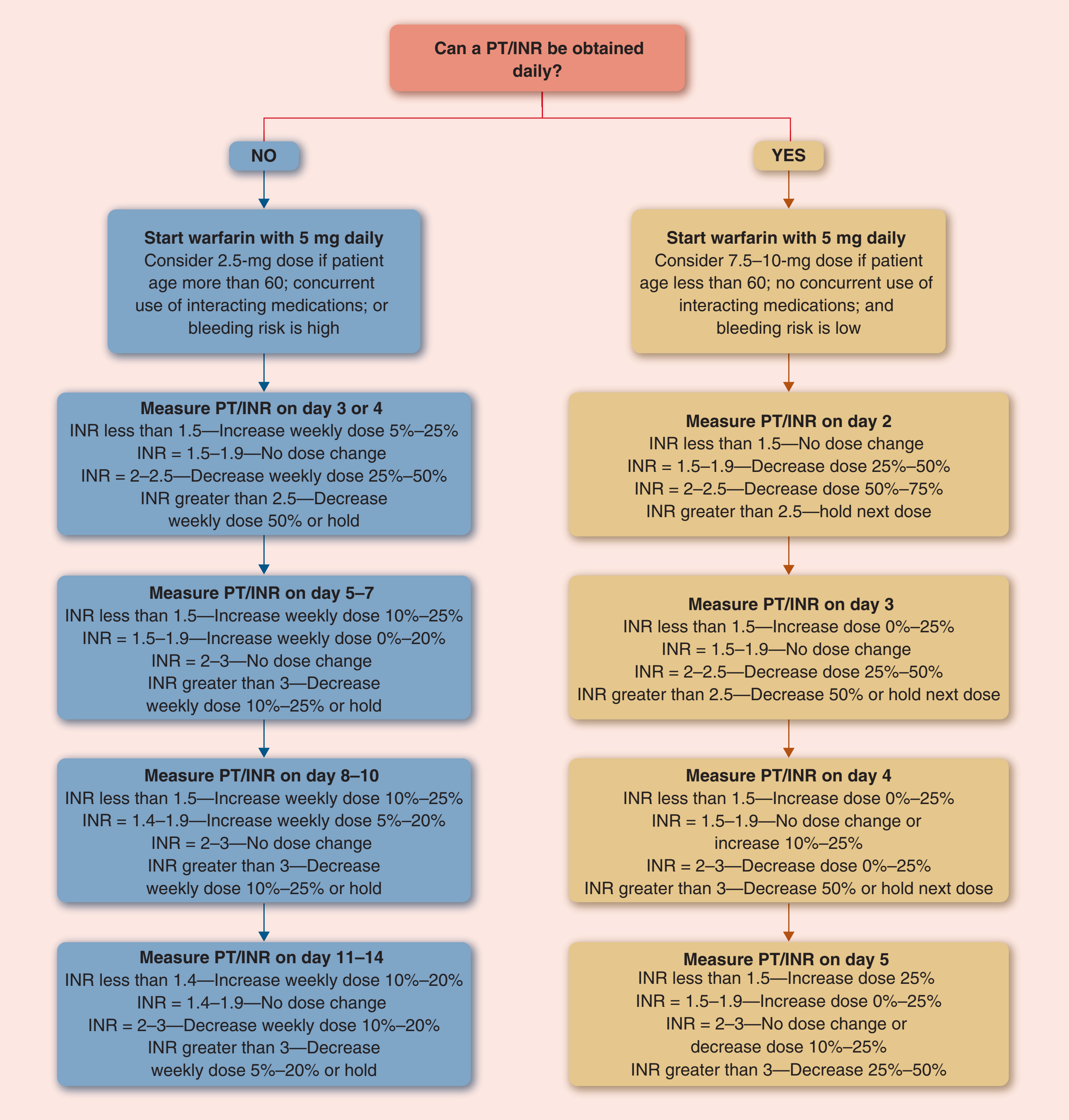

Can a PT/INR be obtained daily?
NO
YES
Start warfarin with 5 mg daily
Consider 2.5-mg dose if patient age more than 60; concurrent use of interacting medications; or bleeding risk is high
Start warfarin with 5 mg daily
Consider 7.5–10-mg dose if patient age less than 60; no concurrent use of interacting medications; and bleeding risk is low
Measure PT/INR on day 3 or 4
INR less than 1.5—Increase weekly dose 5%–25%
INR = 1.5–1.9—No dose change
INR = 2–2.5—Decrease weekly dose 25%–50%
INR greater than 2.5—Decrease weekly dose 50% or hold
Measure PT/INR on day 2
INR less than 1.5—No dose change
INR = 1.5–1.9—Decrease dose 25%–50%
INR = 2–2.5—Decrease dose 50%–75%
INR greater than 2.5—hold next dose
Measure PT/INR on day 5–7
INR less than 1.5—Increase weekly dose 10%–25%
INR = 1.5–1.9—Increase weekly dose 0%–20%
INR = 2–3—No dose change
INR greater than 3—Decrease weekly dose 10%–25% or hold
Measure PT/INR on day 3
INR less than 1.5—Increase dose 0%–25%
INR = 1.5–1.9—No dose change
INR = 2–2.5—Decrease dose 25%–50%
INR greater than 2.5—Decrease 50% or hold next dose
Measure PT/INR on day 8–10
INR less than 1.5—Increase weekly dose 10%–25%
INR = 1.4–1.9—Increase weekly dose 5%–20%
INR = 2–3—No dose change
INR greater than 3—Decrease weekly dose 10%–25% or hold
Measure PT/INR on day 4
INR less than 1.5—Increase dose 0%–25%
INR = 1.5–1.9—No dose change or increase 10%–25%
INR = 2–3—Decrease dose 0%–25%
INR greater than 3—Decrease 50% or hold next dose
Measure PT/INR on day 11–14
INR less than 1.4—Increase weekly dose 10%–20%
INR = 1.4–1.9—No dose change
INR = 2–3—Decrease weekly dose 10%–20%
INR greater than 3—Decrease weekly dose 5%–20% or hold
Measure PT/INR on day 5
INR less than 1.5—Increase dose 25%
INR = 1.5–1.9—Increase dose 0%–25%
INR = 2–3—No dose change or decrease dose 10%–25%
INR greater than 3—Decrease 25%–50%

FIGURE 11–8. Initiation of warfarin therapy. (INR, international normalized ratio; PT, prothrombin time.) (From Witt DM, Clark NP, Vazquez SR. Venous thromboembolism. In: DiPiro JT, Yee GC, Posey LM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill. Available from: https://accesspharmacy.mhmedical.com/content.aspx?bookid=2577&sectionid=21931641. Accessed July 15, 2020.)

Patient Encounter 3, Part 1

A 48-year-old woman presents to the emergency department complaining of shortness of breath, chest pain, and dizziness. She started having left calf pain approximately 5 days ago and feeling short of breath and experiencing chest pain (7/10) last evening. She could not sleep, and her shortness of breath has gotten progressively worse in the last several hours. She was hospitalized because she was suspected to have a PE. Due to the nature of her job, she does not have prescription insurance during the summer months.

PMH: Obesity × 20 years, asthma, stage 4 chronic kidney disease, hypertension; type 2 diabetes mellitus

FH: Mother with history of PE and died of an MI; paternal grandmother had clots (DVT) in her legs

SH: Full-time bus driver

Current Meds: Albuterol metered-dose inhaler as needed; Ortho-Tri-Cyclen Lo by mouth daily, lisinopril 10 mg daily, insulin glargine 40 units once daily, insulin aspart 15 units before meals, renal multivitamin daily; ginseng one to two tablets by mouth daily as needed; multivitamin one tablet by mouth daily

Allergies: NKDA

PE:

VS: BP 138/64 mm Hg, HR 102 beats/min, RR 20 breaths/min, T 38°C (100.4°F), Wt 96 kg (211 lb; BMI 35.3 kg/m^2), Ht 65 in (165 cm)

Labs: CBC and LFTs within normal limits; eGFR 16 mL/min/1.73 m^2; CrCl 12 mL/min (0.2 mL/s)

Procedures/Tests

ECG: Normal sinus rhythm; no ischemic changes

CXR: Cardiomegaly present without infiltrates

V/Q scan: High probability of PE

What symptoms and findings are consistent with diagnosis of PE? What are the most likely etiologies for PE in this case?

What are appropriate initial acute-phase treatment and long-term and extended treatment options for PE in this patient?

If UFH is chosen as the initial acute-phase anticoagulation treatment option for this patient's PE, what is the goal aPTT?

What is the patient's goal INR for warfarin therapy?

How long should she remain on anticoagulation therapy?

Given the list of medications the patient took prior to hospitalization, should any of these be discontinued or changed? If changed, what alternative therapy would you recommend?

recommended and can create false impressions that a therapeutic INR has been achieved in 2 to 3 days and lead to potential future overdosing.[4,10,11,48] Before initiating therapy, screen the patient for any contraindications to anticoagulation therapy and risk factors for major bleeding (Tables 11–11 and 11–12). Conduct a thorough medication history including the use of prescription and nonprescription drugs and any herbal supplements to detect interactions that may affect warfarin dosing requirements.

In patients with acute VTE, a rapid-acting anticoagulant (UFH, LMWH, or fondaparinux) should be overlapped with warfarin for a minimum of 5 days and until the INR is greater than 2 and stable. This is important because the full antithrombotic effect of warfarin will not be reached until 5 to 7 days or even longer after initiating warfarin therapy. Typical maintenance dose of warfarin for most patients will be between 25 and 55 mg per week, although some patients require higher or lower doses stemming from their genotype or other clinical factors. Adjustments in maintenance warfarin dose should be determined based on the total weekly dose and by reducing or increasing the weekly dose by increments of 5% to 25%. When adjusting the maintenance dose, wait at least 7 days to ensure a steady state has been attained on the new dose before checking the INR again. Checking the INR too soon can lead to inappropriate dose adjustments and unstable anticoagulation status.[4,10,11,48]

KEY CONCEPT Warfarin requires frequent laboratory monitoring to ensure optimal outcomes and minimize complications. PT is the most frequently used test to monitor warfarin's anticoagulant effect. PT measures biological activity of factors II, VII, and X. Due to wide variation in reagent sensitivity, different thromboplastins will result in different PT results, potentially leading to inappropriate dosing decisions.[4,10,11,48] To standardize result reporting, the World Health Organization developed a reference thromboplastin and recommended the INR to monitor warfarin therapy. INR corrects for the differences in thromboplastin reagents. Goal or target INR for each patient is based on the indication for warfarin therapy. For treatment and prevention of VTE, the INR target is 2.5 with an acceptable range of 2 to 3. Before initiating warfarin therapy, a baseline PT/INR and CBC should be obtained. After initiating warfarin therapy, INR should be monitored at least every 2 to 3 days during the first week of therapy. Once a stable response to therapy is achieved, INR monitoring is performed less frequently, weekly for the first 1 to 2 weeks, then every 2 weeks, and every 4 to 6 weeks thereafter if the warfarin dose and the patient's health status are stable.[4,10,11,48,50] At each encounter, the patient should be carefully questioned regarding any factors that may influence the INR result. These factors include adherence to therapy, use of interacting medications, consumption of vitamin K–rich foods, alcohol use, and general health status. Patients should also be questioned about symptoms related to bleeding and thromboembolic events. Warfarin dose adjustments should take into account not only the INR result but also patient-related factors that influence the result. Structured anticoagulation therapy management services (anticoagulation clinics) have been demonstrated to improve the efficacy and safety of warfarin therapy. Some patients engage in self-testing and self-management by using a point-of-care PT/INR device approved for home use. Highly motivated and well-trained patients are good candidates for self-testing or self-management.[50]

KEY CONCEPT Similar to other anticoagulants, warfarin's primary side effect is bleeding.[8] Warfarin can unmask an existing lesion. Incidence of warfarin-related bleeding appears to be highest during the first few weeks of therapy. The annual incidence of major bleeding ranges from 1% to 10% depending on the quality of warfarin therapy management. Bleeding in the gastrointestinal tract is most common. Intracranial hemorrhage (ICH) is one of the most serious complications because it often causes severe disability

Patient Encounter 3, Part 2

Following discussion with the patient regarding her insurance, she is discharged home on warfarin therapy. She was referred to a local area antithrombosis center for monitoring of her oral anticoagulation therapy and has been maintained on warfarin 6 mg daily for the last 3 months. The patient presents today for a routine visit for anticoagulation monitoring and her INR is 5.6. She reports that 3 days ago she was started on a 1-week course of metronidazole, which was prescribed by her primary care physician for bacterial vaginosis. She also reports that she is trying to lose weight and her intake of vitamin K–rich foods (kale, turnip greens, brussels sprouts) has increased significantly over the last month. She has no other complaints today and denies any signs or symptoms of bleeding.

What is the most likely explanation for elevated INR?

Should she be given vitamin K? If yes, discuss the dose, route of administration, and an appropriate patient monitoring plan.

How will you manage the patient's warfarin therapy? Outline a plan including specific dose changes, timing of monitoring, and patient education

and death. The intensity of anticoagulation therapy is related to bleeding risk. Higher INRs result in higher bleeding risk, and risk of ICH increases when the INR exceeds 4.[4,10,11] Instability and wide fluctuations in the INR are also associated with higher bleeding risk. In cases of warfarin overdose or overanticoagulation, vitamin K may be used to reverse warfarin's effect. Vitamin K can be given by IV or oral route; the SC route is not recommended as vitamin K is erratically absorbed and frequently ineffective. The IV route is reserved for cases requiring urgent reversal and when patients have life-threatening bleeding. Anaphylactoid reactions have been reported with rapid IV administration; therefore, slow infusion is recommended. An oral dose of vitamin K will reduce INR within 24 hours. If INR is still elevated after 24 hours, another dose of oral vitamin K can be given. The dose of vitamin K should be based on the degree of INR elevation and whether bleeding is present. A dose of 2.5 mg orally is recommended when INR is greater than 10 and there is no active bleeding, while a higher dose of 10 mg given via slow IV is recommended in cases when life-threatening bleeding is present. Higher doses (eg, 10 mg) can lead to prolonged warfarin resistance. In cases of life-threatening bleeding, fresh-frozen plasma or clotting factor concentrates should also be administered, in addition to IV vitamin K. In patients in whom INR is less than 10, and there is no active bleeding or imminent risk of bleeding, simply withholding warfarin until INR decreases to within therapeutic range and reducing the weekly dose with more frequent monitoring is appropriate.[4,10,11,48]

Nonhemorrhagic side effects related to warfarin are rare but can be severe when they occur. Warfarin-induced skin necrosis (incidence $< 0.1\%$) presents as an eggplant-colored skin lesion or a maculopapular rash that can progress to necrotic gangrene. It usually manifests in fatty areas such as the abdomen, buttocks, and breasts, and generally appears during the first week of therapy. Patients with protein C or S deficiency or those who receive large loading doses of warfarin are at greatest risk.[48] The mechanism is thought to be due to imbalances between procoagulant and anticoagulant proteins early in the course of warfarin therapy. Warfarin-induced purple toe syndrome is another rare side effect; patients present with a purplish discoloration of their toes. If these side effects are suspected, warfarin therapy should be discontinued immediately, and an alternative anticoagulant should be started. There is a theoretical risk that warfarin may cause accelerated bone loss with long-term use, but to date there is no evidence to support this concern. Warfarin is teratogenic and should be avoided during pregnancy. Women of childbearing potential should be instructed to use an effective form of contraception.

KEY CONCEPT Warfarin is prone to numerous clinically significant drug–drug and drug–food interactions (Tables 11–18, 11–19, and 11–20).[10,11,48] Patients on warfarin should be questioned at every encounter to assess for any potential interactions with foods, drugs,

Table 11–18

Clinically Significant Drug Interactions With Warfarin

Increase Anticoagulation Effect (↑ INR)	Decrease Anticoagulation Effect (↓ INR)	Increase Bleeding Risk
Acetaminophen	Amobarbital	Argatroban
Acute alcohol ingestion	Butabarbital	Aspirin
Allopurinol	Carbamazepine	Clopidogrel
Amiodarone	Cholestyramine	Danaparoid
Cephalosporins (with MTT side chain)	Chronic alcohol ingestion	Dipyridamole
Chloral hydrate	Dicloxacillin	Low-molecular-weight heparins
Chloramphenicol	Griseofulvin	Nonsteroidal anti-inflammatory drugs
Cimetidine	Nafcillin	Ticlopidine
Ciprofloxacin	Phenobarbital	Unfractionated heparin
Clofibrate	Phenytoin	
Danazol	Primidone	
Disulfiram	Rifampin	
Doxycycline	Secobarbital	
Erythromycin	Sucralfate	
Fenofibrate	Vitamin K	
Fluconazole		
Fluorouracil		
Fluoxetine		
Fluvoxamine		
Gemfibrozil		
Influenza vaccine		
Isoniazid		
Itraconazole		
Lovastatin		
Metronidazole		
Miconazole		
Moxalactam		
Neomycin		
Norfloxacin		
Ofloxacin		
Omeprazole		
Phenylbutazone		
Piroxicam		
Propafenone		
Propoxyphene		
Quinidine		
Sertraline		
Sulfamethoxazole		
Sulfinpyrazone		
Tamoxifen		
Testosterone		
Vitamin E		
Zafirlukast		

INR, international normalized ratio; MTT, methyl-tetrazole-thiomethyl.

Table 11–19

Potential Warfarin Interactions With Herbal and Nutritional Products

Increase Anticoagulation Effect (Increase Bleeding Risk or ↑ INR)		Decrease Anticoagulation Effect (↓ INR)
Arnica flower	Ginkgo	Coenzyme Q_{10}
Angelica root	Horse chestnut	Ginseng
Anise	Licorice root	Green tea
Asafoetida	Lovage root	St. John's wort
Bogbean	Meadowsweet	
Borage seed oil	Onion	
Bromelain	Papain	
Capsicum	Parsley	
Celery	Passionflower herb	
Chamomile	Poplar	
Clove	Quassia	
Cranberry	Red clover	
Danshen	Rue	
Devil's claw	Sweet clover	
Dong quai	Turmeric	
Fenugreek	Vitamin E	
Feverfew	Willow bark	
Garlic		
Ginger		

INR, international normalized ratio.

herbal products, and nutritional supplements. When an interacting drug is initiated or discontinued, more frequent monitoring should be instituted. In addition, the dose of warfarin can be modified (increased or decreased) in anticipation of the expected impact on the INR.[10,11,48] Warfarin-related drug interactions can generally be divided into two major categories: pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions are most commonly due to changes in hepatic metabolism or binding to plasma proteins. Drugs that affect the CYP2C9, CYP3A4, and CYP1A2 have the greatest impact on warfarin metabolism. Interactions that impact the metabolism of the S-isomer result in greater changes in the INR than interactions affecting the R-isomer. Pharmacodynamic drug interactions enhance or diminish the anticoagulant effect of warfarin, increasing the risk of bleeding or clotting, but may not alter the INR. There are increasing reports regarding dietary supplements, nutraceuticals, and vitamins that can interact with warfarin. Patients on warfarin may experience changes in the INR due to fluctuating intake of dietary vitamin K. Patients should be instructed to maintain a consistent diet and avoid large fluctuations in vitamin K intake rather than strictly avoiding vitamin K–rich foods.[4,10,11,48]

Nonpharmacologic Therapy

▶ *Thrombectomy*

Most cases of VTE can be successfully treated with anticoagulation. In some cases, removal of the occluding thrombus by surgical intervention may be warranted. Surgical or mechanical thrombectomy can be considered in patients with massive iliofemoral DVT when there is a risk of limb gangrene due to venous occlusion.[2,12] The procedure can be complicated by recurrence of thrombus formation. In patients who present with massive PE, pulmonary embolectomy can be performed in patients with contraindications to thrombolytic therapy, when thrombolysis has failed clinically, or when thrombolysis will not have sufficient time to take effect. The usual practice is to administer heparin by IV infusion to achieve a therapeutic aPTT during the operation, and postoperatively and thereafter give warfarin for the usual recommended duration.[2,12]

▶ *Inferior Vena Cava Filters*

An IVC filter is indicated in patients with newly diagnosed proximal DVT or PE who have a contraindication to anticoagulation therapy.[2,12] IVC interruption is accomplished through minimally invasive means by insertion via internal jugular vein or femoral

Table 11–20

Vitamin K Content of Select Foods[a]

Very High (> 200 mcg)	High (100–200 mcg)	Medium (50–100 mcg)	Low (< 50 mcg)
Brussels sprouts	Basil	Apple, green	Apple, red
Chickpea	Broccoli	Asparagus	Avocado
Collard greens	Canola oil	Cabbage	Beans
Coriander	Chive	Cauliflower	Breads and grains
Endive	Coleslaw	Lettuce, green leaf, romaine	Carrot
Kale	Cucumber (unpeeled)	Mayonnaise	Celery
Lettuce, red leaf	Green onion/scallion	Pistachios	Cereal
Parsley	Lettuce, butterhead	Squash, summer	Coffee
Spinach	Mustard greens		Corn
Swiss chard	Soybean oil		Cucumber (peeled)
Tea, black			Dairy products
Tea, green			Eggs
Turnip greens			Fruit (varies)
Watercress			Lettuce, iceberg
			Meats, fish, poultry
			Pasta
			Peanuts
			Peas
			Potato
			Rice
			Tomato

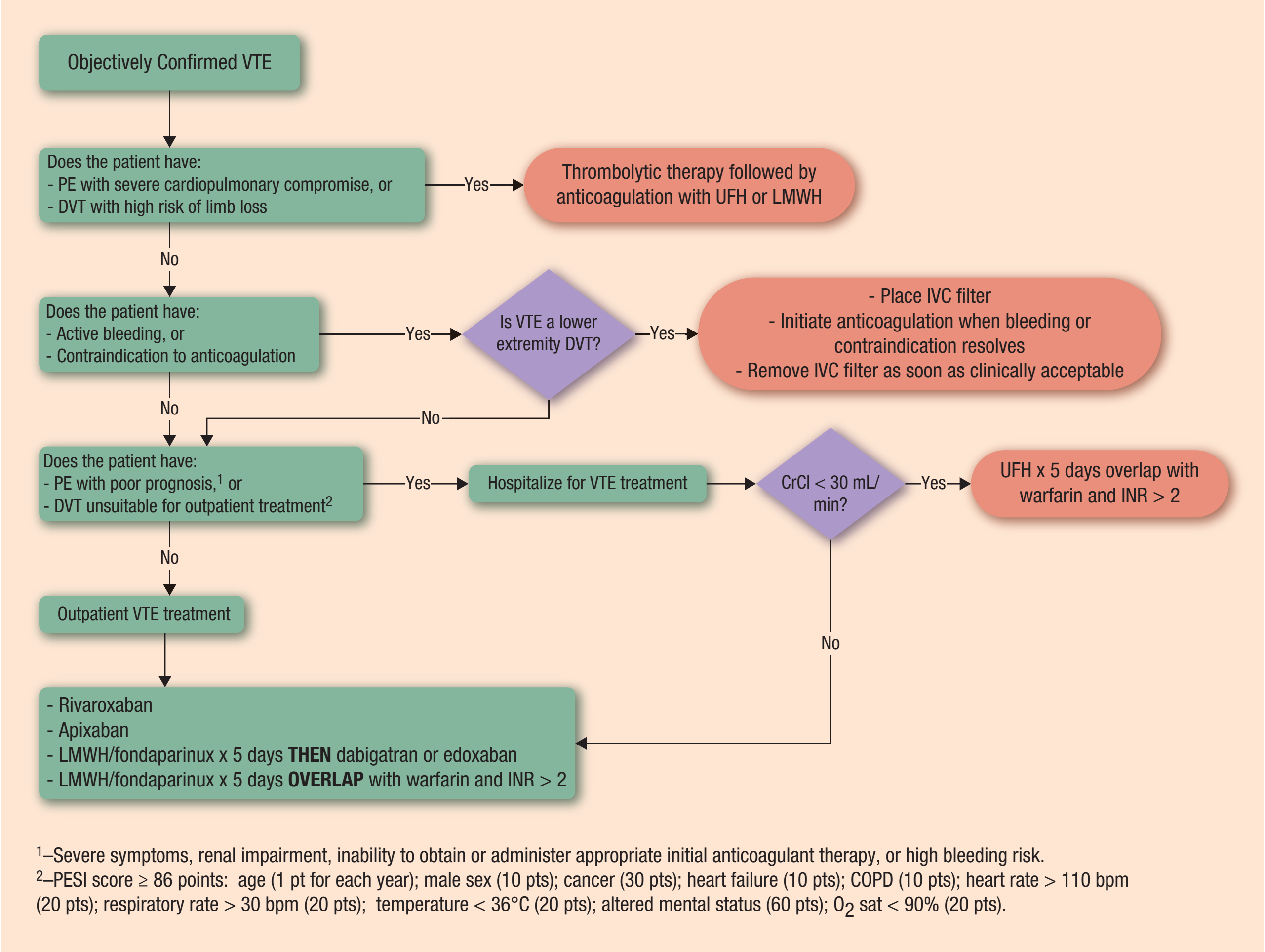
[a] Approximate amount of vitamin K per 100 g (3.5 oz) serving.

vein access and advancing the filter into the IVC using ultrasound or fluoroscopic guidance. One of the risks associated with IVC filters is development of thrombosis on the filter itself. Therefore, anticoagulation therapy should be resumed as soon as contraindications resolve. Temporary or retrievable filters are frequently used, and filters should be removed once therapy is completed.[15]

APPROACH TO TREATING PATIENTS WITH VTE

A treatment algorithm for VTE is presented in Figure 11–9. Note that LMWH or fondaparinux are preferred over UFH for acute VTE treatment; however, in patients with CrCl less than 30 mL/min (0.50 mL/s), UFH is the preferred treatment approach. For the long-term and extended treatment phases, DOACs are recommended over warfarin to prevent recurrent thrombosis. In patients with cancer-associated thrombosis, LMWHs are an alternative option for the acute, long-term, and extended phases of treatment due to efficacy in preventing recurrent thromboembolic events.[2,31,34]

Anticoagulation therapy is continued for a minimum of 3 months but should be given longer depending on the underlying etiology of the VTE, thrombus location, and the patient's risk factors.[2,12] Determining optimal duration of anticoagulation involves weighing the risk of recurrent VTE against the risk of bleeding associated with anticoagulation therapy and determining patient preference regarding treatment duration. Patients with provoked VTE by transient risk factors (eg, surgery, trauma) or an isolated distally located DVT require therapy for 3 months. Patients with unprovoked VTE have a recurrence risk of at least 10% after 1 year and at least 30% at 5 years, thus most such patients require extended if not indefinite anticoagulation, particularly in those with PE or proximally located DVT and PE, and if the patient carries low-to-moderate bleeding risk. Patients with low-to-moderate bleeding risk who have a second unprovoked VTE should receive extended or indefinite anticoagulation and those at high bleeding risk should be treated for 3 months. Patients who are recommended to receive indefinite anticoagulation should have periodic visits to assess bleeding risk and patient preference/quality of life to determine if anticoagulation should continue. Patient preference should always be a strong consideration when deciding on extended duration anticoagulation.[2,12]


Objectively Confirmed VTE
Does the patient have:
- PE with severe cardiopulmonary compromise, or
- DVT with high risk of limb loss
Yes
Thrombolytic therapy followed by anticoagulation with UFH or LMWH
No
Does the patient have:
- Active bleeding, or
- Contraindication to anticoagulation
Yes
Is VTE a lower extremity DVT?
Yes
- Place IVC filter
- Initiate anticoagulation when bleeding or contraindication resolves
- Remove IVC filter as soon as clinically acceptable
No
No
Does the patient have:
- PE with poor prognosis,1 or
- DVT unsuitable for outpatient treatment2
Yes
Hospitalize for VTE treatment
CrCl < 30 mL/min?
Yes
UFH x 5 days overlap with warfarin and INR > 2
No
No
Outpatient VTE treatment
- Rivaroxaban
- Apixaban
- LMWH/fondaparinux x 5 days THEN dabigatran or edoxaban
- LMWH/fondaparinux x 5 days OVERLAP with warfarin and INR > 2

[1]–Severe symptoms, renal impairment, inability to obtain or administer appropriate initial anticoagulant therapy, or high bleeding risk.

[2]–PESI score ≥ 86 points: age (1 pt for each year); male sex (10 pts); cancer (30 pts); heart failure (10 pts); COPD (10 pts); heart rate > 110 bpm (20 pts); respiratory rate > 30 bpm (20 pts); temperature < 36°C (20 pts); altered mental status (60 pts); O_2 sat < 90% (20 pts).

FIGURE 11–9. Acute treatment of VTE. (bpm, beats/min; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance [30 mL/min is equivalent to 0.50 mL/s]; DVT, deep vein thrombosis; INR, international normalized ratio; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; O_2 sat, oxygen saturation [90% is equivalent to 0.90 when expressed as a fraction]; PE, pulmonary embolism; PESI, pulmonary embolism severity index; UFH, unfractionated heparin; VTE, venous thromboembolism.) (From Witt DM, Clark NP, Vazquez SR. Venous thromboembolism. In: DiPiro JT, Yee GC, Posey LM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill. Available from: https://accesspharmacy.mhmedical.com/content.aspx?bookid=2577&sectionid=21931641. Accessed July 15, 2020.)

OUTCOME EVALUATION

- KEY CONCEPT Achieve optimal outcomes by (a) preventing the occurrence of VTE in patients who are at risk, (b) administering effective treatments in a timely manner to patients who develop VTE, (c) preventing treatment-related complications, and (d) reducing the likelihood of long-term complications including recurrent events.
- Given that VTE is often clinically silent and potentially fatal, strategies to increase widespread use of prophylaxis have the greatest potential to improve patient outcomes. Thus, relying

Patient Care Process

Collect Information:

- Obtain and review from the medical record: past medical history, family history, social history, physical assessment findings, and laboratory and diagnostic testing results.
- Complete a medication history of prescription and nonprescription medication and dietary supplement use. Identify any allergies to medications and other substances.
- Interview the patient and review records to identify lifestyle habits such as dietary patterns, alcohol and illicit drug use, smoking status, medication use–related preferences and beliefs, and socioeconomic factors that affect access to medications and health care.

Assess the Information:

- Based on clinical assessment and physical examination, determine whether the patient is experiencing signs or symptoms of VTE (Table 11–1 and Clinical Presentation and Diagnosis of DVT and PE).
- Apply the Wells criteria to determine the probability that the patient's signs, symptoms, and risk factors are the result of DVT and/or PE (Tables 11–2 and 11–3).
- Review relevant laboratory (eg, D-dimer, PT/INR, aPTT, antifactor Xa activity, SCr, CrCl, blood urea nitrogen [BUN], serum albumin, liver function tests, CBC with platelets) and diagnostic tests (eg, venous ultrasound, V/Q, or CT scan). See Clinical Presentation and Diagnosis of DVT and PE.
- Assess pertinent family history (ie, hypercoagulable disorders, pregnancy loss, DVT, PE).
- Determine if diagnosis of VTE is confirmed based on clinical criteria and/or diagnostic testing.
- Assess whether the VTE is a new or recurrent event and whether the VTE is an idiopathic or triggered event.
- Assess severity of VTE and whether patient is a candidate for outpatient therapy.
- Assess risk of bleeding and check for any contraindications to anticoagulation therapy (Tables 11–6, 11–11, and 11–12).
- Assess dietary and medication profiles, including over-the-counter medications and herbal therapies used at home for potential drug–drug and drug–food interactions with anticoagulation therapy (Tables 11–15, 11–18, and 11–19).
- If the patient is already receiving anticoagulation therapy, assess efficacy, safety, and adherence to therapy.

Develop a Care Plan:

- Once diagnosis of VTE has been confirmed with an objective test, initiate anticoagulation therapy at full therapeutic doses. If there is high clinical suspicion of VTE, anticoagulation therapy may be initiated while waiting for results of diagnostic tests (Figure 11–9).
- Determine the most appropriate anticoagulant therapy and dose options based on patient clinical characteristics, insurance coverage, plans for outpatient therapy, complexity of anticoagulation management, and patient preferences (Tables 11–8, 11–9, 11–10, and 11–13).
- Determine optimal duration of anticoagulation therapy by weighing the risk of recurrent VTE against the risk of bleeding and considering patient preferences regarding treatment duration.

Implement the Care Plan:

- Educate the patient on purpose of therapy and importance of adherence, proper monitoring, potential drug–drug and drug–food interactions, dietary consistency with vitamin K–containing foods if treated with warfarin, taking appropriate birth control measures in females, adherence with anticoagulants and with laboratory monitoring, potential side effects, and procedures to follow in case of emergency.
- Address any patient concerns about anticoagulation treatment and its management.
- Devise a structured plan for long-term monitoring of anticoagulation therapy; if treated with warfarin, determine if patient is candidate for anticoagulation self-testing.
- Refer the patient to a specialized anticoagulation monitoring service if available or another designated specialized provider.
- Evaluate patient's medical insurance status and assess coverage level for oral and injectable anticoagulant medications and coverage for follow-up monitoring visits and/or anticoagulation self-testing devices and supplies.

Follow-up: Monitor and Evaluate:

- Follow a structured plan for periodic long-term monitoring of anticoagulation therapy.
- Reevaluate risks and benefits of continuing anticoagulation therapy beyond the initial 3 months; patients who are recommended to receive indefinite anticoagulation should have periodic visits to assess bleeding risk and patient preference/quality of life to determine if anticoagulation should continue.
- Periodically reassess patient adherence, concurrent medications to screen for drug interactions, dietary habits to screen for drug–diet interactions, and renal and liver function tests.
- Monitor the patient to determine if there is worsening or new symptoms related to VTE.
- Evaluate the patient to determine if he/she is experiencing any side effects such as overt bruising or bleeding, as well as changes in stool or urine color.

on early diagnosis and treatment of VTE is unacceptable because many patients will die before treatment can be initiated.

- Effective VTE prophylaxis programs screen all patients admitted to the hospital for VTE risk factors, determine each patient's level of risk, and select and implement prevention strategies that provide sufficient protection for the level of risk.
- Periodically evaluate patients who are receiving VTE prophylaxis for signs and symptoms of DVT, such as swelling, pain, warmth, and redness of lower extremities, and for signs and symptoms of PE, such as chest pain, shortness of breath, palpitations, and hemoptysis.
- Providing effective treatment in a timely manner is the primary goal for patients who develop VTE. Treat DVT and PE quickly and aggressively with effective doses of anticoagulant drugs.
- Short-term aims of therapy are to prevent propagation or local extension of the clot, embolization, and death.
- Regularly monitor patients for development of new symptoms or worsening of existing symptoms.
- All anticoagulant drugs require precise dosing and meticulous monitoring. Closely monitor patients receiving anticoagulant therapy for signs and symptoms of bleeding including epistaxis, hemoptysis, hematuria, hematemesis, hematochezia, melena, severe headache, and joint pain. If major bleeding occurs, stop therapy immediately and treat the source of bleeding. In addition, closely monitor patients for potential drug–drug and drug–food interactions and adherence with the prescribed regimen.
- Long-term goals of therapy are to prevent complications such as PTS, pulmonary hypertension, and recurrent VTE.
- Continue long-term anticoagulation therapy for an appropriate duration based on etiology of the initial clot and presence of ongoing risk factors.

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Abbreviations Introduced in This Chapter

ABW	Adjusted body weight
ACCP	American College of Chest Physicians
ACT	Activated clotting time
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AT	Antithrombin
BCRP	Breast cancer resistance protein
BMI	Body mass index
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CBC	Complete blood count
CrCl	Creatinine clearance
CT	Computed tomography
CYP	Cytochrome P-450
DOAC	Direct oral anticoagulant
DTI	Direct thrombin inhibitor
dTT	Diluted thrombin time
DVT	Deep vein thrombosis
ECT	Ecarin clotting time
eGFR	Estimated glomerular filtration rate
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
FXa	Factor Xa
GCS	Graduated compression stockings
GP	Glycoprotein
HIT	Heparin-induced thrombocytopenia
HITTS	Heparin-induced thrombocytopenia and thrombosis syndrome
IBW	Ideal body weight
ICH	Intracranial hemorrhage
INR	International normalized ratio
IPC	Intermittent pneumatic compression (device)
IV	Intravenous
IVC	Inferior vena cava
LDH	Lactate dehydrogenase
LDUH	Low-dose unfractionated heparin
LFT	Liver function test
LMWH	Low-molecular-weight heparin
MI	Myocardial infarction
MRI	Magnetic resonance imaging
MTT	Methyl-tetrazole-thiomethyl
NSAID	Nonsteroidal anti-inflammatory drug
PAI-1	Plasminogen activator inhibitor-1
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PF	Platelet factor
P-gp	P-glycoprotein
PT	Prothrombin time
PTS	Postthrombotic syndrome
rt-PA	Recombinant tissue plasminogen activator (alteplase)
SCr	Serum creatinine
SBP	Systolic blood pressure
SC	Subcutaneous
SGOT	Serum glutamic-oxaloacetic transaminase
SERM	Selective estrogen receptor modulator
TT	Thrombin time
UFH	Unfractionated heparin
V/Q	Ventilation/perfusion (scan)
VTE	Venous thromboembolism
vWF	von Willebrand factor
WBC	White blood cell

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12 Stroke

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Differentiate types of cerebrovascular disease including transient ischemic attack (TIA), ischemic stroke (cerebral infarction), and hemorrhagic stroke.
2. Identify modifiable and nonmodifiable risk factors associated with ischemic stroke and hemorrhagic stroke.
3. Explain the pathophysiology of ischemic stroke and hemorrhagic stroke.
4. Describe the clinical presentation of TIA, ischemic stroke, and hemorrhagic stroke.
5. Formulate strategies for primary prevention of acute ischemic stroke.
6. Evaluate treatment options for acute ischemic stroke.
7. Determine whether fibrinolytic therapy is indicated in a patient with acute ischemic stroke.
8. Evaluate the role of endovascular therapy in a patient with acute ischemic stroke.
9. Formulate strategies for secondary prevention of acute ischemic stroke.
10. Evaluate treatment options for acute hemorrhagic stroke.

INTRODUCTION

Cerebrovascular disease comprises stroke, as well as carotid stenosis, vertebral stenosis and intracranial stenosis, aneurysms, and vascular malformations. Stroke is the second most common cause of death worldwide and is the fifth leading cause of death in the United States. Stroke is an acute medical emergency, and rapid treatment dependent on the type of stroke (ischemic or hemorrhagic) is critical. Treatment of risk factors and preventive measures are also paramount in the management of stroke. Decades of progress in treatment and prevention have resulted in a decrease in both stroke incidence and stroke case fatality rates.[1] Stroke mortality rates are higher in women than men and geographic variability exists, with higher mortality rates observed in the southeastern United States, termed the “stroke belt.”

EPIDEMIOLOGY

Approximately 795,000 strokes occur in the United States each year. New strokes account for 610,000 of this total; recurrent strokes account for the remaining 185,000. Stroke incidence increases with age, especially after age 55 years, resulting in an increased incidence in the elderly population.[2] Stroke is the leading cause of long-term disability in adults, with 90% of survivors having residual deficits. Moderate-to-severe disability is seen in 70% of stroke survivors, and 15% to 30% of survivors are permanently disabled. The American Heart Association estimates there are currently over 7 million stroke survivors in the United States. Societal impact and economic burden are great, with total costs of $33.9 billion reported in the United States in 2013.

ETIOLOGY AND CLASSIFICATION

Strokes can either be ischemic (87% of all strokes) or hemorrhagic (13% of all strokes). **KEY CONCEPT** Ischemic stroke, which may be thrombotic or embolic, is the abrupt development of a focal neurological deficit that occurs due to inadequate blood supply to an area of the brain. A thrombotic occlusion occurs when a **thrombus** forms inside an artery in the brain. An embolic stroke typically occurs when a piece of thrombus, originating either inside or outside of the cerebral vessels, breaks loose and is carried to the site of occlusion in the cerebral vessels. An extracerebral source of emboli is often the heart, leading to cardioembolic stroke.

KEY CONCEPT Hemorrhagic stroke is a result of bleeding into the brain and other spaces within the central nervous system (CNS) and includes subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), and subdural **hematomas**. SAH results from sudden bleeding into the space between the inner and middle layers of the meninges, most often due to trauma or rupture of a cerebral **aneurysm** or **arteriovenous malformation** (AVM). ICH is bleeding directly into the brain parenchyma, often as a result of chronic uncontrolled hypertension. Subdural hematomas result from bleeding under the dura covering the brain and most often occur as a result of head trauma. For hemorrhagic events associated with stroke, refer to the Clinical Presentation and Diagnosis of Stroke text box.

Cerebral Ischemic Events

There are two main classifications of cerebral ischemic events: transient ischemic attack (TIA) and ischemic stroke (cerebral infarction). A TIA is a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction. TIAs have a rapid onset and short duration, typically lasting less than 1 hour and often less than 30 minutes. Symptoms vary depending on the area of the brain affected; however, no deficit remains after the attack.[3] **KEY CONCEPT** TIAs are a risk factor for acute ischemic stroke and represent a continuum in cerebral ischemic events from TIA to ischemic stroke.[4] Ischemic stroke is similar to TIA; however, tissue injury and infarction are present, and in many patients, residual deficits remain after the event. A standardized tissue-based definition of cerebral infarction has been established as brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury.[5]

Risk Factors

Assessment of risk factors for ischemic stroke and hemorrhagic stroke is an important component of stroke prevention, diagnosis, and treatment. Major goals in the long-term management of ischemic stroke involve primary prevention (prevention of first stroke) and secondary prevention (prevention of a recurrent stroke). Risk factors for ischemic stroke are divided into modifiable and nonmodifiable (Table 12–1). Hypertension is one of the major risk factors for both ischemic and hemorrhagic stroke. Other risk factors for hemorrhagic stroke include trauma, cigarette smoking, cocaine use, heavy alcohol use, anticoagulant use, and cerebral aneurysm and AVM rupture.[6,7] Every patient should have risk factors assessed and treated, if possible, because management can decrease the occurrence and/or recurrence of stroke.

Table 12–1

Nonmodifiable and Modifiable Risk Factors for Ischemic Stroke

Nonmodifiable Risk Factors
- Age (> 55 years)
- Gender (males > females at older ages; females have higher incidence of stroke due to having a longer lifespan; females have increased mortality from stroke)
- Race and ethnicity (American Indian/Alaska Natives, African American, Asian/Pacific Islander, Hispanic)
- Genetic predisposition
- Low birth weight

Well-Documented and Modifiable Risk Factors
- Hypertension (most important risk factor)
- Cardiac disease
  - Atrial fibrillation (most important and treatable cardiac cause of stroke)
  - Valvular heart disease
  - Left atrial enlargement
  - Structural abnormalities such as atrial septal aneurysm
  - Acute myocardial infarction
- Transient ischemic attacks or prior stroke (major independent risk factor)
- Diabetes (independent risk factor)
- Dyslipidemia
- Asymptomatic carotid stenosis
- Oral contraceptive use (with estrogen content > 50 mcg)
- Postmenopausal hormone therapy
- Sickle cell disease
- Lifestyle factors
  - Cigarette smoking
  - Excessive alcohol use
  - Physical inactivity
  - Obesity
  - Diet
  - Cocaine and intravenous drug use
  - Low socioeconomic status

Less Well-Documented or Potentially Modifiable Risk Factors
- Increased hematocrit
- Metabolic syndrome
- Hyperhomocysteinemia
- Migraine (risk not clear)
- Sleep disordered breathing (ie, sleep apnea)

PATHOPHYSIOLOGY

Ischemic Stroke

In ischemic stroke, there is an interruption of the blood supply to an area of the brain either due to thrombus formation or an embolism. Loss of cerebral blood flow results in tissue hypoperfusion, tissue hypoxia, and cell death. Thrombus formation usually starts with lipid deposits in the vessel wall that cause turbulent blood flow. This leads to vessel injury and exposure of vessel collagen to blood. This vessel injury initiates the platelet aggregation process due to the exposed subendothelium. Platelets release adenosine diphosphate (ADP), which causes platelet aggregation and consolidation of the platelet plug. Thromboxane A_2 is released, contributing to platelet aggregation and vasoconstriction. The vessel injury also activates the coagulation cascade, which leads to thrombin production. Thrombin converts fibrinogen to fibrin, leading to clot formation as fibrin molecules, platelets, and blood cells aggregate. Refer to Figures 8–3, 11–3, and 11–4 for a depiction of these processes.

After the initial event, secondary events occur at the cellular level that contribute to cell death. Regardless of the initiating event, the cellular processes that follow may be similar. Excitatory amino acids such as glutamate accumulate within the cells, causing intracellular calcium accumulation. Inflammation occurs and oxygen free radicals are formed resulting in the common pathway of cell death.

There is often a core of ischemia containing unsalvageable brain cells. Surrounding this core is an area termed the ischemic penumbra. In this area, cells are still salvageable; however, this is time-sensitive. Without restoration of adequate perfusion, cell death continues throughout a larger area of the brain, ultimately leading to neurological deficits.

Hemorrhagic Stroke

The pathophysiology of hemorrhagic stroke is related to the presence of blood in the brain tissue and/or surrounding spaces resulting in compression. The hematoma that forms may continue to grow and enlarge after the initial bleed, and early growth is associated with a poor outcome. Brain tissue swelling and injury is a result of inflammation caused by thrombin and other blood products. This can lead to increased intracranial pressure (ICP) and herniation. Delayed cerebral ischemia, or vasospasm, is a potential consequence of aneurysmal SAH that results in vasoconstriction of cerebral vessels and clinical symptoms of ischemia.

PRIMARY PREVENTION OF ISCHEMIC STROKE

Aspirin

Use of aspirin (ASA) in patients with no history of stroke or ischemic heart disease reduced the incidence of nonfatal myocardial infarction (MI) but not stroke. Primary prevention guidelines recommend ASA for general cardiovascular prophylaxis (not specific to stroke) in men and women with a 10-year cardiovascular risk of greater than 10% and in women who are at high risk for stroke. ASA may be considered for prevention of a first stroke in patients with chronic kidney disease, and cilostazol may be considered for prevention of a first stroke in patients with peripheral arterial disease. The benefits must be weighed against the risk of major bleeding. Due to lack of benefit observed in clinical trials, ASA is not recommended for primary prevention in patients with diabetes and asymptomatic peripheral arterial disease, or in those at low risk.[8]

Clinical Presentation and Diagnosis of Stroke

General

- Patient may not be able to reliably report history due to cognitive or language deficits. A reliable history may have to come from a family member or another witness.

Symptoms of Ischemic Stroke

- The patient may complain of weakness on one side of the body, facial droop, inability to speak, loss of vision, vertigo, headache, or falling.

Signs of Ischemic Stroke

- Patients usually have multiple signs of neurological dysfunction, and specific deficits are determined by the area of the brain involved.
- Hemiparesis or monoparesis occur commonly, as does a hemisensory deficit.
- Patients with vertigo and double vision are likely to have posterior circulation involvement.
- Aphasia is seen commonly in patients with anterior circulation strokes.
- Patients may also suffer from dysarthria, visual field defects, and altered levels of consciousness.

Signs and Symptoms of Hemorrhagic Stroke

- A sudden severe headache, nausea, vomiting, and photophobia may be the first signs and symptoms. Patients may complain the headache is "the worst headache of my life."
- Neck pain and nuchal rigidity (stiffness) may also be experienced.

**It is important to note that diagnosis of type of stroke cannot be made solely on signs and symptoms because overlap occurs between types of stroke.

Laboratory Tests

- There are no specific laboratory tests for stroke.
- Tests for hypercoagulable states, such as protein C deficiency and antiphospholipid antibody, should be done only when cause of stroke cannot be determined based on presence of well-known risk factors.

Other Diagnostic Tests

- Computed tomography (CT) scan of the head will reveal an area of hyperintensity (white) identifying that a hemorrhage has occurred. CT scan will either be normal or hypointense (dark) in an area where an infarction has occurred. It may take 24 hours (and rarely longer) to reveal the area of infarction on a CT scan.
- Magnetic resonance imaging (MRI) of the head will reveal areas of ischemia earlier and with better resolution than a CT scan. Diffusion-weighted imaging can reveal an evolving infarct within minutes.
- Carotid Doppler studies will determine whether the patient has a high degree of stenosis (blockage of an artery) in the carotid arteries, which are the vessels that supply blood to the brain (extracranial disease).
- Electrocardiogram (ECG) will determine whether the patient has atrial fibrillation (AF), a major risk factor for cardioembolic stroke.
- Transthoracic echocardiogram will identify whether there are heart valve abnormalities or problems with wall motion of the heart resulting in emboli to the brain.

▶ *Diabetes*

Diabetes is an independent risk factor for stroke. Intensive glycemic control has not been shown to reduce stroke risk in either type 1 or type 2 diabetes mellitus. Adequate control of blood pressure (BP) to a target level of less than 130/80 mm Hg and management of dyslipidemia are recommended in individuals with diabetes. The use of a statin is also recommended to prevent a first stroke.[8-10] Hypertension guidelines recommend initial therapy that includes a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACE-I), or angiotensin receptor blocker (ARB).[9] The guidelines suggest that in Black patients with diabetes, initial antihypertensive therapy should include a thiazide-type diuretic or a CCB.[9]

Patient Encounter Part 1

A 63-year-old, 101.2-kg (223 lb), 5 ft 9 in (175 cm) White man presents to the emergency department with weakness in his right arm and leg, a right facial droop and speech difficulty that began suddenly 90 minutes earlier. He was attending a family event and was well prior to symptom onset. His past medical history is significant for hypertension, diabetes, and obesity. Social history includes alcohol use of three to four drinks per day on five to six nights per week and smoking one pack per day for 30 years. Current medications include metformin 500 mg twice daily, empagliflozin 10 mg daily, hydrochlorothiazide 50 mg daily, and amlodipine 5 mg daily.

What signs and symptoms does the patient have that are suggestive of stroke?

What nonmodifiable and modifiable risk factors does he have for acute ischemic stroke?

▶ *Dyslipidemia*

Clinical studies have found a relationship between total cholesterol levels and stroke rate. Statin use, in addition to lifestyle modifications, is recommended for primary prevention of ischemic stroke in patients estimated to have a high 10-year risk of cardiovascular events.[8] Treatment recommendations are based on current guidelines for treatment of blood cholesterol.[10] The benefit of other lipid-lowering therapies on stroke risk has not been established.[8]

▶ *Hypertension*

Hypertension is the most important and well-documented risk factor for stroke. Lowering BP in hypertensive patients reduces the relative risk of both ischemic and hemorrhagic stroke. All patients should have BP monitored and controlled appropriately based on current guidelines for BP management.[9] In patients without cardiovascular disease (CVD), treatment with BP-lowering medications is recommended in patients with an estimated 10-year atherosclerotic CVD (ASCVD) risk of 10% or greater and systolic blood pressure (SBP) greater than or equal to 130 mm Hg or diastolic blood pressure (DBP) greater than or equal to 80 mm Hg, or in those patients with an estimated 10-year ASCVD risk less than 10% and an SBP greater than or equal to 140 mm Hg or a DBP greater than or equal to 90 mm Hg.[9] A meta-analysis of multiple trials found that more intensive BP lowering reduced the risk of stroke by 20% over a less-intensive BP-lowering strategy.[11] Many patients require two or more drug therapies to achieve BP control. For primary prevention of stroke, reduction in BP is the main goal because one antihypertensive agent has not been clearly shown to be more beneficial than any other. Refer to Chapter 6, "Hypertension."

▶ *Smoking Cessation*

The relationship between smoking and both ischemic and hemorrhagic stroke is clear. Smoking status should be assessed at every patient visit. Patients should be assisted and encouraged in smoking cessation as stroke risk declines over time after cessation. Effective treatment options are available including counseling, nicotine replacement products, and oral agents.

▶ *Other Treatments*

A number of other disease states and lifestyle factors should be addressed as primary prevention of stroke. AF is an important and well-documented risk for stroke. See Chapter 10, "Arrhythmias," for information on stroke prevention in AF. Asymptomatic carotid stenosis, cardiac disease, sickle cell disease, obesity, excessive alcohol use, and physical inactivity are other risks that should be assessed and managed appropriately.

TREATMENT

Desired Outcomes

Short-term treatment goals for acute ischemic stroke include reducing secondary brain damage by reestablishing and maintaining adequate perfusion to marginally ischemic areas of the brain and protecting these areas from the effects of ischemia (ie, neuroprotection). **KEY CONCEPT** Long-term treatment goals for acute ischemic stroke include prevention of a recurrent stroke through reduction and modification of risk factors and by use of appropriate treatments.

Short-term treatment goals for hemorrhagic stroke include rapid neurointensive care to maintain adequate oxygenation, breathing, and circulation. Management of increased ICP and BP are important in the acute setting. Long-term management includes prevention of complications and of a recurrent bleed and delayed cerebral ischemia. Prevention of long-term disability and death related to stroke is important regardless of stroke type.

General Approach

KEY CONCEPT All patients should have a brain CT or MRI scan to differentiate an ischemic stroke from a hemorrhagic stroke because treatment differs, and fibrinolytic therapy must be avoided until hemorrhagic stroke is ruled out. A noncontrast CT or MRI scan is the most important initial diagnostic test in patients with acute stroke. For those with an ischemic stroke, an evaluation should be done to determine the appropriateness of reperfusion therapy. In hemorrhagic stroke, a surgical evaluation should be completed to assess the need for surgical clipping of an aneurysm or other procedure to control the bleeding and prevent rebleeding and other complications. Figure 12–1 provides an algorithm for initial management of the acute stroke patient.

Early Management of Acute Ischemic Stroke

Acute ischemic stroke is a medical emergency. Identification of the time of symptom onset and symptom presentation are important determinants in treatment. The time the patient was last without symptoms is used as the time of stroke onset. Because patients typically do not experience pain, determining the onset time can be difficult. It is also important to document risk factors, previous functional status, and the National Institutes of Health Stroke Scale (NIHSS) to assess stroke severity and current disability due to stroke. The NIHSS is a 42-point scale that quantifies neurological deficits in stroke patients. It is easy to perform and is used as a measure of daily functioning.

▶ *Supportive Measures*

Acute complications of ischemic stroke include cerebral edema, increased ICP, seizures, and hemorrhagic conversion (ie, conversion of ischemic stroke into hemorrhagic stroke). In the acute setting, supportive interventions and treatments to prevent acute complications should be initiated. Continuous cardiac monitoring, most commonly with a Holter monitor, should be continued for the first 24 hours to screen for AF and other cardiac diseases.[12] Tissue oxygenation should be maintained acutely. Measure oxygen saturation using pulse oximetry and supplement the patient with oxygen if necessary. Oxygen saturation should be maintained at 94% (0.94) or greater.[12] Volume status and electrolytes should be corrected. If required, blood glucose should be corrected because both hyperglycemia and hypoglycemia may worsen brain ischemia. When blood glucose less than 60 mg/dL (3.3 mmol/L) is present, bolus with 25 mL of 50% dextrose immediately. Patients with elevated blood glucose poststroke have been documented to have worse outcomes; therefore, lowering blood glucose to between 140 and 180 mg/dL (7.8–10.0 mmol/L) with subcutaneous insulin is a reasonable approach.[12,13] If the patient is febrile, treat with acetaminophen because fever is associated with brain ischemia and increased morbidity and mortality after stroke. Alternatively, cooling devices can be used.[12] Low-dose unfractionated heparin (UFH) or low-dose low-molecular-weight heparin (LMWH) administered subcutaneously significantly decreases the risk of developing venous thromboembolism (VTE) poststroke. Low-dose UFH or LMWH should be initiated for VTE prophylaxis in patients who are not candidates for intravenous (IV) fibrinolytic therapy. In patients receiving fibrinolytic therapy, VTE prophylaxis with low-dose UFH or LMWH should be delayed until 24 hours after fibrinolytic administration to avoid bleeding complications.

In the setting of acute ischemic stroke, up to 80% of patients have an elevated BP in the first 24 to 48 hours.[9,12] BP should be checked three times with each reading taken 5 minutes apart. BP should be optimized; however, hypertension should generally not be treated in the acute period (12–24 hours) because it may cause decreased blood flow in ischemic areas, potentially increasing the infarction size. The cautious use of antihypertensive medications may be necessary in patients with severely elevated BP (SBP > 220 mm Hg or DBP > 120 mm Hg) who are otherwise candidates for fibrinolytic therapy or endovascular therapy. Antihypertensive therapy may also be necessary

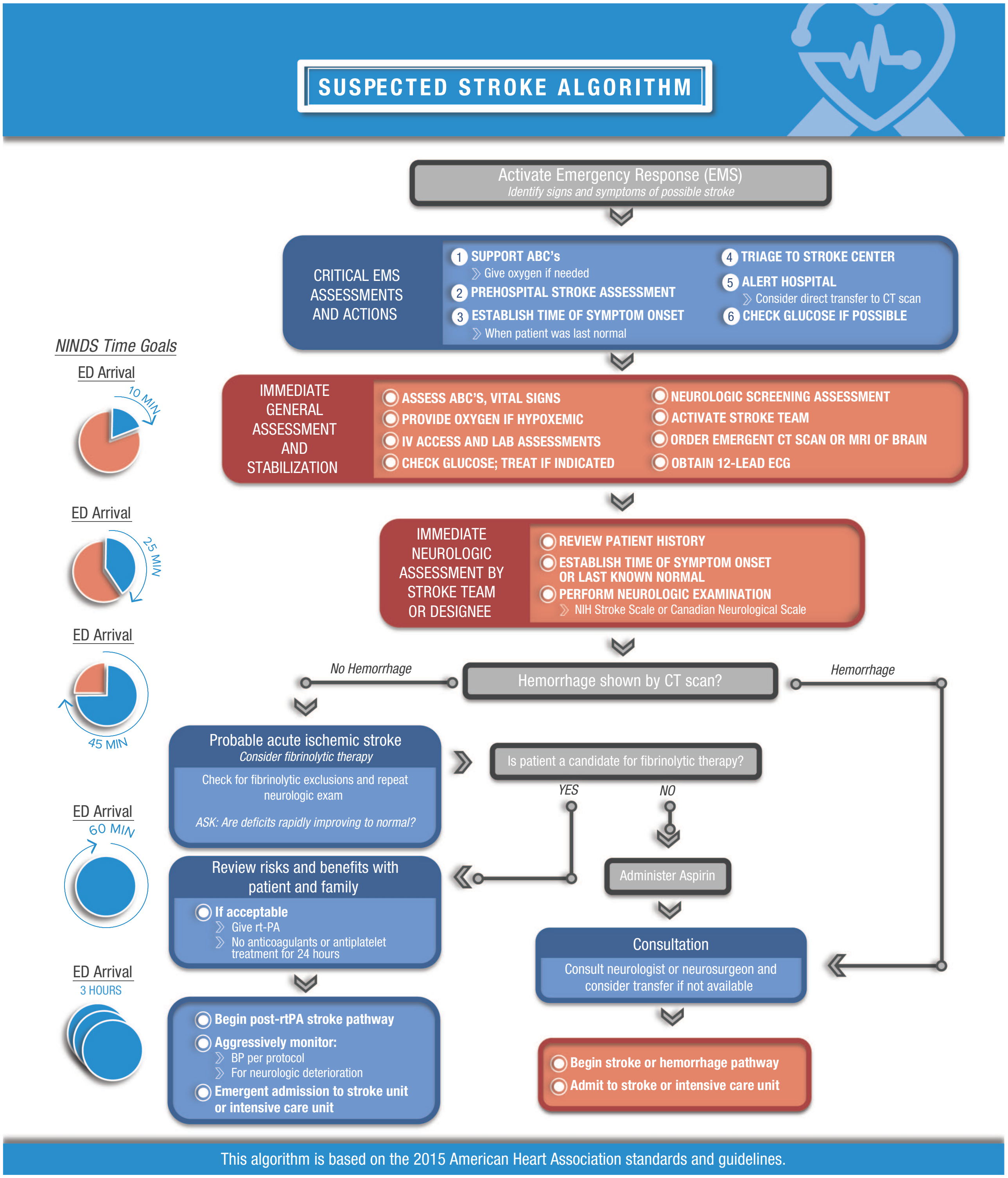
SUSPECTED STROKE ALGORITHM
Activate Emergency Response (EMS)
Identify signs and symptoms of possible stroke
CRITICAL EMS ASSESSMENTS AND ACTIONS
1 SUPPORT ABC's
Give oxygen if needed
2 PREHOSPITAL STROKE ASSESSMENT
3 ESTABLISH TIME OF SYMPTOM ONSET
When patient was last normal
4 TRIAGE TO STROKE CENTER
5 ALERT HOSPITAL
Consider direct transfer to CT scan
6 CHECK GLUCOSE IF POSSIBLE
NINDS Time Goals
ED Arrival
10 MIN
IMMEDIATE GENERAL ASSESSMENT AND STABILIZATION
ASSESS ABC'S, VITAL SIGNS
PROVIDE OXYGEN IF HYPOXEMIC
IV ACCESS AND LAB ASSESSMENTS
CHECK GLUCOSE; TREAT IF INDICATED
NEUROLOGIC SCREENING ASSESSMENT
ACTIVATE STROKE TEAM
ORDER EMERGENT CT SCAN OR MRI OF BRAIN
OBTAIN 12-LEAD ECG
ED Arrival
25 MIN
IMMEDIATE NEUROLOGIC ASSESSMENT BY STROKE TEAM OR DESIGNEE
REVIEW PATIENT HISTORY
ESTABLISH TIME OF SYMPTOM ONSET OR LAST KNOWN NORMAL
PERFORM NEUROLOGIC EXAMINATION
NIH Stroke Scale or Canadian Neurological Scale
ED Arrival
45 MIN
No Hemorrhage
Hemorrhage shown by CT scan?
Hemorrhage
Probable acute ischemic stroke
Consider fibrinolytic therapy
Check for fibrinolytic exclusions and repeat neurologic exam
ASK: Are deficits rapidly improving to normal?
Is patient a candidate for fibrinolytic therapy?
YES
NO
ED Arrival
60 MIN
Review risks and benefits with patient and family
If acceptable
Give rt-PA
No anticoagulants or antiplatelet treatment for 24 hours
Administer Aspirin
ED Arrival
3 HOURS
Consultation
Consult neurologist or neurosurgeon and consider transfer if not available
Begin post-rtPA stroke pathway
Aggressively monitor:
BP per protocol
For neurologic deterioration
Emergent admission to stroke unit or intensive care unit
Begin stroke or hemorrhage pathway
Admit to stroke or intensive care unit
This algorithm is based on the 2015 American Heart Association standards and guidelines.

FIGURE 12–1. Suspected stroke treatment algorithm. (ABC, airway, breathing, and circulation; BP, blood pressure; CT, computed tomography; ECG, electrocardiogram; ED, emergency department; EMS, emergency medical services; IV, intravenous; MRI, magnetic resonance imaging; NIH, National Institutes of Health; NINDS, National Institute of Neurological Disorders and Stroke; rt-PA, alteplase.) (Reproduced with permission from Professional Medical Certifications. Suspected Stroke Algorithm. © 2018 Professional Medical Certifications. Available at https://promedcert.com/acls-algorithms/algorithm-acls-suspected-stroke.)

in patients with stroke and other medical disorders, including aortic aneurysm rupture, MI, and heart failure, that require immediate lowering of BP. Tables 12–2 and 12–3 provide recommendations on BP management in those eligible and not eligible for fibrinolytic therapy. These recommendations apply to patients being evaluated for endovascular therapy as well as similar BP guidelines have been utilized in these patients.[12] In those not eligible for fibrinolytic or endovascular therapy, if BP reduction is necessary, aim for a 15% reduction in SBP and DBP in the first 24 hours after stroke onset.

Table 12–2

Blood Pressure (BP) Recommendations for Ischemic Stroke (Eligible for Reperfusion Therapy)

Before treatment: If systolic BP > 185 mm Hg or diastolic BP > 110 mm Hg	Use either labetalol 10–20 mg IV over 1–2 minutes (may repeat once after 10 minutes) or nicardipine 5 mg/hour IV (titrate up by 2.5 mg/hour every 5–15 minutes; maximum dose 15 mg/hour) or clevidipine 1–2 mg/hour IV (titrate by doubling the dose every 2–5 minutes; maximum dose 21 mg/hour) or may consider other agents (hydralazine, enalaprilat)
During and after treatment to maintain BP ≤ 180/105 mm Hg:	
• If systolic BP > 180–230 mm Hg or diastolic BP > 105–120 mm Hg	Use either labetalol 10 mg IV over 1–2 minutes followed by labetalol continuous IV infusion 2–8 mg/min or nicardipine 5 mg/hour IV (titrate up by 2.5 mg/hour every 5–15 minutes; maximum dose 15 mg/hour) or clevidipine 1–2 mg/hour IV (titrate by doubling the dose every 2–5 minutes; maximum dose 21 mg/hour)
• If BP not controlled or diastolic BP > 140 mm Hg	Nitroprusside 0.3–0.5 mcg/kg/min titrated by 0.5 mcg/kg/min to response; maximum dose 10 mcg/kg/min

IV, intravenous.

▸ *Fibrinolytic Therapy*

Alteplase American Stroke Association guidelines recommend alteplase (rt-PA; Activase) as first-line acute treatment for ischemic stroke and strongly encourage early diagnosis and treatment of appropriate patients.[12] Alteplase is an IV fibrinolytic approved for acute ischemic stroke treatment within 3 hours of symptom onset based on the results of the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Trial.[14] Patients treated with alteplase were 30% more likely to have minimal or no disability at 3 months. ICH within 36 hours after stroke onset occurred in 6.4% of those given alteplase versus 0.6% in those given placebo. There was no significant difference in mortality between the two groups at 3 months or 1 year. A dose of 0.9 mg/kg (maximum 90 mg) is recommended; the first 10% is given as an IV bolus, and the remainder is infused over 1 hour.

Subsequent studies that followed the NINDS trial protocol have supported alteplase use in acute ischemic stroke with similar rates for response and ICH occurrence when administered up to 4.5 hours after stroke onset. Current clinical guidelines support this recommendation.[12] Pooled data analyses have found that alteplase provides a beneficial effect on stroke outcomes measured at 3 to 6 months independent of patient age and stroke severity with better neurological outcomes obtained the sooner alteplase is given after stroke symptom onset.[12,15,16] Additional exclusion criteria were initially utilized when alteplase was administered between 3 and 4.5 hours after symptom onset including age greater than 80, use of oral anticoagulants regardless of international normalized ratio (INR), NIHSS greater than 25, and the combination of stroke and diabetes. A scientific advisory from the American Heart Association/American Stroke Association has provided guidance on inclusion and exclusion criteria for alteplase based on clinical trial data and provides levels of evidence for each criteria.[17] This advisory and current guidelines recommend that alteplase may be given 3 to 4.5 hours after symptom onset in patients regardless of age, in those on warfarin with an INR less than or equal to 1.7, in mild disabling stroke, and in those with diabetes and stroke.[12,17] **KEY CONCEPT** Current guidelines recommend alteplase use within 4.5 hours after stroke onset in selected patients regardless of age to improve stroke outcomes. The guidelines recommend that alteplase be started as soon as possible within this window of time and recommend that centers establish internal treatment goals.[12] Alteplase is commonly withheld in patients with minor or rapidly improving stroke symptoms and in patients with stroke symptoms upon awakening. A recent cohort analysis found the risk of stroke to be 9.5% at 5 years after a TIA or mild stroke.[18] An observational study demonstrated a benefit to alteplase treatment in minor stroke.[19] However, a clinical trial comparing aspirin or alteplase within 3 hours of stroke symptom onset for acute, nondisabling stroke found no difference in outcome at 90 days.[20] This study was stopped early due to low recruitment, so while suggestive, these results are not conclusive. Further research is underway to determine a definitive recommendation for minor stroke.[21] Alteplase is currently contraindicated in minor, nondisabling stroke.[12]

Trials have evaluated patients with unknown onset of stroke, but who are greater than 4.5 hours after last known to be well or symptoms upon awakening.[22,23] These trials used specific enrollment criteria based on imaging and compared alteplase to placebo between 4.5 and 9 hours from the time last known to be well.

Table 12–3

Blood Pressure (BP) Recommendations for Ischemic Stroke (Not Eligible for Reperfusion Therapy)

Systolic BP < 220 mm Hg and diastolic BP < 120 mm Hg	Observe unless other end-organ involvement
Systolic BP ≥ 220 mm Hg or diastolic BP 121–140 mm Hg	Labetalol 10–20 mg IV over 1–2 minutes (may repeat every 10–20 minutes; maximum dose 300 mg) or nicardipine IV 5 mg/hour (titrate up by 2.5 mg/hour every 5–15 minutes; maximum dose 15 mg/hour; titrate to response) or clevidipine 1–2 mg/hour IV (titrate by doubling the dose every 2–5 minutes; maximum dose 21 mg/hour; titrate to response)
Diastolic BP > 140 mm Hg	Nitroprusside 0.3–0.5 mcg/kg/min titrated by 0.5 mcg/kg/min to response; maximum dose 10 mcg/kg/min

IV, intravenous.

Table 12–4

Inclusion and Exclusion Criteria for Alteplase (rt-PA) Use in Acute Ischemic Stroke

Inclusion Criteria
- 18 years of age or older
- Clinical diagnosis of ischemic stroke causing a measurable neurological deficit
- Time of symptom onset well established to be < 4.5 hours before treatment would begin

Exclusion Criteria
- Nondisabling mild stroke (NIHSS 0–5)
- Evidence of multilobar infarction on CT scan of the brain (> 1/3 cerebral hemisphere) prior to treatment
- Clinical presentation suggestive of SAH even with a normal head CT or intracranial hemorrhage on imaging
- Active internal bleeding
- Known bleeding diathesis, including but not limited to (a) platelet count less than $100 \times 10^3/\text{mm}^3$ (100×10^9/L); (b) full-dose heparin within 24 hours with an elevated aPTT (> 40 seconds); or (c) current oral anticoagulant use (eg, warfarin) or recent use with an elevated PT (> 15 seconds) or INR (> 1.7)
- Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
- Blood glucose concentration < 50 mg/dL (2.8 mmol/L)
- Intracranial or intraspinal surgery, significant head trauma, or previous stroke within 3 months
- Previous intracranial hemorrhage
- Intracranial neoplasm
- GI malignancy
- Clinical presentation suggestive of infective endocarditis or aortic arch dissection
- Gastrointestinal hemorrhage within previous 21 days
- SBP > 185 mm Hg or DBP > 110 mm Hg at time of treatment, or patient requires aggressive treatment to reduce BP to within these limits
- Ischemic stroke or severe head trauma within 3 months

Relative Exclusion Criteria
- Consider risk to benefit of IV rt-PA if any relative contraindications are present:
  - Pregnancy
  - Major surgery or serious trauma within 14 days
  - Recent arterial puncture at a noncompressible site in previous 7 days
  - Lumbar puncture within 7 days
  - Known unruptured AVM or aneurysm
  - Urinary tract bleeding
  - Acute MI or MI within 3 months
  - Witnessed seizure at onset of stroke symptoms with postictal residual neurological impairments

Additional Criteria for Treatment Between 3 and 4.5 Hours
- Benefit uncertain in severe strokes (NIHSS ≥ 25)

aPTT, activated partial thromboplastin time; AVM, arteriovenous malformation; BP, blood pressure; CT, computed tomography; DBP, diastolic blood pressure; ECT, ecarin clotting time; GI, gastrointestinal; INR, international normalized ratio; IV, intravenous; MI, myocardial infarction; NIHSS, National Institute of Health Stroke Scale; PT, prothrombin time; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure; TT, thrombin time.

In patients meeting the enrollment criteria, alteplase may be an option in this timeframe if thrombectomy is not available. Table 12–4 details the inclusion and exclusion criteria for administration of alteplase in acute ischemic stroke.

Efficacy is measured by elimination of existing neurological deficits and long-term improvement in neurological status and functioning based on neurological examinations and other outcome measures. BP measurements and neurological examinations should be completed every 15 minutes during and after the infusion of alteplase for 2 hours, every 30 minutes for the next 6 hours, and then every hour until 24 hours after alteplase administration. Patients should be assessed using the NIHSS at baseline and 24 hours after the administration of alteplase.

The major adverse effects of fibrinolytic therapy are bleeding, including ICH and serious systemic bleeding. Mental status changes and a severe headache may indicate ICH. Signs of systemic bleeding include easy bruising; hematemesis; guaiac-positive stools; black, tarry stools; hematoma formation; hematuria; bleeding gums; and nosebleeds. Angioedema is a potential side effect that may cause airway obstruction.

Antiplatelet agents, anticoagulants, and invasive procedures such as insertion of a central line, placement of a nasogastric tube, and bladder catheterization should be avoided for 24 hours after infusion of alteplase to prevent bleeding complications. A CT scan should be obtained 24 hours after IV infusion of alteplase before initiating anticoagulants or antiplatelet agents.

Other Fibrinolytics Tenecteplase is a thrombolytic having more fibrin-specificity and a longer half-life than alteplase. It is administered as a single IV push injection due to these properties. Clinical trials that have been completed evaluating tenecteplase for acute ischemic stroke have compared different dosages and administration times. A meta-analysis of completed trials revealed no difference in outcome at 90 days between tenecteplase and alteplase.[24] The acute stroke guidelines state that tenecteplase 0.4 mg/kg IV bolus may be considered in patients with minor neurological impairment and no major intracranial occlusion.[12] Tenecteplase 0.25 mg/kg (maximum 25 mg) IV bolus may also be useful in place of alteplase in patients without contraindications to thrombolytics eligible for thrombectomy.[12] Fibrinolytic agents, other than alteplase and tenecteplase, and the defibrinogenating

Patient Encounter Part 2

In the emergency department, an IV line is placed, a physical and neurological examination is completed, and the patient is moved to the stroke unit. A head noncontrast CT scan is negative for hemorrhagic stroke and reveals a diffuse hypodensity on the left. The patient's BP on admission to the stroke unit is 188/112 mm Hg, glucose is 138 mg/dL (7.7 mmol/L), temperature is 37.1°C (98.8°F), and NIHSS score is 12. The patient denies other exclusions to IV alteplase. The neurologist is evaluating him for alteplase administration and endovascular therapy.

Identify acute treatment goals for the patient.

Is he a candidate for IV alteplase at this time?

What acute management would be appropriate for the patient in the stroke unit?

agents are not recommended for treatment unless associated with a clinical trial.[12]

Intra-arterial Fibrinolytics Early clinical trials evaluating intra-arterial (IA) fibrinolytics evaluated pro-urokinase (r-pro UK). A statistically significant benefit with treatment was found in one trial.[25] Pro-urokinase is not Food and Drug Administration (FDA)-approved for acute stroke treatment and is not available in the United States. Since embolectomy devices have advanced and are now the preferred endovascular therapy, the use of IA fibrinolytics without endovascular therapy is not recommended as first-line therapy in patients with acute ischemic stroke.[12]

▶ *Heparin*

Full-dose IV UFH has been previously used in acute stroke therapy; however, no adequately designed trials have been conducted to establish its efficacy and safety. Current acute ischemic stroke treatment guidelines do not recommend routine, urgent full-dose anticoagulation with UFH due to lack of a proven benefit in improving neurological function and the risk of intracranial bleeding.[12,26] The major complications of heparin include conversion of ischemic stroke into hemorrhagic stroke, bleeding, and thrombocytopenia. Occurrence of severe headache and mental status changes may indicate ICH. Signs of bleeding mirror those listed for alteplase therapy.

▶ *LMWHs and Heparinoids*

Full-dose LMWHs and heparinoids are not recommended in the treatment of acute ischemic stroke.[12,27] Studies with these agents have generally been negative, with no convincing evidence of improved outcomes after ischemic stroke. Increased risks of bleeding complications and hemorrhagic transformation have been observed.

▶ *Thrombin Inhibitors*

Several thrombin inhibitors have been approved for stroke prevention in patients with AF and may have a potential benefit in acute stroke treatment. Currently, use of these agents in acute stroke treatment is not well established, and it is recommended that their use be in conjunction with a clinical trial.[12] A clinical trial evaluated the use of dabigatran within 24 hours of stroke onset to prevent early stroke recurrence in patients without AF.[28] Argatroban was evaluated in patients receiving alteplase administered as a bolus within 1 hour of alteplase administration followed by an infusion for 48 hours. The study found an increased likelihood of a good outcome at 90 days.[29] Further clinical trials are needed to establish the role of these agents in the acute setting.

▶ *Antiplatelet Agents*

ASA use in acute ischemic stroke has been studied in two large randomized trials. Patients who received ASA within 48 hours of onset of acute ischemic stroke symptoms were less likely to suffer early recurrent stroke, death, and disability. **KEY CONCEPT** ASA therapy with an initial dose of 160 to 325 mg is recommended in most patients with acute ischemic stroke within 24 to 48 hours after stroke symptom onset. ASA dose may then be decreased to 75 to 100 mg daily to reduce bleeding complications. Administration should not replace other acute stroke treatments and should be delayed for 24 hours in patients receiving alteplase or tenecteplase. In minor stroke or TIA, ASA plus clopidogrel has been compared to ASA alone started within 24 hours of stroke onset in two large clinical trials.[30,31] A meta-analysis of these trials found that in patients with minor stroke or TIA, aspirin plus clopidogrel started within 24 hours of symptom onset and continued for 21 days reduced the risk of subsequent stroke.[32] The risk of moderate-to-severe bleeding is mitigated by discontinuing dual antiplatelet therapy at 21 days. The current stroke guidelines incorporated this treatment as a new recommendation.[12]

▶ *Nonpharmacologic Therapy*

Carotid Endarterectomy It is not well established whether carotid endarterectomy (CEA; removal of a thrombus from the carotid artery) is of value when performed emergently or urgently after stroke, meaning within the first 24 hours after symptom onset.[12] Trials have concluded that patients with TIA or mild-to-moderate stable stroke undergoing CEA within 48 hours may have an acceptable surgical risk. However, patients with unstable neurological status and more severe strokes demonstrated worse outcomes.[12,33] More research is needed to delineate the role of CEA in acute treatment.

Endovascular Treatment The current stroke guidelines include updated information and recommendations for endovascular treatment based on the results of clinical trials.[12] Clinical trials initially evaluated endovascular therapy with new-generation stent retrievers in patients meeting specific criteria within 6 hours of symptom onset. A meta-analysis of five clinical trials has demonstrated an improved outcome at 90 days in patients who received endovascular therapy compared to those not receiving endovascular therapy.[34] The majority of patients in these trials received IV alteplase initially followed by endovascular therapy. IV alteplase should not be withheld if indicated, even if endovascular treatments are being considered. Stent retrievers provide immediate restoration of blood flow through expansion of the stent at the site of occlusion and clot removal as the stent is removed. Criteria include a prestroke modified Rankin score of 0 to 1, IV alteplase use within 4.5 hours of symptom onset, age 18 years and older, causative occlusion of the internal carotid artery or proximal middle cerebral artery, NIHSS score of 6 or greater, Alberta Stroke Program Early CT (ASPECT) score 6 or greater, and treatment within 6 hours of symptom onset. Endovascular therapy using stent retrievers

Patient Encounter Part 3

The patient has received two doses of IV labetalol 20 mg over 1 to 2 minutes in the stroke unit. It is now 3.5 hours since his symptoms began. He is still experiencing weakness in his right arm and leg and continues to have facial drooping and dysarthria. His current BP in the stroke unit is 176/104 mm Hg. The neurologist has also requested additional diagnostic testing including a CT angiogram to assess whether he is a candidate for endovascular therapy. The CT angiogram reveals blockage in the first segment of the middle cerebral artery.

Is he a candidate for IV alteplase at this time? If so, what is the correct dosing for this patient?

Is he a candidate for endovascular therapy at this time?

plus standard care with IV alteplase, when appropriate, may improve outcomes in select patients with acute ischemic stroke due to large vessel occlusion, if administered within 6 hours of symptom onset. More rapid endovascular treatment has also shown better clinical outcomes.[12,34]

Subsequent to these initial trials, clinical trials have evaluated endovascular therapy implemented beyond 6 hours after stroke onset and in those patients with mild stroke.[35-37] In both trials comparing endovascular therapy more than 6 hours after symptom onset plus alteplase compared to alteplase alone, those receiving endovascular therapy had a higher rate of functional independence versus the alteplase only groups. Both of these trials found no significant difference in the rate of symptomatic ICH.[35,36] The decision regarding treatment in patients with large vessel occlusion and mild stroke based on NIHSS score and stroke symptoms has been difficult, as no consensus exists for this scenario. A meta-analysis evaluating five trials meeting criteria has been completed.[37] Results demonstrated that in patients with large vessel occlusion and NIHSS score less than or equal to 5, those patients who received either thrombectomy or IV alteplase experienced a higher rate of good and excellent outcomes at 90 days. These data suggest patients with minor stroke may benefit from treatment with endovascular therapy and that it may be a useful treatment in patients not eligible for IV alteplase. The stroke guidelines suggest that it is reasonable to maintain BP less than 180/105 mm Hg during and for 24 hours after endovascular therapy.[12]

Secondary Prevention Following an Ischemic Stroke

Secondary prevention is aimed at preventing another stroke in patients that have had an initial stroke and is an important component of treatment. Once the acute ischemic stroke has been managed, typically within the first 24 to 48 hours after symptom onset, the focus shifts to secondary prevention and developing plans to prevent another stroke and manage risk factors. Antiplatelet and anticoagulant agents should be held for 24 hours following alteplase administration.

▶ *Nonpharmacologic Therapy*

Carotid Endarterectomy The benefit of CEA for prevention of recurrent stroke in specific patients has been established.[38] CEA is recommended to prevent ipsilateral stroke in patients with symptomatic carotid artery stenosis of 70% or greater when the surgical risk is less than 6%. In patients with symptomatic stenosis of 50% to 69%, a moderate reduction in risk is seen in clinical trials. CEA is recommended when anesthesia risk is low based on patient factors including age, sex, and comorbidities, and surgical risk is less than 6%. CEA is not beneficial for symptomatic carotid stenosis less than 50% and should not be considered in these patients. Patients with asymptomatic carotid artery stenosis of 60% to 99% may benefit from CEA if surgical complication rates for stroke, MI, and death are less than 3%, and the patient has a life expectancy greater than 5 years. CEA is recommended within 14 days of the initial stroke.[39]

Carotid Artery Stenting Carotid artery stenting (CAS) has evolved as a less invasive procedure with shorter recovery times for appropriate patients. CAS is an alternative to CEA in high-risk surgical candidates with greater than 50% symptomatic carotid stenosis when performed by skilled clinicians with a surgical risk less than 6%.[39] Age is an important factor when deciding between CAS and CEA. Patients older than 70 years may have improved outcomes with CEA. In patients younger than 70 years, CEA and CAS have similar risks for stroke, MI, death, and ipsilateral stroke.[39] In asymptomatic patients with 60% to 99% stenosis, CAS may be considered when the surgical risk is less than 3%, and the patient's life expectancy exceeds 5 years.[39]

▶ *Pharmacologic Therapy*

Aspirin ASA is an option for initial therapy for secondary prevention of ischemic stroke due to its established efficacy. A wide range of doses have been used (50–1500 mg/day); however, current guidelines recommend an ASA dose of 50 to 325 mg daily as monotherapy.[40] Lower ASA doses are currently recommended to decrease the risk of bleeding complications.[40] Adverse effects of ASA include gastrointestinal (GI) intolerance, GI bleeding, and hypersensitivity reactions.

Clopidogrel Clopidogrel is slightly more effective than ASA and similar in efficacy to the combination of extended-release (ER) dipyridamole plus ASA.[41] Usual dose is 75 mg orally taken once daily. There have been 11 case reports of thrombotic thrombocytopenic purpura (TTP) occurring secondary to clopidogrel. Most occurred within the first 2 weeks of therapy; therefore, clinicians should be aware of the potential for development of TTP with clopidogrel. Proton pump inhibitors may decrease the effectiveness of clopidogrel. An H_2-blocker may be preferred in patients who require both acid suppression and clopidogrel. A meta-analysis found that patients who are carriers of cytochrome P450 (CYP) *2C19* loss-of-function alleles (*2, *3, and *8) have an increased risk of stroke and vascular events.[42] This results from a decrease in the active metabolite of clopidogrel, potentially requiring increased doses or use of an alternate agent such as ticagrelor. Use of ticagrelor requires further investigation before this could be recommended.[42] Clopidogrel is an option for initial monotherapy for secondary prevention of ischemic stroke and is considered first-line therapy in patients who also have peripheral arterial disease or are allergic to ASA.

Extended-Release Dipyridamole Plus Aspirin Combination therapy with ER dipyridamole plus ASA has been found to be more effective in preventing stroke than either agent alone.[40] Headache and diarrhea were common adverse effects of dipyridamole; bleeding was more common in all treatment groups that included ASA. A trial comparing the combination of ER dipyridamole plus ASA to clopidogrel found no difference in outcomes;

Patient Encounter Part 4

The patient received IV alteplase and mechanical thrombectomy 24 hours ago. He has been in the intensive care unit (ICU) for 24 hours, and the team is planning for transfer to the step-down unit.

What treatments would you recommend to reduce the risk of another stroke in the next 24 to 48 hours?

What treatments would you recommend at discharge to reduce the risk of another stroke?

however, adverse events occurred more frequently in the combination of ER dipyridamole plus ASA group. The currently available formulation is a combination product containing 25-mg ASA and 200-mg ER dipyridamole. This combination is an option for initial therapy for secondary stroke prevention but is not appropriate for patients who are intolerant to ASA.

Current Clinical Trials Clinical trials have been completed to evaluate other combinations of antiplatelet agents and to compare them against one another. Low-dose ASA plus clopidogrel combination therapy did not show a significant benefit in reducing recurrent stroke compared with either clopidogrel alone or aspirin alone. An increased risk of major bleeding was observed.[43,44] Trials have evaluated early initiation (within 24 hours) of the combination of ASA and clopidogrel and its effect in the months following a TIA or minor stroke.[30,31] In patients with minor stroke or TIA, combination therapy reduced the risk of recurrent stroke or TIA. Continuation beyond 21 days is not recommended due to an increased risk of hemorrhage and lack of benefits. Initiating this combination days to years after a minor stroke or TIA is also not recommended due to an increased bleeding risk.

Summary of Antiplatelet Therapy for Secondary Stroke Prevention KEY CONCEPT Current stroke treatment guidelines recommend ASA or combination therapy with ER dipyridamole plus ASA as initial antiplatelet therapy for the secondary prevention of stroke. Clopidogrel is another option for initial treatment and is recommended in patients unable to tolerate ASA and those with peripheral arterial disease.[40] Initial choice of agent should be individualized based on patient factors and cost. Therapeutic failure in this patient population is challenging because no data are available to guide a treatment decision. When a patient is on therapeutic doses of ASA, yet experiences a recurrent TIA or stroke, switching to either clopidogrel or the combination of ER dipyridamole and ASA is a reasonable option. If failure occurs on either clopidogrel or the combination of ASA and ER dipyridamole, switching to the alternate drug may be appropriate.

Oral Anticoagulants Recent clinical trials have not found oral anticoagulation to be better than antiplatelet therapy in those patients without AF or carotid stenosis. In patients without AF, antiplatelet therapy is recommended over oral anticoagulants for secondary prevention of stroke. On the other hand, patients with AF and a previous TIA or stroke have the highest risk of recurrent stroke. Long-term anticoagulation with warfarin or other newer agents is effective and therefore recommended in the primary and secondary prevention of cardioembolic stroke.[40] The newer oral anticoagulants have only been studied for stroke prevention in nonvalvular AF. The goal INR when monitoring warfarin for this indication is 2 to 3. Refer to Chapter 10, "Arrhythmias," for more information on stroke prevention in AF.

▶ *Blood Pressure Management*

Hypertension is a major risk factor for stroke, and BP control is an important strategy for secondary stroke prevention. Current stroke guidelines and the 2017 hypertension guidelines recommend initiation of antihypertensive treatment for untreated patients with TIA or stroke and an established BP of 140/90 mm Hg or greater. Patients previously treated with antihypertensives should be reinitiated on therapy several days after acute ischemic stroke. The optimal regimen to achieve the BP goal has not been established. Diuretics, either alone or in combination with an ACE-I, have been shown to be beneficial in reducing stroke recurrence.[9,40]

▶ *Other Recommendations*

Management of diabetes and lipids based on treatment guidelines, cessation of smoking, increased physical activity, and reducing alcohol use in heavy drinkers are additional recommendations for management of patients with previous stroke or TIA.[40] Statin therapy is recommended in patients with previous stroke or TIA, regardless of history of coronary heart disease. Table 12–5 provides drug and dosing recommendations for treatment of ischemic stroke.

Treatment of Acute Hemorrhagic Stroke

▶ *Supportive Measures*

Acute hemorrhagic stroke is considered to be a medical emergency due to ICH, SAH, or subdural hematoma. Initially, patients experiencing a hemorrhagic stroke should be transported to a neurointensive care unit. KEY CONCEPT There is no proven treatment for ICH. Management is based on neurointensive care treatment and prevention of complications. Treatment should be provided to manage the needs of the critically ill patient including management of increased ICP, seizures, infections, and prevention of rebleeding and delayed cerebral ischemia in patients with SAH. In those with severely depressed consciousness, rapid endotracheal intubation and mechanical ventilation may be necessary. BP is often elevated after hemorrhagic stroke; appropriate management is important to prevent rebleeding and expansion of the hematoma. In patients presenting with SBP greater than 220 mm Hg, BP lowering using continuous IV infusion is recommended.[9,45] When SBP is between 150 and 220 mm Hg, lowering of the SBP to less than 140 mm Hg does not improve outcomes and may cause harm compared to a less aggressive BP-lowering goal in the acute period.[9,46] BP can be controlled with IV boluses of labetalol 10 to 80 mg every 10 minutes up to a maximum of 300 mg or with IV infusions of labetalol (0.5–2 mg/min) or nicardipine (5–15 mg/hour). Deep vein thrombosis prophylaxis with intermittent compression stockings should be implemented early after admission. In those patients with SAH, once the aneurysm has been treated, heparin may be instituted. In ICH patients with lack of mobility after 1 to 4 days, heparin or LMWH may be started.[45,47]

▶ *Nonpharmacologic Therapy*

Patients with hemorrhagic stroke are evaluated for surgical treatment of SAH and ICH. In SAH, either clipping of the aneurysm or coil embolization is recommended within 72 hours after the initial event to prevent rebleeding. Coil embolization, also called coiling, is a minimally invasive procedure in which

Table 12–5

Recommendations for Pharmacotherapy of Ischemic Stroke

	Primary Agents	Alternatives
Acute treatment	Alteplase 0.9 mg/kg IV (maximum dose 90 mg); 10% as IV bolus, remainder infused over 1 hour in select patients within 4.5 hours of onset	Alteplase (various doses) intra-arterially within 6 hours after onset in select patients
	Tenecteplase 0.25 mg/kg IV bolus (maximum dose 25 mg); may choose over alteplase prior to thrombectomy	
	ASA 160–325 mg started within 48 hours of onset; hold for 24 hours if alteplase or tenecteplase given (may reduce dose to 50–100 mg daily after 48 hours)	If minor stroke or TIA, ASA 75 mg plus clopidogrel 75 mg daily started within 24 hours of onset × 21 days
Secondary prevention (noncardioembolic stroke)	ASA 50–325 mg daily ASA 25 mg + ER dipyridamole 200 mg twice daily	Clopidogrel 75 mg daily
Cardioembolic	Warfarin (INR 2–3) Apixaban 5 mg twice daily; decrease to 2.5 mg twice daily if patient has at least two of the following: age ≥ 80 years, weight ≤ 60 kg (132 lb) or serum creatinine ≥ 1.5 mg/dL (133 μmol/L) Rivaroxaban 20 mg daily with the evening meal; decrease to 15 mg daily with the evening meal if CrCl 15–50 mL/min (0.25–0.83 mL/s)	Edoxaban 60 mg once daily; decrease to 30 mg once daily if CrCl 15–30 mL/min (0.25–0.50 mL/s) Dabigatran 150 mg twice daily; decrease to 75 mg twice daily if CrCl 15–30 mL/min (0.25–0.50 mL/s)
All patients	BP control Statin therapy	

ASA, aspirin; BP, blood pressure; CrCl, creatinine clearance; ER, extended-release; INR, international normalized ratio; IV, intravenous; TIA, transient ischemic attack.

Table 12–6

Monitoring the Stroke Patient

Treatment	Parameter(s)	Monitoring Frequency	Comments
Ischemic Stroke			
All stroke patients	CT scan	Upon arrival	
	Neurological examination		
	BP	Every 5 minutes × 3	
Alteplase	CT scan	24 hours after alteplase infusion	
	BP	Every 15 minutes × 2 hours, every 30 minutes × 6 hours, every 1 hour × 16 hours; then every shift	
	Neurological function	Neurological examination every 15 minutes × 2 hours, every 30 minutes × 6 hours, every 1 hour × 16 hours; NIHSS 24 hours after alteplase infusion and at discharge	
	Bleeding	Clinical signs of bleeding every 2 hours × 24 hours	
ASA	Bleeding	Daily	
	Hb/Hct, platelets[a]		
Clopidogrel	Bleeding	Daily	
	Hb/Hct, platelets[a]		
ASA/ER dipyridamole	Headache, bleeding	Daily	
	Hb/Hct, platelets[a]		
Warfarin	Bleeding, INR, Hb/Hct[a]	INR daily × 3 days; weekly until stable; then monthly	
Oral anticoagulants	Bleeding	Each visit	
	Hb/Hct, renal and liver function	Yearly; if decreased renal function, every 3–6 months	
Hemorrhagic Stroke			
	BP, neurological function, ICP	Every 2 hours in ICU	May require treatments to lower systolic BP to < 180 mm Hg
Nimodipine for SAH	BP, neurological function, fluid status	Every 2 hours in ICU	

[a] Hb/Hct and platelets should be monitored at baseline and every 6 months for ASA, clopidogrel, ASA/ER dipyridamole, and warfarin treatment.

ASA, aspirin; BP, blood pressure; CT, computed tomography; ER, extended-release; Hb, hemoglobin; Hct, hematocrit; ICP, intracranial pressure; ICU, intensive care unit; INR, international normalized ratio; NIHSS, National Institutes of Health Stroke Scale; SAH, subarachnoid hemorrhage.

a platinum coil is threaded into the aneurysm. The flexible coil fills up the space to block blood flow into the aneurysm thereby preventing rebleeding. Surgical removal of the hematoma in patients with ICH is controversial because trials have not consistently shown improved outcomes. Minimally invasive clot removal techniques have been evaluated; however, these procedures are considered investigational because outcomes are not certain. Current guidelines note that surgical treatment of ICH is uncertain and is not recommended except in specific patient situations.[45]

▶ *Pharmacologic Therapy*

Calcium Antagonists Oral nimodipine is recommended in SAH to prevent delayed cerebral ischemia. It is recommended to begin oral nimodipine promptly after the initial event but no later than 96 hours following SAH. Delayed cerebral ischemia occurs 4 to 14 days after the initial aneurysm rupture and is a common cause of neurological deficits and death. Nimodipine 60 mg orally every 4 hours for 21 days following aneurysmal SAH reduces the risk of a poor outcome and delayed cerebral ischemia.

Hemostatic Therapy Current guidelines do not recommend treatment with recombinant factor VIIa due to an uncertain benefit and increased risk of thromboembolic events.[45] Tranexamic acid has been shown to reduce rebleeding in SAH and expansion of the hematoma in ICH. However, improved outcomes have not been established.[48]

OUTCOME EVALUATION

- Measure stroke outcomes based on neurological status and functioning of the patient after the acute event.
- Implement early rehabilitation which can reduce functional impairment after a stroke. Stroke rehabilitation guidelines have been endorsed by the American Heart Association and American Stroke Association. These guidelines recommend that patients receive care in a multidisciplinary setting or stroke unit, receive early assessment using the NIHSS, and that rehabilitation is started as soon as possible after the stroke. Other recommendations include screening for dysphagia (difficulty in swallowing) and aggressive secondary stroke prevention treatments.[49]
- Continued effort has been placed on stroke systems of care and developing mechanisms for more urgent assessment and treatment of suspected stroke.
- Table 12–6 provides monitoring guidelines for the acute stroke patient.

Patient Care Process

Collect Information:

- Assess signs and symptoms including time of symptom onset and time of arrival in the emergency department, obtaining information from patient or family members. Time the patient was last known to be well is used as the stroke onset time.
- Review results of completed prehospital stroke screening tests.
- Review the neurological and physical examination findings, including the NIHSS, evaluating for potential causes of stroke.
- Perform a comprehensive medication history, obtaining information from patient or family members.
- Determine the patient's baseline functional status.
- Determine the patient's risk factors for stroke.

Assess the Information:

- Determine if patient is experiencing an acute ischemic stroke.
- Determine if thrombolytic therapy is indicated based on inclusion and exclusion criteria.
- Review relevant laboratory tests (eg, BP, temperature, glucose, oxygen saturation).
- Assess the patient's weight.
- Review CT or MRI scan results to rule out hemorrhagic stroke.
- Review the results of other diagnostic tests (eg, ECG, Doppler studies).
- Evaluate the inclusion and exclusion criteria for fibrinolytic therapy.
- Evaluate patient for IV and endovascular treatment acutely.

Develop a Care Plan:

- Manage the patient's airway, breathing, and circulation (ABCs) initially in the acute phase of treatment.
- Transfer the patient to a stroke center if available.
- Begin IV alteplase if patient is within 4.5 hours of the onset of symptoms and meets inclusion and exclusion criteria.
- Hold other anticoagulants and antiplatelet agents for 24 hours after the infusion of alteplase.
- Begin antiplatelet therapy to prevent a recurrent stroke.
- Manage patient's stroke risk factors.

Implement the Care Plan:

- If fibrinolytic therapy is indicated, initiate treatment protocol for alteplase administration and follow recommended monitoring plan.
- Develop a plan for long-term management of risk factors to prevent a recurrent stroke.
- Educate the patient on risk factors and lifestyle factors to reduce the risk of stroke recurrence.
- Educate the patient on the importance of adherence to their medication regimen.

Follow-up: Monitor and Evaluate:

- Monitor the patient's BP and neurological status every 15 minutes × 2 hours, every 30 minutes × 6 hours, and then every hour for 24 hours after alteplase infusion.
- Obtain a follow-up CT scan 24 hours after the alteplase infusion.
- Evaluate functional status 24 hours after the alteplase infusion.
- Monitor patient's risk factors poststroke.

Abbreviations Introduced in This Chapter

ABCs	Airway, breathing, and circulation
ACE-I	Angiotensin-converting enzyme inhibitor
ADP	Adenosine diphosphate
AF	Atrial fibrillation
aPTT	Activated partial thromboplastin time
ARB	Angiotensin receptor blocker
ASA	Aspirin
ASCVD	Atherosclerotic cardiovascular disease
ASPECT	Alberta Stroke Program Early CT
AVM	Arteriovenous malformation
BP	Blood pressure
CAS	Carotid artery stent
CCB	Calcium channel blocker
CEA	Carotid endarterectomy
CNS	Central nervous system
CrCl	Creatinine clearance
CT	Computed tomography
CVD	Cardiovascular disease
CYP	Cytochrome P450
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ECT	Ecarin clotting time
ER	Extended-release
FDA	Food and Drug Administration
GI	Gastrointestinal
Hb	Hemoglobin
Hct	Hematocrit
IA	Intra-arterial
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
ICU	Intensive care unit
INR	International normalized ratio
IV	Intravenous
LMWH	Low-molecular-weight heparin
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
PT	Prothrombin time
rt-PA	Alteplase
r-pro UK	Pro-urokinase
SAH	Subarachnoid hemorrhage
SBP	Systolic blood pressure
TIA	Transient ischemic attack
TTP	Thrombotic thrombocytopenic purpura
TT	Thrombin time
UFH	Unfractionated heparin
VTE	Venous thromboembolism

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13

Dyslipidemia

Joel C. Marrs and Matthew D. Kostoff

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Identify the common types of lipid disorders.
2. Identify the statin-benefit groups and intensity of statin therapy according to the American College of Cardiology/American Heart Association.
3. Recommend appropriate therapeutic lifestyle changes (TLC) and pharmacotherapy interventions for dyslipidemia.
4. Determine a patient's atherosclerotic cardiovascular disease risk and corresponding treatment goals according to the National Lipid Association, American Association of Clinical Endocrinologist/American College of Endocrinology, and American Heart Association/American College of Cardiology.
5. Identify patients who are indicated for nonstatin therapy according to the American Heart Association/American College of Cardiology.
6. Describe components of a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for dyslipidemias.
7. Educate patients about the disease state, appropriate TLC, and drug therapy required for effective treatment.

INTRODUCTION

KEY CONCEPT Hypercholesterolemia, or dyslipidemia, plays a major role in atherosclerosis and plaque formation leading to coronary heart disease (CHD) as well as other forms of atherosclerotic cardiovascular disease (ASCVD), such as carotid and peripheral artery disease.[1] CHD is the leading cause of death in adults in the United States and most industrialized nations. It is also the chief cause of premature, permanent disability in the US workforce.

EPIDEMIOLOGY AND ETIOLOGY

It is estimated that 92.8 million US adults have high cholesterol with a value of 200 mg/dL (5.17 mmol/L) or greater.[2] Further, one out of every three US adults has high low-density lipoprotein (LDL) cholesterol ($\geq$ 130 mg/dL [3.36 mmol/L]).[2] Elevated cholesterol values are a major risk factor for development of ASCVD. Annually, approximately 805,000 Americans experience a new heart attack or recurrent event.[2] Lowering cholesterol reduces atherosclerotic progression and mortality from CHD and stroke. Development of CHD is a lifelong process. Except in rare cases of severely elevated serum cholesterol levels, years of poor dietary habits, sedentary lifestyle, and life-habit risk factors (eg, smoking, overweight/obesity) contribute to the development of atherosclerosis.[3,4]

PATHOPHYSIOLOGY

Cholesterol and Lipoprotein Metabolism

Cholesterol, an essential substance manufactured by most cells in the body, is used to maintain cell wall integrity and for the biosynthesis of bile acids and steroid hormones. Cholesterol, triglycerides, and phospholipids circulate in the blood as lipoproteins. The major lipoproteins are chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL, and high-density lipoprotein (HDL). Each lipoprotein has various proteins called apolipoproteins (Apos) embedded on the surface that serve four main purposes: (a) required for assembly and secretion of lipoproteins; (b) serve as major structural components of lipoproteins; (c) act as ligands for binding to receptors on cell surfaces; and (d) can be cofactors for inhibition of enzymes involved in the breakdown of triglycerides from chylomicrons and VLDL.[5]

A measured total cholesterol is the total cholesterol molecules in all these major lipoproteins. The estimated value of LDL cholesterol is found using the Friedewald equation (after fasting for 9–12 hours):

LDL cholesterol (mg/dL) = total cholesterol – (HDL cholesterol + triglycerides/5), when lipids are expressed in units of mg/dL;

or

LDL cholesterol (mmol/L) = total cholesterol – (HDL cholesterol + triglycerides/2.2), when lipids are expressed in units of mmol/L

Where triglycerides/5 or triglycerides/2.2 estimate VLDL cholesterol in units of mg/dL or mmol/L, respectively.

This formula becomes inaccurate if serum triglycerides are greater than 400 mg/dL (4.52 mmol/L), if chylomicrons are present, or the patient has familial dysbetalipoproteinemia. In each of these cases, LDL cholesterol must be directly measured, which can be done for any patient at most laboratoriess.[3] Non-HDL cholesterol is carried by all atherogenic Apos B-containing lipoproteins including VLDL, IDL, and LDL. It is calculated as:

$$\text{Non-HDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol}$$

Non-HDL cholesterol can be determined in a nonfasting state. More recently, some laboratories have transitioned to using the Martin-Hopkins equation to estimate LDL cholesterol instead of the Friedewald equation.[6] The Martin-Hopkins equation is calculated as:

$$\text{LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - \text{triglyceride/adjustable factor}$$

The Martin-Hopkins equation has demonstrated improved estimation of LDL cholesterol compared to the Friedewald equation.

Cholesterol from the diet as well as from bile enters the small intestine and is emulsified by bile salts into micelles (Figure 13–1), which are microscopic particles of digested fat and cholesterol. These micelles interact with the duodenal enterocyte and jejunal enterocyte surfaces, and cholesterol is transported from the micelles into enterocytes by the Niemann-Pick C1 Like 1 (NPC1L1) transporter. Cholesterol within enterocytes is esterified and packaged into chylomicrons along with triglycerides, phospholipids, and Apos, which are then released into the lymphatic circulation. In the lymph and blood, chylomicrons are converted to chylomicron remnants. During this process, referred to as reverse cholesterol transport, chylomicrons also interact with HDL particles (Figure 13–2) and exchange triglyceride and cholesterol content (facilitated by cholesterol ester transfer protein, or CETP), and HDL particles acquire Apos A and C. Chylomicron remnant particles are then taken up by LDL-related protein (LRP).

In the liver, cholesterol and triglycerides are incorporated into VLDL along with phospholipids and Apo B-100 (Figure 13–3). VLDL loses its triglyceride content through interaction with lipoprotein lipase (LPL) to form VLDL remnant and IDL. IDL can be cleared from the circulation by hepatic LDL receptors or further converted to LDL (by further depletion of triglycerides) through the action of hepatic lipases (HLs). Approximately 50% of IDL is converted to LDL. LDL particles are cleared from the circulation primarily by hepatic LDL receptors by interaction with Apo B-100. They can also be taken up by extrahepatic tissues or enter the arterial wall, contributing to atherogenesis. Biosynthesis of cholesterol is directly regulated by the amount of cholesterol present in an individual. Therefore, higher ingestion of cholesterol through food consumption results in decreased production of endogenous cholesterol in the liver. In the liver, cholesterol is produced through the mevalonate pathway (Figure 13–3) where the production of mevalonate is the rate-limiting and irreversible step in cholesterol synthesis. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) is converted to mevalonate by HMG-CoA reductase (site of action for statins).

Cholesterol is transported from the arterial wall or other extrahepatic tissues back to the liver by HDL (Figure 13–2). Triglyceride-rich HDL is hydrolyzed by HL, generating fatty acids (FA) and nascent (immature) HDL particles, or mature HDL can bind to scavenger receptors (SR-BI) on hepatocytes and transfer their cholesterol ester content for excretion in the bile.

A variety of genetic mutations can occur during lipoprotein synthesis and metabolism that cause lipid disorders. The major genetic disorders and their effect on serum lipids are presented in Table 13–1. Disorders that increase serum cholesterol are generally those that affect the number or affinity of LDL receptors and

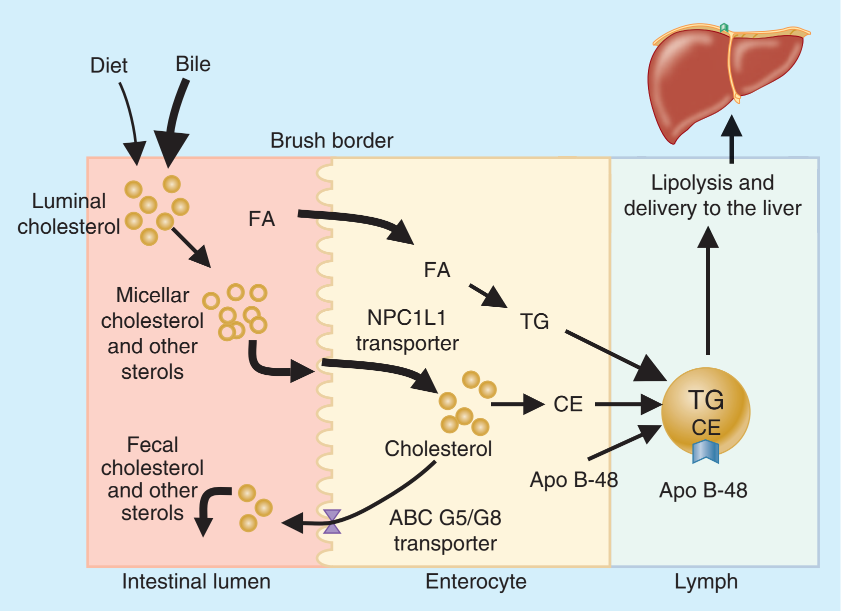

FIGURE 13–1. Intestinal cholesterol absorption and transport. Cholesterol from food and bile enters the gut lumen and is emulsified by bile acids into micelles. Micelles bind to the intestinal enterocytes, and cholesterol and other sterols are transported from the micelles into the enterocytes by a sterol transporter. Triglycerides synthesized by absorbed fatty acids, along with cholesterol and Apo B-48, are incorporated into chylomicrons. Chylomicrons are released into the lymphatic circulation and converted to chylomicron remnants (through loss of triglyceride) and then taken up by the hepatic LDL receptor-related protein (LRP). (ABC G5/G8, ATP-binding cassette G5/G8; Apo, apolipoprotein; CE, cholesterol ester; FA, fatty acid; LDL, low-density lipoprotein; NPC1L1, Niemann-Pick C1 Like 1; TG, triglyceride.)

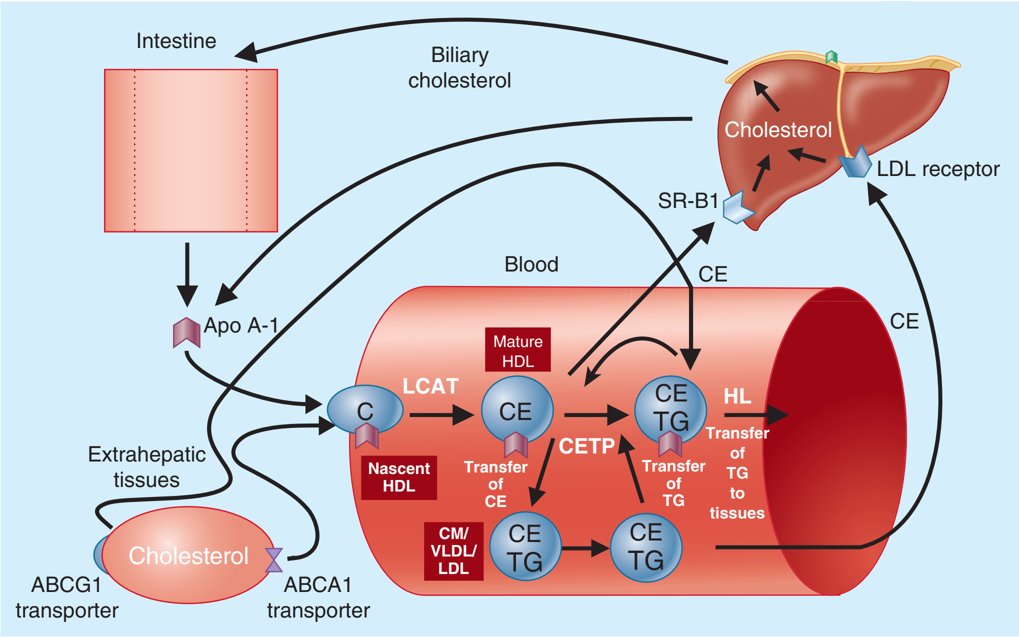
Intestine
Biliary cholesterol
Cholesterol
LDL receptor
SR-B1
Blood
CE
CE
Apo A-1
Mature HDL
LCAT
C
CE
CE TG
HL
CETP
Transfer of TG to tissues
Transfer of CE
Transfer of TG
Nascent HDL
Extrahepatic tissues
CM/ VLDL/ LDL
CE TG
CE TG
Cholesterol
ABCG1 transporter
ABCA1 transporter

FIGURE 13–2. Reverse cholesterol transport. Cholesterol is transported from the arterial wall or other extrahepatic tissues back to the liver by HDL. Esterified cholesterol from HDL can be transferred to Apo B–containing particles in exchange for triglycerides. Cholesterol esters transferred from HDL to VLDL and LDL are taken up by hepatic LDL receptors or delivered back to extrahepatic tissue. (ABCA1, ATP-binding cassette A1; ABCG1, ATP-binding cassette G1; Apo, apolipoprotein; C, cholesterol; CE, cholesterol ester; CETP, cholesterol ester transfer protein; CM, chylomicrons; HDL, high-density lipoprotein; HL, hepatic lipase; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; SR-B1, scavenger receptors; TG, triglyceride; VLDL, very low-density lipoprotein.)

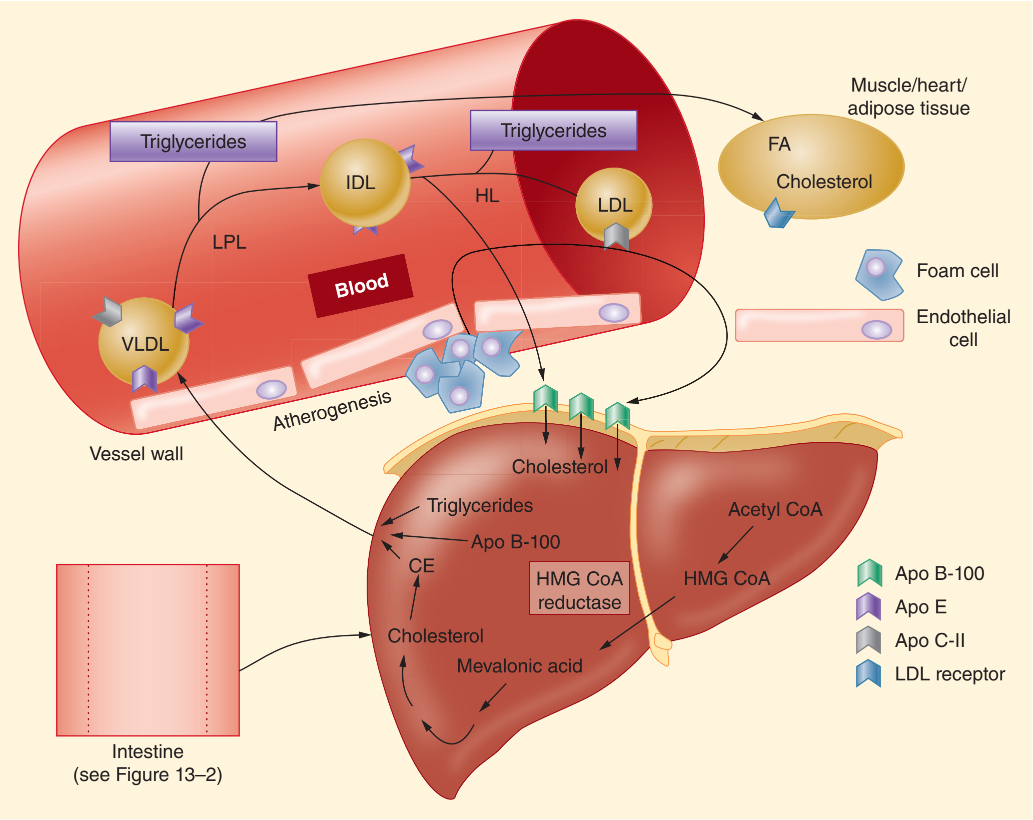
Muscle/heart/ adipose tissue
FA
Cholesterol
Triglycerides
Triglycerides
IDL
HL
LDL
LPL
Blood
VLDL
Foam cell
Endothelial cell
Atherogenesis
Vessel wall
Cholesterol
Triglycerides
Apo B-100
CE
HMG CoA reductase
Acetyl CoA
HMG CoA
Cholesterol
Mevalonic acid
Intestine (see Figure 13–2)
Apo B-100
Apo E
Apo C-II
LDL receptor

FIGURE 13–3. Endogenous lipoprotein metabolism. In liver cells, cholesterol and triglycerides are packaged into VLDL particles and exported into blood where VLDL is converted to IDL. Intermediate-density lipoprotein can be either cleared by hepatic LDL receptors or further metabolized to LDL. LDL can be cleared by hepatic LDL receptors or can enter the arterial wall, contributing to atherosclerosis. (Acetyl CoA, acetyl coenzyme A; Apo, apolipoprotein; CE, cholesterol ester; FA, fatty acid; HL, hepatic lipase; HMG-CoA, 3-hydroxy-3-methyglutaryl coenzyme A; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; VLDL, very low-density lipoprotein.)

Table 13–1

Selected Characteristics of Primary Dyslipidemias

Disorder	Estimated Frequency	Metabolic Defect	Main Lipid Parameter
Autosomal dominant hypercholesterolemia			
Familial hypercholesterolemia homozygous	1/250,000–1/1 million	LDL-receptor negative	LDL-C > 500 mg/dL (12.93 mmol/L)
heterozygous	1/250–1/500	Reduction in LDL receptors	LDL-C 250–500 mg/dL (6.47–12.93 mmol/L)
Familial defective Apo B-100	1/1000	Single-nucleotide mutation	LDL-C 250–500 mg/dL (6.47–12.93 mmol/L)
PCSK9 gain-of-function mutations	Rare	Single-nucleotide mutation	LDL-C 250–500 mg/dL (6.47–12.93 mmol/L)
Polygenic hypercholesterolemia	Common	Metabolic and environmental	LDL-C 160–250 mg/dL (4.14–6.47 mmol/L)
Familial combined dyslipidemia	1/200–300	Overproduction of VLDL and/or LDL	LDL-C 250–350 mg/dL (6.47–9.05 mmol/L) TG 200–800 mg/dL (2.26–9.04 mmol/L)
Familial hyperapobetalipoproteinemia	5%	Increase Apo B production	Apo B > 125 mg/dL (1.25 g/L)
Familial dysbetalipoproteinemia (type III)	0.5%	Apo E2/2 phenotype	LDL-C 300–600 mg/dL (7.76–15.52 mmol/L)
Familial hypertriglyceridemia			
Type I	1/500,000–1/1 million	LPL-Apo CII system	TG > 1000 mg/dL (11.3 mmol/L)
Type IV	1/300	Unknown	TG 200–500 mg/dL (2.26–5.65 mmol/L)
Type V	1/205,000	Metabolic and environmental	TG > 1000 mg/dL (11.3 mmol/L)
Hypoalphalipoproteinemia	3%–5%	Defect in HDL catabolism	HDL-C < 35 mg/dL (0.91 mmol/L)

Apo, apolipoprotein; C, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; PCSK9, proprotein convertase subtilisin/kexin type 9; TG, triglyceride; VLDL, very low-density lipoprotein.

are known as familial hypercholesterolemia (FH). These patients commonly present with corneal arcus of the eye, xanthomas of extensor tendons of the hand and Achilles tendon, premature CHD (male < 45 years old and female < 55 years old), and/or have a first-degree relative with raised cholesterol and/or premature CHD (male first-degree relative < 55 years old and female first-degree relative < 65 years old). Elevations in triglycerides are generally associated with overproduction of triglyceride-rich VLDL, mutations in Apo E, or lack of LPL or Apo CII, which cause hyperchylomicronemia. Most individuals have mild-to-moderate elevations in cholesterol known as polygenic hypercholesterolemia, thought to be caused by various more subtle genetic

Clinical Presentation and Diagnosis

Physical Findings

- Dyslipidemia is usually asymptomatic.
- Corneal arcus of the eye and xanthomas may be seen in patients with genetic disorders that cause a marked increase in serum LDL cholesterol (> 250 mg/dL [6.47 mmol/L]).
- Those with severely elevated serum triglycerides (> 500 mg/dL [5.65 mmol/L]) and especially those with extremely elevated serum triglycerides (> 1000 mg/dL [11.3 mmol/L]) can develop pancreatitis (inflammation of the pancreas) and tuberoeruptive xanthomas.

Indications for Lipid Panel

- All adults more than 20 years of age should be screened at least every 5 years using a fasting blood sample to obtain a lipid profile (total cholesterol, non-HDL cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides). A nonfasting lipid profile can be used for risk assessment for most patients for primary and secondary prevention assessment. If the triglycerides are elevated in the nonfasting state, then it may be necessary to recheck a fasting lipid profile to assess LDL cholesterol, but non-HDL cholesterol can accurately be assessed irrespective of fasting state.
- Children between 2 and 20 years old should be screened for high cholesterol if their parents have premature CHD (male first-degree relatives < 55 years old and female first-degree relatives < 65 years old) or if one of their parents has a total cholesterol greater than 240 mg/dL (6.21 mmol/L). Early screening will help identify children at highest risk of developing CHD in whom early education and dietary intervention are warranted.

Lipid Panel

- Non-HDL cholesterol exceeding 100 mg/dL (2.59 mmol/L) or LDL cholesterol exceeding 70 mg/dL (1.81 mmol/L) should have an assessment of ASCVD risk if 40 to 75 years of age and a primary prevention patient without diabetes.
- Serum triglycerides exceeding 150 mg/dL (1.70 mmol/L) and serum HDL cholesterol less than 40 mg/dL (1.03 mmol/L) in men and less than 50 mg/dL (1.29 mmol/L) in women may increase risk of ASCVD and should be evaluated.

Indications for Other Tests

- Conditions that may produce lipid abnormalities (such as those listed in Table 13–2) should be screened for using appropriate tests. If present, these conditions should be properly addressed as they can be secondary causes for dyslipidemia.

Table 13–2

Secondary Conditions and Drugs That May Cause Dyslipidemia

	↑ LDL Cholesterol	↑ Triglycerides	↓ HDL Cholesterol
Other Conditions			
Anorexia nervosa	√		
Chronic kidney disease	√	√	
Diabetes mellitus		√	√
Hemodialysis patients		√	
Hypothyroidism	√	√	
Nephrotic syndrome	√	√	√
Obesity		√	√
Obstructive liver disease/biliary cirrhosis	√		
Renal disease		√	
Drugs			
Anabolic steroids	√		√
Atypical antipsychotics		√	√
β-Blockers		√	√
Corticosteroids	√	√	
Cyclosporine	√		
Estrogen		√	
Isotretinoin		√	√
Progestins	√		√
Protease inhibitors		√	√
Thiazide diuretics	√	√	

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

defects as well as environmental factors such as diet, sedentary lifestyle, and overweight/obesity.[3,4]

Pathophysiology of Clinical Atherosclerotic Cardiovascular Disease

Lipoproteins are the "root cause" of atherosclerosis. The process begins when lipoproteins migrate between the endothelial cells into the arterial wall where they are modified by oxidation (Figure 13–4). Oxidized lipoproteins promote endothelial dysfunction by disturbing the production of nitric oxide, an endogenous vasodilator that maintains vasomotor tone, as well as increasing expression of cell-adhesion molecules on vascular endothelial cells leading to recruitment of monocytes (a variety of white blood cells) into the intima (inner layer of the wall of an artery or vein). Monocytes differentiate into macrophages (large scavenger cells) and express SR-BI, allowing enhanced uptake of these oxidized lipoproteins. The macrophages continue to accumulate lipoproteins and ultimately develop into lipid-laden foam cells. Accumulation of foam cells leads to formation of a lipid-rich core, which marks the transition to a more complicated atherosclerotic plaque. Such plaques may result in ischemic heart disease and acute coronary syndromes, further discussed in Chapters 8 and 9, respectively. Aggressive lipid lowering can restore endothelial function, decrease cardiovascular disease (CVD) risk, and improve patient cardiovascular (CV) outcomes.[3,4]

TREATMENT

KEY CONCEPT The American Heart Association/American College of Cardiology (AHA/ACC), National Lipid Association (NLA), and American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) guidelines emphasize that lifestyle therapies are an important element of risk reduction efforts in ASCVD prevention, whether or not pharmacotherapy is also used.[3,4,7,8] Therapeutic lifestyle changes (TLC) should be the first approach tried in all patients (Table 13–3), but pharmacotherapy should be instituted concurrently in higher-risk patients. TLC includes dietary restrictions as well as regular exercise and weight reduction if overweight or obese. Additionally, consumption of plant stanols/sterols and dietary fiber should be encouraged as they may reduce LDL cholesterol by 20% to 25%.

The rate-limiting enzyme in cholesterol biosynthesis is HMG-CoA reductase. Isolation of a specific inhibitor of this enzyme resulted in the first marketed statin called lovastatin.[9] By reducing cholesterol synthesis, statins were shown to upregulate the LDL receptor. Statins have now become the mainstay therapy for both familial and nonfamilial hypercholesterolemia.

In November 2018, the AHA and ACC released guidelines for treating high blood cholesterol to reduce risk of ASCVD in adults, which represented a reinforcement of the 2013 ACC/AHA guidelines.[3,4] Major changes in 2018 included reinforcement of statin-benefit groups, addition of LDL cholesterol thresholds and percent reduction in LDL cholesterol goals, and recommendations for specific nonstatin therapies in addition to statins in high- and very-high-risk patients to reduce ASCVD. The 2013 ACC/AHA guidelines shifted to a focus on statin-benefit groups versus other medical organizations recommending traditional cholesterol targets (eg, LDL goals, percent reduction in LDL). This approach was reinforced in 2018, with the exception of adding percent cholesterol goals and LDL cholesterol thresholds as highlighted in Table 13–4.[3,4,7,8] In this chapter, the 2013 ACC/AHA guideline,[3] the 2018 AHA/ACC guideline,[4] the NLA recommendations,[7] and the AACE/ACE guidelines[8] are reviewed.

ALGRAWANY

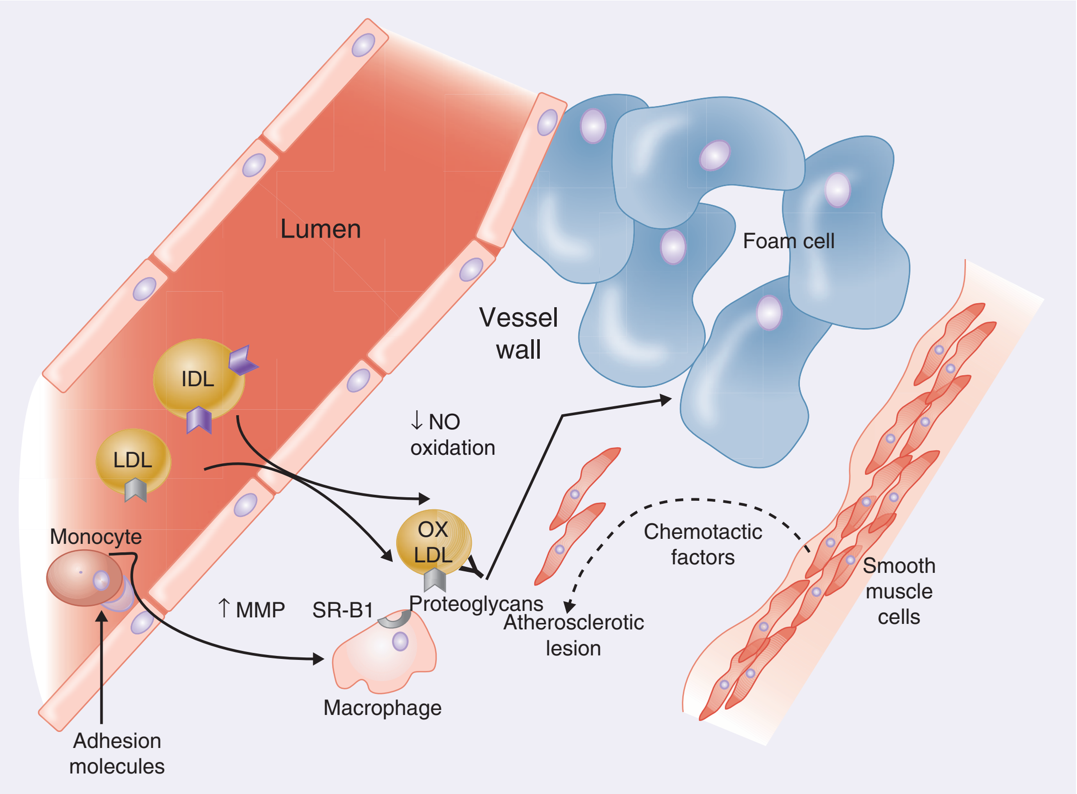

FIGURE 13–4. The process of atherogenesis. Atherosclerosis is initiated by the migration and retention of LDL and remnant lipoprotein particles into the vessel wall. These particles undergo oxidation and are taken up by macrophages in an unregulated fashion. The oxidized particles participate to induce endothelial cell dysfunction, leading to a reduced ability of the endothelium to dilate the artery which leads to a **prothrombotic state**. The unregulated uptake of cholesterol by macrophages leads to foam cell formation and the development of a blood clot–favoring fatty lipid core. The enlarging lipid core eventually causes an encroachment of the vessel lumen. Early in the process, smooth muscle cells are activated and recruited from the media to the intima, helping to produce a collagen matrix that covers the growing clot protecting it from circulating blood. Later, macrophages produce and secrete **matrix metalloproteinases** that degrade the collagen matrix, leading to unstable plaque that may cause a myocardial infarction. (IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; MMP, matrix metalloproteinases; NO, nitric oxide; OX, oxygen; SR-B1, scavenger receptors.)

Table 13–3

Essential Components of Therapeutic Lifestyle Changes

Component	Recommendation
Dietary cholesterol	< 200 mg/day (5.17 mmol/L)
Saturated fats	Total fat range should be 25%–35% of calories consumed for most cases < 7% of total calories and reduce intake of trans fatty acids
Therapeutic options for LDL-lowering plant stanols/sterols	2 g/day
Increased viscous (soluble) fiber	10–25 g/day
Total calories	Adjust caloric intake to maintain desirable body weight and prevent weight gain
Physical activity	≥ 150 min/week of moderate intensity physical activity or ≥ 75 min/week of vigorous-intensity physical activity

LDL, low-density lipoprotein.

The 2018 AHA/ACC guidelines identify four groups of adult patients targeted for statin treatment for both primary and secondary prevention (Figures 13–5 and 13–6), including:

- Established clinical ASCVD (secondary prevention).
- Primary prevention with elevation of LDL cholesterol levels 190 mg/dL (4.91 mmol/L) or higher.
- Primary prevention with diabetes mellitus (DM), age 40 to 75 years regardless of LDL cholesterol levels.
- Primary prevention without DM, age 40 to 75 years, with an estimated 10-year risk of 7.5% or greater, and LDL cholesterol levels 70 to 189 mg/dL (1.81–4.89 mmol/L).

If patients have established ASCVD or have LDL cholesterol levels 190 mg/dL (4.91 mmol/L) or greater, they are indicated for high-intensity statin and do not need their risk estimated with the pooled cohort equation (PCE) risk estimator. The pooled PCE risk estimator was developed to assist with decisions regarding initiation of statin therapy for primary prevention (http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/). The PCE estimates the risk of having a nonfatal/fatal stroke or myocardial infarction over a 10-year period if the patient is between 40 and 79 years of age. The PCE should be used to evaluate primary prevention patients and not

Table 13–4

US Guidelines for Management of Dyslipidemias

Source	Fasting Lipid Panel Measurement for Risk Assessment	Recommended Lipoprotein Target of Therapy	Treatment Goals and Thresholds
2013 American College of Cardiology/American Heart Association: Blood Cholesterol Guideline for ASCVD Prevention[3]	Yes Used to evaluate for more severe forms and secondary dyslipidemias and to assess anticipated therapeutic response and adherence to statin therapy	No recommendation	No recommendation
National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia (2014)[7]	Fasting or nonfasting	Non-HDL-C and LDL-C Apo B (secondary target)	LDL-C: < 70 mg/dL (1.81 mmol/L) for very high-risk patients < 100 mg/dL (2.59 mmol/L) for high-risk, moderate-risk, and low-risk patients Non-HDL-C: < 100 mg/dL (2.59 mmol/L) for very high-risk patients < 130 mg/dL (3.36 mmol/L) for high-risk, moderate-risk, and low-risk patients Apo B: < 80 mg/dL (0.80 g/L) for very high-risk patients < 90 mg/dL (0.90 g/L) for high-risk, moderate-risk, and low-risk patients
American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease (2020)[8]	Yes	Non-HDL-C and LDL-C and Apo B	LDL-C: < 55 mg/dL (1.42 mmol/L) for extreme-risk patients < 70 mg/dL (1.81 mmol/L) for very high-risk patients < 100 mg/dL (2.59 mmol/L) for high-risk and moderate-risk patients < 130 mg/dL (3.36 mmol/L) for low-risk patients Non-HDL-C: < 80 mg/dL (2.07 mmol/L) for extreme-risk patients < 100 mg/dL (2.59 mmol/L) for very high-risk patients < 130 mg/dL (3.36 mmol/L) for high-risk and moderate-risk patients < 160 mg/dL (4.14 mmol/L) for low-risk patients Apo B: < 70 mg/dL (0.70 g/L) for extreme-risk patients < 80 mg/dL (0.80 g/L) for very high-risk patients < 90 mg/dL (0.90 g/L) for high-risk and moderate-risk patients TG: <150 mg/dL (1.70 mmol/L) for all risk categories
2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol[4]	Fasting or nonfasting	LDL-C and non-HDL-C	LDL-C and non-HDL-C: ≥ 50% reduction in LDL-C in patients with clinical ASCVD, consider adding nonstatin if LDL-C > 70 mg/dL (1.81 mmol/L) and non-HDL-C >100 mg/dL (2.59 mmol/L) if very high risk ≥ 50% reduction in LDL-C in patients with LDL-C ≥ 190 mg/dL (4.91 mmol/L), consider adding nonstatin if LDL > 100 mg/dL (2.59 mmol/L) ≥ 50% reduction in LDL-C in patients with diabetes and ASCVD risk factors ≥ 30% reduction in LDL-C in intermediate-risk patients with diabetes and ASCVD risk factors ≥ 30% reduction in LDL-C in intermediate-risk patients (ASCVD risk score ≥ 7.5% to < 20%)

Apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non–high-density lipoprotein cholesterol; TG, triglycerides.

secondary prevention patients. Specifically, it should be utilized in patients who are between the ages of 40 and 75 who have an LDL cholesterol between 70 and 189 mg/dL (1.81 and 4.89 mmol/L). The PCE estimate is then utilized to categorize patients into four risk groups which include low risk (< 5%), borderline risk (5%–7.4%), intermediate risk (7.5%–19.9%), and high risk (> 20%). It should be emphasized this risk estimator is part of the patient-clinician discussion regarding potential benefit of statin therapy and not the sole determinant for initiation of therapy. A fasting or nonfasting lipid panel should be used for initial calculation of the pooled cohort risk estimator. Clinical judgment, which includes risks and benefits, cost,

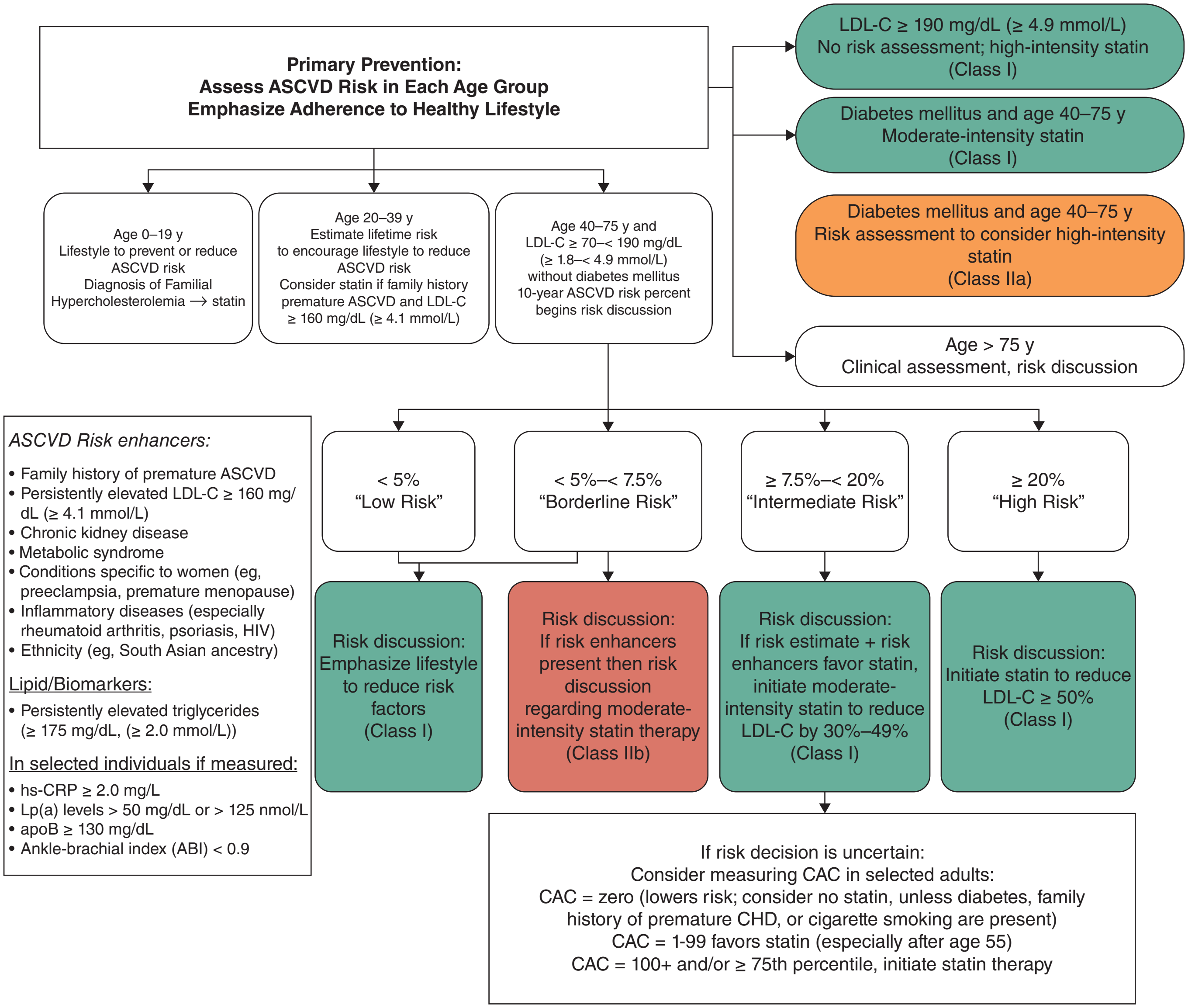
Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle
Age 0–19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia → statin
Age 20–39 y
Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥ 160 mg/dL (≥ 4.1 mmol/L)
Age 40–75 y and LDL-C ≥ 70–< 190 mg/dL (≥ 1.8–< 4.9 mmol/L) without diabetes mellitus
10-year ASCVD risk percent begins risk discussion
LDL-C ≥ 190 mg/dL (≥ 4.9 mmol/L)
No risk assessment; high-intensity statin
(Class I)
Diabetes mellitus and age 40–75 y
Moderate-intensity statin
(Class I)
Diabetes mellitus and age 40–75 y
Risk assessment to consider high-intensity statin
(Class IIa)
Age > 75 y
Clinical assessment, risk discussion
ASCVD Risk enhancers:
• Family history of premature ASCVD
• Persistently elevated LDL-C ≥ 160 mg/dL (≥ 4.1 mmol/L)
• Chronic kidney disease
• Metabolic syndrome
• Conditions specific to women (eg, preeclampsia, premature menopause)
• Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
• Ethnicity (eg, South Asian ancestry)
Lipid/Biomarkers:
• Persistently elevated triglycerides (≥ 175 mg/dL, (≥ 2.0 mmol/L))
In selected individuals if measured:
• hs-CRP ≥ 2.0 mg/L
• Lp(a) levels > 50 mg/dL or > 125 nmol/L
• apoB ≥ 130 mg/dL
• Ankle-brachial index (ABI) < 0.9
< 5%
"Low Risk"
< 5%–< 7.5%
"Borderline Risk"
≥ 7.5%–< 20%
"Intermediate Risk"
≥ 20%
"High Risk"
Risk discussion:
Emphasize lifestyle to reduce risk factors
(Class I)
Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy
(Class IIb)
Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30%–49%
(Class I)
Risk discussion:
Initiate statin to reduce LDL-C ≥ 50%
(Class I)
If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥ 75th percentile, initiate statin therapy

FIGURE 13–5. Summary of statin initiation recommendations for the treatment of blood cholesterol in patients for the primary prevention of clinical ASCVD. Colors correspond to class of recommendation. (apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); y, year.) (From Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73(24):e285–e350, with permission.)

and potential drug–drug interactions, must be exercised. This is especially important since the risk estimator has been shown to overestimate or underestimate risk in some patient populations. If initiation of statin therapy is uncertain based on quantitative risk assessment, additional ASCVD risk enhancers can be considered such as:

- LDL cholesterol 160 mg/dL (4.14 mmol/L) or higher.
- Persistently elevated triglycerides 175 mg/dL (2 mmol/L) or higher (three or more readings).
- Family history of premature ASCVD, chronic kidney disease, inflammatory disease, ethnicity (eg, South Asian ancestry).
- Apo B 130 mg/dL (1.3 g/L) or higher.
- Lipoprotein (a), or Lp(a), 50 mg/dL (0.5 g/L) or higher.
- High-sensitivity C-reactive protein (hs-CRP) of 2 mg/L or higher.
- Coronary artery calcium (CAC) score of 100 or higher.
- Ankle-brachial index (ABI) less than 0.9.
- Elevated lifetime ASCVD risk.

In adults 40 to 75 years of age without diabetes mellitus and with LDL cholesterol between 70 and 189 mg/dL (1.81 and 4.89 mmol/L) who fall into the intermediate-risk category (score of ≥ 7.5%–19.9%) the AHA/ACC guidelines recommend checking a CAC score to help with the decision about starting a statin or not.[4] The guidelines do not give specific

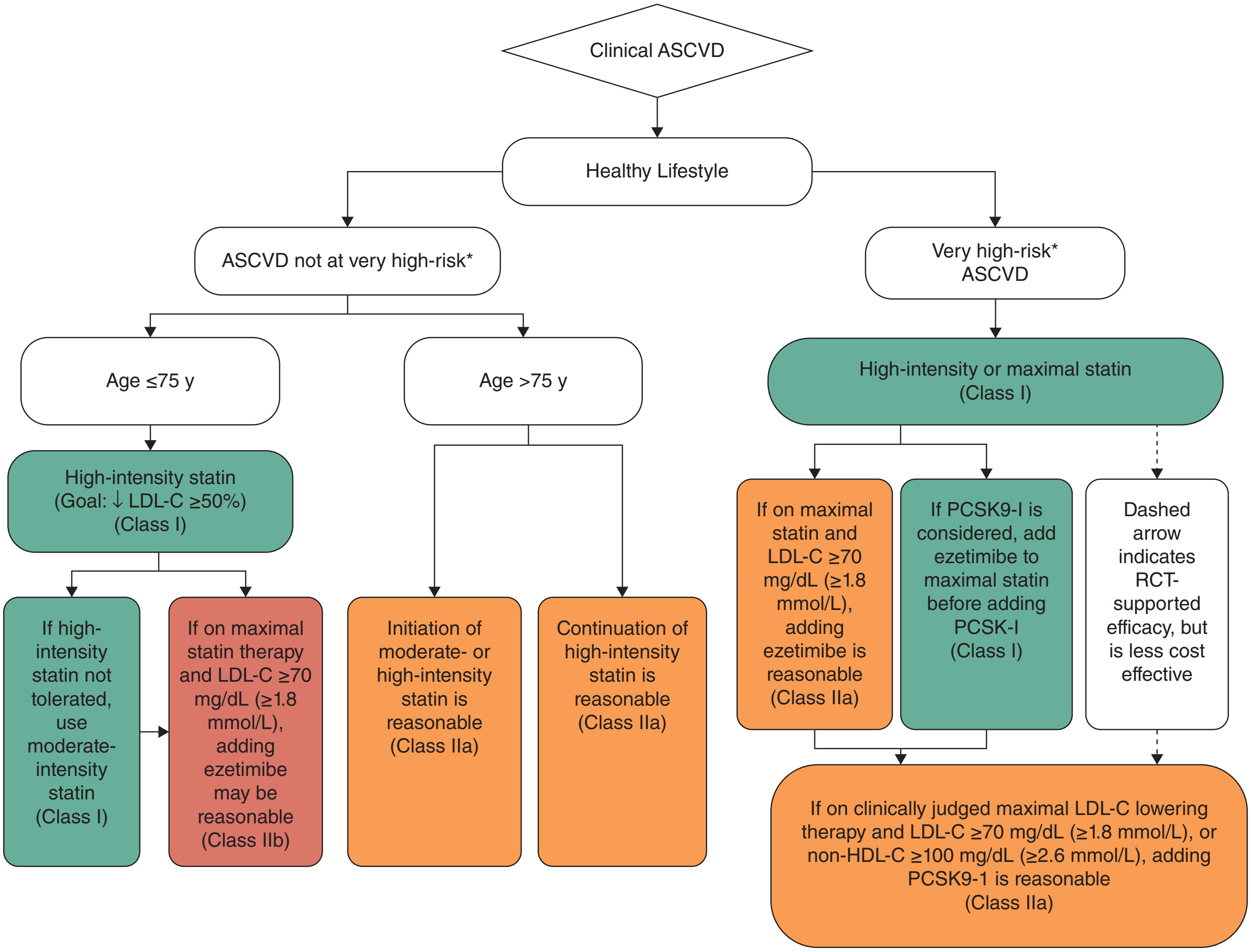
Clinical ASCVD
Healthy Lifestyle
ASCVD not at very high-risk*
Very high-risk* ASCVD
Age ≤75 y
Age >75 y
High-intensity or maximal statin (Class I)
High-intensity statin (Goal: ↓ LDL-C ≥50%) (Class I)
If high-intensity statin not tolerated, use moderate-intensity statin (Class I)
If on maximal statin therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe may be reasonable (Class IIb)
Initiation of moderate- or high-intensity statin is reasonable (Class IIa)
Continuation of high-intensity statin is reasonable (Class IIa)
If on maximal statin and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe is reasonable (Class IIa)
If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK-I (Class I)
Dashed arrow indicates RCT-supported efficacy, but is less cost effective
If on clinically judged maximal LDL-C lowering therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), or non-HDL-C ≥100 mg/dL (≥2.6 mmol/L), adding PCSK9-1 is reasonable (Class IIa)

FIGURE 13–6. Summary of statin initiation recommendations for the treatment of blood cholesterol in patients with established clinical atherosclerotic cardiovascular disease (ASCVD). Colors correspond to class of recommendation. Clinical ASCVD consists of ACS, those with history of MI, stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin. *Very high risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions. (ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9-I, proprotein convertase subtilisin/kexin 9 inhibitor; RCT, randomized controlled trial; y, year.) (From Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73(24):e285–e350, with permission.)

recommendations about when to check the other risk-enhancing factors, but list them as options to help with the decision to initiate statin therapy based on a patient's individual risk.

Once the decision to initiate statin therapy is made, the dose intensity is based on the patient's specific statin-benefit group (Figures 13–5 and 13–6). High-intensity statin therapy on average lowers LDL cholesterol by approximately 50% or more and moderate-intensity statin therapy lowers LDL cholesterol approximately 30% to 49% (see Table 13–5). The 2013 ACC/AHA expert panel concluded they could not find evidence for or against titration of drug therapy to specific LDL cholesterol and/or non-HDL cholesterol goals, but thresholds for LDL cholesterol and percent LDL cholesterol goals were added to the 2018 guidelines.[3,4] A follow-up LDL cholesterol 4 to 12 weeks after initiating therapy is used to assess response (percent LDL cholesterol lowering from baseline) and statin adherence, and not for determining if specific LDL cholesterol concentrations have been achieved.

In 2014, the NLA issued its recommendation for patient-centered management of dyslipidemia and reaffirmed the importance of setting cholesterol goals for prevention of ASCVD.[7] The NLA emphasized that non-HDL cholesterol is a better primary target for modification than LDL cholesterol and is now considered a co-target with LDL cholesterol. Non-HDL cholesterol is preferred by the NLA as it has demonstrated greater accuracy than LDL cholesterol for predicting ASCVD events both on and off statin treatment and its lack of need for measurement in the fasting state and low cost. **KEY CONCEPT** The NLA recommendations for "desirable" cholesterol levels are presented in Table 13–6.

Table 13–5

High, Moderate, and Low-Intensity Statin Therapy as Indicated by the American Heart Association/American College of Cardiology (AHA/ACC) Guidelines[4]

	High Intensity	Moderate Intensity	Low Intensity
LDL-C Lowering[a]	≥ 50%	30%–49%	< 30%
Statins	**Atorvastatin (40[b])–80 mg** **Rosuvastatin 20 (40) mg**	**Atorvastatin 10** (20) **mg** **Rosuvastatin** (5) **10 mg** **Simvastatin 20–40 mg** **Pravastatin 40** (80) **mg** **Lovastatin 40** (80) **mg** Fluvastatin XL 80 mg **Fluvastatin 40 mg twice daily** Pitavastatin 1–4 mg	Simvastatin 10 mg **Pravastatin 10–20 mg** **Lovastatin 20 mg** Fluvastatin 20–40 mg

Boldface type indicates specific statins and doses that were evaluated in randomized controlled trials (RCTs).

[a] Low-density lipoprotein cholesterol (LDL-C) lowering that should occur with the dosage listed below each intensity.

[b] Evidence from one RCT only: down-titration if unable to tolerate atorvastatin 80 mg.

Table 13–6

National Lipid Association Classifications of Cholesterol and Triglyceride Levels in mg/dL (mmol/L)[7]

Lipids	
Non-HDL Cholesterol[a]	
< 130 (3.36)	Desirable
130–159 (3.36–4.12)	Above desirable
160–189 (4.13–4.90)	Borderline high
190–219 (4.91–5.68)	High
≥ 220 (5.69)	Very high
LDL Cholesterol	
< 100 (2.59)	Desirable
100–129 (2.59–3.35)	Above desirable
130–159 (3.36–4.12)	Borderline high
160–189 (4.13–4.90)	High
≥ 190 (4.91)	Very high
HDL Cholesterol	
< 40 (1.03) (men)	Low
< 50 (1.29) (women)	Low
Triglycerides	
< 150 (1.70)	Normal
150–199 (1.70–2.25)	Borderline high
200–499 (2.26–5.64)	High
≥ 500 (5.65)	Very high[b]

[a] Non-HDL-C = total cholesterol minus HDL cholesterol.

[b] Severe hypertriglyceridemia is another term used for very high triglycerides in pharmaceutical product labeling.

HDL, high-density lipoprotein; LDL, low-density lipoprotein; non-HDL, non–high-density lipoprotein.

In 2020, AACE/ACE updated their guidelines with continued emphasis on lifestyle recommendations.[8] They provide five different risk categories ranging from low risk to extreme risk. For each of these risk categories, treatment goals are provided for LDL cholesterol, non-HDL cholesterol, Apo B, and triglycerides. Their treatment goals for extreme risk patients go as low as an LDL cholesterol less than 55 mg/dL (1.42 mmol/L) and non-HDL cholesterol less than 80 mg/dL (2.07 mmol/L). The AACE/ACE also support measuring Lp(a) in higher-risk individuals and the use of icosapent ethyl to prevent ASCVD.

Recommendations for Treatment

▶ *Step 1: Screening and Classification of Initial Lipoprotein Lipid Levels*

Determine lipoprotein profile in either the fasting or nonfasting state. KEY CONCEPT The AHA/ACC recommends that either a fasting or nonfasting lipid panel can be performed. They specifically recommend a fasting lipid panel on a different day if a patient has ingested a high-fat meal in the preceding 8 hours, or if tested and the LDL cholesterol is less than 70 mg/dL (1.81 mmol/L), as the Friedewald calculated LDL cholesterol is less reliable. The NLA and AACE/ACE recommend that all adults older than 20 years are screened at least every 5 years to obtain a lipid profile (see Clinical Presentation and Diagnosis).[7,8] Children between 2 and 20 years old should be screened for high cholesterol if their parents have premature CHD or if one of their parents has total cholesterol greater than 240 mg/dL (6.21 mmol/L).

▶ *Step 2: Rule Out Secondary Causes of Dyslipidemia*

Certain secondary causes (drugs and diseases) can cause abnormalities in serum lipids and should be evaluated (Table 13–2). Every effort should be made to correct or control underlying diseases such as hypothyroidism and DM. Concurrent medications known to induce lipid abnormalities should be evaluated for discontinuation if alternative medications can be used prior to instituting long-term lipid-modifying therapy.[5,7]

▶ *Step 3: Identify Patients with Very High-Risk Conditions*

Individuals with established clinical ASCVD (Figure 13–6) or DM with greater or equal to two ASCVD risk factors (Table 13–7) or evidence of atherosclerosis-mediated end-organ damage are considered very high risk or extreme risk. NLA and AACE/ACE set non-HDL cholesterol and LDL cholesterol goals for very-high-risk patients at less than 100 mg/dL (2.59 mmol/L) and less than 70 mg/dL (1.81 mmol/L), respectively.[7,8] The 2020 AACE/ACE guidelines set non-HDL cholesterol and LDL cholesterol goals for extreme-risk patients (see Table 13–4) at less than 80 mg/dL (2.07 mmol/L) and less than 55 mg/dL (1.42 mmol/L), respectively.[8] AHA/ACC, NLA, and AACE/ACE recommend statin therapy as initial pharmacotherapy when non-HDL cholesterol or LDL cholesterol is equal to or above these targets/thresholds.[4,7,8] For patients with DM, consideration can be given to use at least moderate-to-high-intensity statin therapy, irrespective of baseline cholesterol levels. The 2018 AHA/ACC guidelines recommend nonstatin therapy (ezetimibe or proprotein convertase subtilisin/kexin 9 [PCSK9] inhibitors) in addition to maximum tolerated statin therapy in patients who are very high risk and continue to have an LDL cholesterol above the 70 mg/dL (1.81 mmol/L) threshold .[4]

Table 13–7

Risk Factors for Atherosclerotic Cardiovascular Disease (ASCVD) According to the National Lipid Association (NLA)[a,7]

Risk Factor	Definition
Age (years)	Male ≥ 45; female ≥ 55
Family history of premature CHD events[b]	Male first-degree relative at < 55 years Female first-degree relative at < 65 years
Hypertension[c]	SBP ≥ 140 mm Hg DBP ≥ 90 mm Hg
Low HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females
Cigarette smoking	Current

[a] Levels of non-HDL cholesterol and LDL cholesterol are not listed because these risk factors are used to assess risk category and treatment goals for atherogenic lipoprotein cholesterol levels. Diabetes is not listed because it is considered a high- or very high-risk condition for ASCVD risk assessment purposes.

[b] CHD is defined as myocardial infarction, coronary death, or a coronary revascularization procedure.

[c] Note, blood pressure values used by the NLA differ from the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCMA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults.

CHD, coronary heart disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

Table 13–8

Risk-Enhancing Factors for Clinician-Patient Risk Discussion According to American Heart Association/American College of Cardiology (AHA/ACC)[4]

Risk-Enhancing Factors

- **Family history of premature ASCVD** (male < 55 years; female, < 65 years)
- **Primary hypercholesterolemia** (LDL-C, 160–189 mg/dL [4.14–4.89 mmol/L); non–HDL-C 190–219 mg/dL [4.91–5.66 mmol/L])[a]
- **Metabolic syndrome**
- **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
- **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS
- **History of premature menopause** (before age 40 years) and **history of pregnancy-associated conditions that increase later ASCVD risk** such as preeclampsia
- **High-risk race/ethnicities** (eg, South Asian ancestry)
- **Lipid/biomarkers**: Associated with increased ASCVD risk
  - Persistently[a] elevated, primary hypertriglyceridemia (≥ 175 mg/dL [1.98 mmol/L])
  - If measured:
    1. **Elevated high-sensitivity C-reactive protein** (≥ 2 mg/L)
    2. **Elevated Lp(a)**: A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥ 50 mg/dL (0.5 g/L; 125 nmol/L) constitutes a risk-enhancing factor, especially at higher levels of Lp(a).
    3. **Elevated apoB** ≥ 130 mg/dL (1.3 g/L): A relative indication for its measurement would be triglycerides ≥ 200 mg/dL (2.26 mmol/L). ApoB level ≥ 130 mg/dL (1.3 g/L) corresponds to an LDL-C > 160 mg/dL (4.14 mmol/L) and constitutes a risk-enhancing factor.
    4. **ABI** < 0.9

[a] Optimally, three determinations.

ABI, ankle-brachial index; AIDS, acquired immunodeficiency syndrome; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); RA, rheumatoid arthritis.

▶ *Step 4: Identify Patients with High-Risk Conditions*

The 2018 AHA/ACC guidelines set criteria for nonstatin therapy for patients with high residual risk after receiving maximum tolerated statin doses based on their statin-benefit group, described in Figure 13–6. The 2018 AHA/ACC guidelines have set a LDL cholesterol goal of a 50% reduction in those with established clinical ASCVD and recommend the addition of nonstatin therapy with either ezetimibe or a PCSK9 inhibitor when this goal and/or LDL cholesterol target of less than 70 mg/dL (1.81 mmol/L) are not achieved.[4] The NLA and AACE/ACE set non-HDL cholesterol and LDL cholesterol goals at less than 130 mg/dL (3.36 mmol/L) and less than 100 mg/dL (2.59 mmol/L) for high-risk primary prevention patients and at less than 100 mg/dL (2.59 mmol/L) and less than 70 mg/dL (1.81 mmol/L) for secondary prevention patients, respectively.[7,8] Pharmacotherapy can be considered when the desired LDL-cholesterol lowering is not achieved or LDL or non-HDL cholesterol is equal to or above the targets. If it is not possible to attain desirable LDL and non-HDL cholesterol levels in patients with severe hypercholesterolemia phenotype, a reduction of at least 50% is recommended.[4,7,8] For FH patients with multiple or poorly controlled other major ASCVD risk factors, clinicians may consider aiming for even lower levels of atherogenic cholesterol.[7,8]

▶ *Step 5: Identify Patients Without Established ASCVD and Need for Risk Assessment*

Individuals without clinical ASCVD should be screened for major ASCVD risk factors, and quantitative risk scoring should be obtained for adults 20 years or older (eg, pooled cohort equation ASCVD risk calculation). Consideration of additional risk-enhancing factors (Table 13–8) may also be useful for some patients if the patient or provider are uncertain about initiating a statin and want additional factors assessed to determine the best plan. If ASCVD risk score reaches the high-risk threshold (> 20%), assign patient to high-risk category. If risk-enhancing factors are present, consider assigning to the high-risk category. If no indication is present to assign to high risk, then patients should be considered low risk, borderline risk, or intermediate risk based on their ASCVD risk score and presence of risk-enhancing factors (Figure 13–5).

The NLA and AACE/ACE have established goals for non-HDL cholesterol and LDL cholesterol of less than 130 mg/dL (3.36 mmol/L) and less than 100 mg/dL (2.59 mmol/L), respectively, in patients considered high risk (eg, two or more CV risk factors and a 10%–20% estimated risk of ASCVD in 10 years).[7,8] Pharmacotherapy can be considered when non-HDL cholesterol or LDL cholesterol are equal to or above 160 mg/dL (4.14 mmol/L) and 130 mg/dL (3.36 mmol/L), respectively. For individuals with one or no major ASCVD risk factors, the NLA set goals for non-HDL cholesterol and LDL cholesterol at less than 130 mg/dL (3.36 mmol/L) and less than 100 mg/dL

(2.59 mmol/L), respectively. Pharmacotherapy can be considered when non-HDL cholesterol or LDL cholesterol are equal to or above 190 mg/dL (4.91 mmol/L) and 160 mg/dL (4.14 mmol/L), respectively. Consider assigning to a higher-risk category based on other known risk indicators, when present.

▶ *Step 6: Treatment of Elevated Triglycerides*

KEY CONCEPT Patients with severely elevated serum triglycerides exceeding 500 mg/dL (5.65 mmol/L) are at increased risk of pancreatitis, especially when levels are extremely elevated above 1000 mg/dL (11.3 mmol/L).[4,7,8] Reducing triglycerides in these individuals becomes the primary target for intervention. Reduction in fats and carbohydrates and abstaining from ethanol should be considered, and secondary causes (Table 13–2) should be assessed. Increase in exercise should be encouraged. Weight loss should also be encouraged if the individual is overweight. When pharmacotherapy is instituted, the goal is to reduce triglycerides to less than 150 mg/dL (1.70 mmol/L). Once triglycerides are less than 500 mg/dL (5.65 mmol/L), and the risk of pancreatitis is reduced, the primary focus of intervention should once again be on non-HDL and LDL cholesterol. Niacin, fibrates, and long-chain omega-3 fatty acids (OM3FA) are the most effective agents in patients with fasting triglyceride concentrations greater than 1000 mg/dL (11.3 mmol/L).[4,7,8] For patients with triglycerides 500 to 999 mg/dL (5.65–11.29 mmol/L), a triglyceride-lowering agent or a statin (if no history of pancreatitis) may be reasonable. Bile acid sequestrants should be avoided in patients with a triglyceride value of 300 mg/dL (3.39 mmol/L) or higher as they can increase triglycerides. Fibrate therapy needs to be used with caution in patients with renal dysfunction, and gemfibrozil should not be used in patients with stage 4 chronic kidney disease (CKD) or greater. Individuals with triglycerides between 200 and 499 mg/dL (2.26 and 5.64 mmol/L) have increased triglyceride-rich remnant lipoproteins and small-dense LDL particles, which are considered more atherogenic than large buoyant LDL particles. For patients with high triglycerides between 200 and 499 mg/dL (2.26 and 5.64 mmol/L), statins will generally be first line since they are most effective in reducing non-HDL and LDL-cholesterol levels. In 2019, the findings from the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) results were published.[10] Based on the major CV event lowering seen in patients treated with icosapent ethyl, the Food and Drug Administration (FDA) approved this drug in December 2019 as adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with triglyceride levels greater than or equal to 150 mg/dL (1.70 mmol/L) and established ASCVD or DM and two or more additional risk factors for CV disease (ie, male > 55 years of age or female > 65 years of age, tobacco smoker, hypertension, low HDL cholesterol, hs-CRP > 3 mg/L, renal dysfunction, retinopathy, albuminuria, ABI greater than 0.9).

Patient Encounter Part 1

A 60-year-old African American woman with hypertension, hypothyroidism, and type 2 diabetes mellitus has been referred for a follow-up of her cholesterol. Her current medication regimen includes lisinopril 40 mg daily, amlodipine 10 mg daily, hydrochlorothiazide 25 mg daily, metformin 1000 mg twice daily, and empagliflozin 10 mg daily. Her blood glucose is 150 mg/dL (8.3 mmol/L). Her laboratory test results are within normal limits. Her blood pressure today is 140/84 mm Hg with a heart rate of 70 beats/min. She is a nonsmoker. Her fasting lipid profile is total cholesterol 200 mg/dL (5.17 mmol/L), triglycerides 160 mg/dL (1.81 mmol/L), HDL cholesterol 46 mg/dL (1.19 mmol/L), non-HDL cholesterol 154 mg/dL (3.98 mmol/L), and LDL cholesterol 122 mg/dL (3.15 mmol/L).

What is your assessment of the patient's cholesterol results?

Should an assessment of her risk factors for ASCVD or an ASCVD risk score be conducted?

Does this patient have clinical ASCVD?

What treatment group does she fit according to AHA/ACC guidelines?

What additional information do you need to evaluate the patient?

Develop a care plan for the patient.

Pharmacotherapy

▶ *Statins (HMG-CoA Reductase Inhibitors)*

KEY CONCEPT Statins are very effective LDL-lowering medications and are proven to reduce the risk of CHD, stroke, and death. Thus, AHA/ACC, NLA, and AACE/ACE consider statins the preferred LDL-lowering medications.[4,7,8] Statins are effective in reducing ASCVD and in some cases, mortality. This effectiveness has been demonstrated in both male and female genders, the elderly, patients with DM and hypertension, those with or without preexisting ASCVD, and following an acute coronary syndrome.[11-16] Statins inhibit conversion of HMG-CoA to L-mevalonic acid and subsequently cholesterol (Figure 13–7). Statins lower LDL cholesterol levels by approximately 21% to 63% (Table 13–9), are moderately effective at reducing triglycerides, and modestly raise HDL cholesterol. Statins are routinely recommended to take in the evening as that is when the body produces the most cholesterol (most important for statins with shorter half-lives, but those with a long half-life [eg, atorvastatin, rosuvastatin] can be taken any time of day). Additionally, statins also inhibit other important by-products in the cholesterol biosynthetic pathway that affect intracellular transport, membrane trafficking, and gene transcription. This may explain some of the cholesterol-independent benefits (so-called pleiotropic effects) of statins such as reducing lipoprotein oxidation, enhancing endothelial synthesis of nitric oxide, and inhibiting thrombosis. These pleiotropic effects are thought to contribute to the early benefits of statins on CHD risk, while the decrease in serum lipids accounts for the later benefits.

KEY CONCEPT Statins are well tolerated, with less than 4% of patients in clinical trials discontinuing therapy due to adverse side effects (Table 13–10). Elevations in liver function tests (LFTs) and statin-associated muscle symptoms (SAMS) (including myalgia, myopathy, and rhabdomyolysis) are important adverse effects associated with statins. Liver toxicity, defined as LFT elevations greater than three times the upper limit of normal, is reported in less than 2% of patients. Incidence is higher at higher doses, but the progression to liver failure is exceedingly rare. LFTs should be obtained at baseline and as clinically indicated thereafter. Myalgia is defined as muscle aches or pains not associated with creatine kinase (CK) elevations. Myopathy, defined as unexplained muscle weakness or pain associated with CK elevations greater than 10 times the upper limit of normal, is reported to range

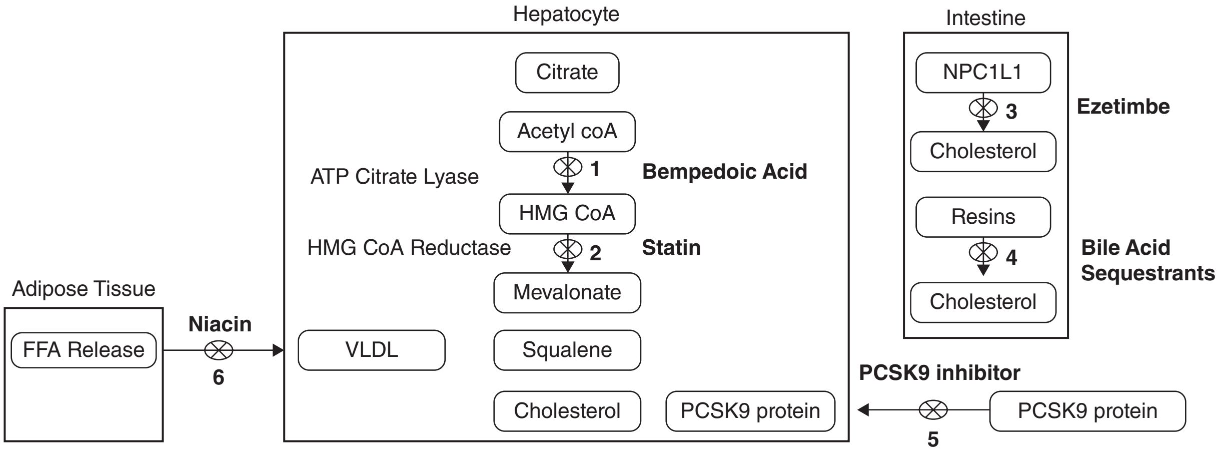

FIGURE 13–7. Mechanism of action for major lipid-lowering medication classes to target low-density lipoprotein. Bempedoic acid (1) inhibits ATP citrate lyase which blocks the synthesis of cholesterol in the hepatocyte resulting in reduced cholesterol production. Statins (2) inhibit HMG CoA reductase, which blocks the synthesis of cholesterol in the hepatocyte resulting in reduced cholesterol production. Ezetimibe (3) inhibits the action of the transporter NPC1L1, reducing intestinal absorption of dietary and biliary cholesterol, which reduces the delivery of chylomicron cholesterol to the hepatocyte via the portal circulation. Bile acid sequestrants (4) bind to bile acids in the gut, resulting in a resin–bile acid complex that is then excreted in the feces leading to hepatic cholesterol conversion to bile and an upregulation of LDL receptors. PCSK9 inhibitors (5) are monoclonal antibodies to PCSK9 and bind to PCSK9 within the circulation, resulting in less breakdown of the LDL receptor resulting in upregulation of LDL receptor expression by the hepatocyte. Niacin (6) inhibits FFA release from adipose tissue, which results in a reduction in VLDL leading to an overall reduction in LDL. (ATP, adenosine triphosphate; CoA, coenzyme A; FFA, free fatty acid; HMG-CoA, β-hydroxy β-methylglutaryl-CoA; LDL, low-density lipoprotein; NPC1L1, Niemann-Pick C1 Like 1; PCSK9, proprotein convertase subtilisin/kexin type 9; VLDL, very low-density lipoprotein.)

from 0% to less than 0.5% for the currently marketed statins at approved doses. Rhabdomyolysis, defined as muscle symptoms with marked elevation in CK of at least 40 times the upper limit of normal and creatinine elevation usually associated with myoglobinuria and brown urine, is very rare.[17,18] The risks associated with statin-induced myopathy include the following[17,18]:

- Small body frame and frailty.
- Multisystem disease (eg, CKD, especially due to DM).
- Perioperative periods.
- Multiple medications (see next bullet).
- Specific concomitant medications or consumptions (check specific statin package insert for warnings): fibrates (especially gemfibrozil, but other fibrates too), nicotinic acid (rarely), cyclosporine, azole antifungals, macrolide antibiotics, protease inhibitors, nefazodone, verapamil, amiodarone, large quantities of grapefruit juice (usually > 1 quart [about 950 mL] per day), and alcohol abuse (independently predisposes to myopathy).

The AHA scientific statement on statin safety and associated adverse events gives guidance on how to manage SAMS.[18] It is reasonable to check a baseline CK in patients at risk for myopathy. Follow-up CK should only be obtained in patients complaining of muscle pain, weakness, tenderness, or brown urine. Common secondary causes of muscle symptoms should be ruled out (eg, vitamin D deficiency, hypothyroidism, muscle disorders). If a patient presents with a CK elevation less than three times the upper limit of normal, they can continue their current statin dose and monitor for ongoing muscle symptoms. If their CK is greater than three times the upper limit of normal but less than 10 times, they can continue their statin therapy if mild symptoms and repeat a CK in 1 week. If the CK is decreasing or stable, they can be continued on their statin and continue to monitor for muscle symptoms, but if CK is increasing, then the statin should be stopped and the CK reassessed when the patient's symptoms have resolved. If CK is greater than 10 times the upper limit of normal, they should immediately have their statin stopped and be instructed to increase their fluid intake. If the CK is greater than 40 times the upper limit of normal, they would meet the definition of rhabdomyolysis and should immediately go to the hospital to be assessed as they are at a high risk of acute renal failure. Patient assessment for symptoms of myopathy should be done 6 to 12 weeks after starting or changing therapy and at each visit.

Some evidence suggests that statins increase the risk for development of DM. The FDA warns of increased blood sugar and glycosylated hemoglobin (HbA_{1c}) levels on statin labels. In addition, the FDA has added to statin labels that cognitive impairment, such as memory loss, forgetfulness and confusion, has been reported by some statin users. There have been some evaluations showing an association with cognitive impairment, but these symptoms appear to be reversible when stopping the statin, and one should always rule out other secondary causes. The FDA continues to believe the cardiovascular benefits of statins outweigh these small increased risks.

With the exception of pravastatin and pitavastatin, the other statins undergo biotransformation by the cytochrome P-450 (CYP) system with lovastatin and simvastatin having the highest risk of drug–drug interactions. Therefore, drugs known to inhibit statin metabolism should be used cautiously or avoided and are highlighted in an AHA scientific statement on statin–drug interactions.[19] Medications such as cyclosporine and gemfibrozil can inhibit drug transporters in the gut and liver that can increase statin concentrations. The time until maximum effect on lipids for statins is generally 4 to 6 weeks.

▶ *Cholesterol Absorption Inhibitors*

Ezetimibe blocks biliary and dietary cholesterol as well as phytosterol (plant sterol) absorption by interacting with the NPC1L1

Table 13–9

Effects of Lipid-Lowering Drugs on Serum Lipids at FDA-Approved Doses

Lipid-Lowering Drug	LDL Cholesterol	HDL Cholesterol	Triglycerides	Total Cholesterol
Statins				
Atorvastatin	–26% to –60%	+5% to +13%	–17% to –53%	–25% to –45%
Fluvastatin	–22% to –36%	+3% to +11%	–12% to –25%	–16% to –27%
Fluvastatin ER	–33% to –35%	+7% to +11%	–19% to –25%	–25%
Lovastatin	–21% to –42%	+2% to +10%	–6% to –27%	–16% to –34%
Pitavastatin	–31% to –45%	+1% to +8%	–13% to –22%	–23% to –31%
Pravastatin	–22% to –34%	+2% to +12%	–15% to –24%	–16% to –25%
Rosuvastatin	–45% to –63%	+8% to +14%	–10% to –35%	–33% to –46%
Simvastatin	–26% to –47%	+8% to +16%	–12% to –34%	–19% to –36%
Cholesterol Absorption Inhibitor				
Ezetimibe	–18%	+1% to +2%	–7% to –9%	–12% to –13%
Bile Acid Sequestrants				
Cholestyramine	–15% to –30%	+3% to +5%	May increase in patients with elevated triglycerides	–10% to –25%
Colesevelam	–15% to –18%	+3% to +5%		–70% to –10%
Colestipol	–15% to –30%	+3% to +5%		–10% to 25%
Nicotinic Acid				
Niacin ER	–5% to –17%	+14% to +26%	–11% to –38%	–3% to –12%
Niacin IR	–5% to –25%	+15% to +39%	–20% to –60%	–3% to –25%
Fibric Acid Derivatives				
Fenofibrate	–31% to +45%	+9% to +23%	–23% to –54%	–9% to –22%
Gemfibrozil	–30% to +30%	+10% to +30%	–20% to –60%	–2% to –16%
Omega-3-Fatty Acids				
Omega-3 ethyl esters	+45%	+9%	–45%	–10%
Icosapent ethyl	–5%	–4%	–27%	–7%
Microsomal Transfer Protein Inhibitors				
Lomitapide	–40%	–7%	–45%	–36%
Antisense Oligonucleotide				
Mipomersen	–25%	+15%	–18%	–21%
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors				
Alirocumab	–48% to –71%			–46% to –59%
Evolocumab	–48% to –71%			–46% to –59%
Adenosine Triphosphate Citrate Lyase (ACL) Inhibitors				
Bempedoic Acid	–15% to –25%	–5%		–11%

ER, extended-release; FDA, Food and Drug Administration; HDL, high-density lipoprotein; IR, immediate-release; LDL, low-density lipoprotein.

transporter (Figure 13–2 and Figure 13–7).^{5} Less cholesterol is delivered to the liver, which leads to an upregulation of LDL receptors. This causes a reduction in serum cholesterol and a compensatory increase in cholesterol biosynthesis. Because statins inhibit cholesterol biosynthesis, this compensatory increase by ezetimibe can be blocked when coadministered with a statin.

KEY CONCEPT Ezetimibe reduces LDL cholesterol by an average of 18%. However, larger reductions can be seen in some individuals, presumably due to higher absorption of cholesterol. These individuals appear to have a blunted response to statin therapy. Ezetimibe lowers triglycerides by 7% to 9% and modestly increases HDL cholesterol (see Table 13–9).

Ezetimibe is contraindicated in patients with active liver disease or unexplained persistent elevations in LFTs. Since statins are the standard of care, a placebo-controlled randomized trial of the effects of ezetimibe monotherapy on CHD morbidity and mortality has never been conducted. Ezetimibe combined with simvastatin was associated with a reduced incidence of ischemic cardiovascular events in low-risk patients with mild-to-moderate

Patient Encounter 2, Part 1

A 52-year-old man presents to your clinic for a physical examination. He states that he was diagnosed with peripheral artery disease 2 years ago, and he tries to take his medications every day. He has not had his cholesterol evaluated in the last 2 years. He reports having claudication pain about one to two times a month. His family has no history of cardiovascular disease. Both his parents are alive. He is married with three children. He is a former smoker who quit 2 years ago. He exercises regularly (three times a week most weeks riding his bike). He has not eaten yet this morning.

Does this patient have clinical ASCVD?

Can the patient be evaluated today for LDL cholesterol?

Should an assessment of his risk factors for ASCVD or an ASCVD risk score be conducted?

What additional information do you need to evaluate the patient?

Table 13–10

Formulation, Dosing, and Common Adverse Effects of Lipid-Lowering Drugs

Lipid-Lowering Drug	Dosage Forms	Usual Adult Maintenance Dose Range	Adverse Effects
Statins			
Atorvastatin	10-, 20-, 40-, 80-mg tablets	10–80 mg once daily (at any time of day). Dose adjustment in patients with renal dysfunction is not necessary	Most frequent side effects are constipation, abdominal pain, diarrhea, and nausea. Statins should be dose reduced and/or discontinued promptly if serum transaminase levels (liver function tests) rise to three times upper limit of normal or if patient develops signs or symptoms of myopathy. Dose equivalence should be considered when switching HMG-CoA reductase inhibitors
Fluvastatin	20-, 40-mg capsules; 80-mg extended-release tablets	20–40 mg/day as a single dose (evening) or 40 mg twice daily; 80-mg extended-release once daily. Dose adjustments for mild-to-moderate renal impairment are not necessary	
Lovastatin	10-, 20-, 40-mg tablets	10–80 mg/day as a single dose (with evening meal) or divided twice daily with food; 20–60 mg/day as a single dose. In patients with severe renal insufficiency (creatinine clearance < 30 mL/min [0.5 mL/s]), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously	
Pravastatin	10-, 20-, 40-, 80-mg tablets	10–80 mg/day as a single dose at bedtime. In patients with a history of significant renal or hepatic dysfunction, a starting dose of 10 mg daily is recommended	
Pitavastatin	1-, 2-, 4-mg tablets	1–4 mg/day as a single dose can be taken with or without food, at any time of day. Moderate renal impairment (glomerular filtration rate 30–60 mL/min/1.73 m^2 [0.29–0.58 mL/s/m^2]) and end-stage renal disease on hemodialysis: Starting dose of 1 mg once daily and maximum dose of 2 mg once daily	
Rosuvastatin	5-, 10-, 20-, 40-mg tablets	5–40 mg/day (at any time of day); 40 mg reserved for those who do not achieve LDL cholesterol goal on 20 mg. In patients with history of significant renal dysfunction or Asian, starting dose of 5 mg daily is recommended	
Simvastatin	5-, 10-, 20-, 40-, 80-mg tablets	5–40 mg/day as a single dose in the evening, or divided. Recommended starting dose for patients at high risk of CHD is 40 mg/day. In patients with mild-to-moderate renal insufficiency, dosage adjustment is not necessary. However, caution should be exercised in patients with severe renal insufficiency; such patients should be started at 5 mg/day and be closely monitored. Due to increased risk of myopathy, including rhabdomyolysis, use of the 80-mg dose should be restricted to patients who have been taking simvastatin 80 mg chronically (eg, for 12 months or more) without evidence of muscle toxicity.	
Cholesterol Absorption Inhibitors			
Ezetimibe	10-mg tablets	10 mg once daily. No dosage adjustment is necessary in patients with renal or mild hepatic insufficiency	Overall incidence of adverse events reported with ezetimibe alone was similar to that reported with placebo and generally similar between ezetimibe with a statin and statin alone. The frequency of increased transaminases was slightly higher in patients receiving ezetimibe plus a statin compared with those receiving statin monotherapy (1.3% vs 0.4%)
Bile Acid Sequestrants			
Cholestyramine	4-g packets	4–24 g/day in two or more divided doses	Main side effects are nausea, constipation, bloating, and flatulence, although these may be less with colesevelam. Increasing fluid and dietary fiber intake may relieve constipation and bloating. Impairs absorption of fat-soluble vitamins
Colesevelam	625-mg tablets	3750 mg/day as a single dose or divided twice daily, with meals	
	3.75-g oral suspension packet	One packet once a day with meals	
Colestipol	5-g packets	5–30 g/day as a single dose or divided	
	1-g tablets	2–16 g/day as a single dose or divided	

(Continued)

Table 13–10

Formulation, Dosing, and Common Adverse Effects of Lipid-Lowering Drugs (*Continued*)

Lipid-Lowering Drug	Dosage Forms	Usual Adult Maintenance Dose Range	Adverse Effects
Nicotinic Acid (Prescription Products)			
Niacin ER	250-, 500-, 750-, 1000-mg extended-release tablets	1000–2000 mg once daily at bedtime. Use with caution in patients with renal impairment	Side effects include flushing, itching, gastric distress, headache, hepatotoxicity, hyperglycemia, and hyperuricemia
Niacin IR	250-, 500-mg tablets	1–6 g/day in two to three divided doses. Do not exceed 6 g daily	
Fibric Acid Derivatives			
Fenofibrate	54-, 160-mg tablets[a]	54–160 mg/day; the dosage should be minimized in severe renal impairment	Most common side effects are nausea, diarrhea, abdominal pain, and rash. Increased risk of rhabdomyolysis when given with a statin. Fibric acids are associated with gallstones, myositis, and hepatitis
Gemfibrozil	600-mg tablets	1200 mg/day in two doses, 30 minutes before meals; should be avoided in hepatic or severe renal impairment	
Omega-3-Fatty Acids			
Omega-3 ethyl esters	1-g capsule containing at least 0.9 g of OM3FA ethyl ester (EPA~0.465 g and DHA ~0.375 g)	4 g/day taken as single 4-g dose (four capsules) or two 2-g doses (two capsules twice daily)	All products are obtained from oil of fish. Should be used with caution in patients with known hypersensitivity to fish and/or shellfish. Side effects of Lovaza/Omtryg include: • Eructation, 4% • Dyspepsia, 3% • Taste perversion, 4% Side effects of Vascepa include: • Arthralgia, 2.3%
Icosapent ethyl	0.5-, 1-g capsule containing 1 g of icosapent ethyl	2 g twice daily with meals	
Microsomal Transfer Protein Inhibitors			
Lomitapide	5-,10-, 20-, 30-, 40-, and 60-mg capsules	5 mg once daily. Titrate dose based on acceptable safety/tolerability: increase to 10 mg daily after at least 2 weeks; and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and up to the maximum recommended dose of 60 mg daily	Gastrointestinal side effects and elevation in liver enzymes and hepatic fat are common
Antisense Oligonucleotide			
Mipomersen	200-mg subcutaneous injection	200 mg once weekly as a subcutaneous injection	Injection site reactions, hepatic fat, and liver enzyme elevations are common
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors			
Alirocumab	75- or 150-mg subcutaneous injection	75–150 mg once every 2 week subcutaneous injection or 300 mg once every month subcutaneous injection	Injection site reactions, nasopharyngitis, influenza, upper respiratory tract infections, urinary tract infection, elevation in liver enzymes
Evolocumab	140- or 420-mg subcutaneous injection	140 mg once every 2 week subcutaneous injection or 420 mg once every month subcutaneous injection	Injection site reactions, nasopharyngitis, influenza, upper respiratory tract infections, urinary tract infection, back pain
Adenosine Triphosphate Citrate Lyase (ACL) Inhibitors			
Bempedoic acid	180-mg tablets	180 mg once daily. No dosage adjustment for patients with renal or hepatic insufficiency provided in labeling	Hyperuricemia
Combination Products			
Ezetimibe and simvastatin	10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg	Dosage range is 10/10 mg/day through 10/40 mg/day. Recommended usual starting dose is 10/10 or 10/20 mg/day. Initiation of therapy with 10/10 mg/day may be considered for patients requiring less aggressive LDL cholesterol reductions. Due to increased risk of myopathy, including rhabdomyolysis, use of the 10/80-mg dose of Vytorin should be restricted to patients who have been taking Vytorin 10/80 mg chronically (eg, for 12 months or more) without evidence of muscle toxicity	See previous entries for each drug (ezetimibe and simvastatin)
Bempedoic acid and ezetimibe	180 mg/10 mg	180 mg/10 mg once daily	See previous entries for each drug (bempedoic acid and ezetimibe)

[a] Dose strengths vary depending on brand.

CHD, coronary heart disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ER, extended-release; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; IR, immediate-release; LDL, low-density lipoprotein; OM3FA, omega-3 fatty acid.

asymptomatic aortic stenosis compared with placebo,[20] as well as reduced incidence of major atherosclerotic events in a wide range of patients with advanced CKD.[21] Ezetimibe combined with simvastatin was shown to further reduce ASCVD events in patients who have suffered a recent MI compared to simvastatin alone.[22] Additionally, ezetimibe combined with bempedoic acid has been shown to be safe and effective at lowering LDL cholesterol. Ezetimibe is primarily used in combination with a statin when adequate reductions in atherogenic cholesterol are not achieved (Figure 13–6) or in those patients who are intolerant to statin therapy. The time until maximum effect on lipids for ezetimibe is generally 2 weeks.

▶ *Bile Acid Sequestrants*

Cholestyramine, colestipol, and colesevelam are the oral bile acid–binding resins or sequestrants (BAS) currently available in the United States. Resins are highly charged molecules that bind to bile acids in the gut (Figure 13–7). The resin–bile acid complex is then excreted in the feces. The loss of bile causes a compensatory conversion of hepatic cholesterol to bile, reducing hepatocellular stores of cholesterol and resulting in an upregulation of LDL receptors which then results in a decrease in serum cholesterol. Resins have been shown to reduce CHD events in patients without CHD.[23]

KEY CONCEPT Resins are moderately effective in lowering LDL cholesterol but do not lower triglycerides. Moreover, in patients with elevated triglycerides, the use of a resin may increase triglycerides. This may be due to a compensatory increase in HMG-CoA reductase activity which increases secretion of VLDL. The increase in HMG-CoA reductase activity can be blocked with a statin, resulting in enhanced reductions in serum lipids. Resins reduce LDL cholesterol from 15% to 30%, with a modest increase in HDL cholesterol (3%–5%) (Table 13–9). Resins are most often used as adjuncts to statins in patients who require additional lowering of atherogenic cholesterol and are an option to add to statins if ezetimibe and PCSK9 inhibitors are not an option, per the 2018 AHA/ACC guidelines.[4] Additionally, they are an option to lower LDL cholesterol in patients who are completely statin intolerant or cannot tolerate a moderate or high dose of statin and need further LDL-cholesterol lowering. Since these drugs are not absorbed, adverse effects are limited to the gastrointestinal (GI) tract (Table 13–10). About 20% of patients taking cholestyramine or colestipol report constipation and symptoms such as flatulence and bloating. A large number of patients stop therapy because of the GI effects. Resins should be started at the lowest dose and escalated slowly over weeks to months as tolerated until the desired response is obtained. Patients should be instructed to prepare the powder formulations in 6 to 8 ounces (approximately 180–240 mL) of noncarbonated fluids, usually juice (enhances palatability) or water. Fluid intake should be increased to minimize constipation. Colesevelam is better tolerated with fewer GI side effects, although it is more expensive.[24] Colesevelam also has an indication for improvement of glycemic control in type 2 DM. All resins have the potential to prevent absorption of other drugs such as digoxin, warfarin, thyroxine, thiazides, β-blockers, fat-soluble vitamins, and folic acid. Potential drug interactions can be avoided by taking a resin either 1 hour before or 4 hours after these other agents. The time until maximum effect on lipids for resins is generally 2 to 4 weeks.

▶ *Adenosine Triphosphate Citrate Lyase Inhibitors*

Bempedoic acid decreases LDL cholesterol by its adenosine triphosphate citrate lyase (ACL) inhibition in the liver (Figure 13–7). By inhibiting ACL, an enzyme upstream of HMG-CoA reductase, bempedoic acid decreases conversion of mitochondrial-derived citrate to cytosolic acetyl-CoA carboxylase, creating less substrate for cholesterol and FA synthesis.[25]

KEY CONCEPT Bempedoic acid reduces LDL cholesterol by an average of 15% to 25% and up to 38% when combined with ezetimibe. In 2020, the FDA-approved bempedoic acid and the combination of bempedoic acid with ezetimibe for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established ASCVD who require additional LDL-cholesterol lowering after maximally tolerated statin therapy.[26] Overall, bempedoic acid has demonstrated good tolerance in clinical trials, and the only noted adverse event seen has been increases in uric acid. The ongoing Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen (CLEAR) Outcomes trial aims to evaluate whether bempedoic acid can reduce CV events in patients with statin intolerance, but the trial is not set to conclude for another few years.[27,28]

▶ *Niacin*

Niacin (vitamin B_3) has broad applications in the treatment of lipid disorders when used at doses higher than those used as a nutritional supplement. Niacin inhibits FA release from adipose tissue and FA and triglyceride production in liver cells. This results in a reduction in the number of VLDL particles secreted (Figure 13–3), which leads to an overall reduction in LDL cholesterol and a decrease in the number of small dense LDL particles (Figure 13–7). Niacin also reduces the uptake of HDL-Apo A1 particles and increases uptake of cholesterol esters by the liver, thus improving the efficiency of reverse cholesterol transport between HDL particles and vascular tissue (Figure 13–3). Niacin is indicated for patients with elevated triglycerides, low HDL cholesterol, and elevated LDL cholesterol.[7,8]

Several different niacin formulations are available: immediate-release (IR), sustained-release (SR), and extended-release (ER).[29] These formulations differ in terms of dissolution and absorption rates, metabolism, efficacy, and side effects. Limitations of niacin IR and SR are flushing and hepatotoxicity, respectively. These differences appear related to the dissolution and absorption rates of niacin formulations and their subsequent metabolism. Niacin IR is available by prescription (Niacor) as well as a dietary supplement, which is not regulated by the FDA.[29] Currently, all SR products are available only as dietary supplements.

Niacin ER (Niaspan) was developed as a once-daily formulation to be taken at bedtime, with the goal of reducing the incidence of flushing without increasing the risk of hepatotoxicity. Niaspan is the only long-acting niacin product approved by the FDA for dyslipidemia.

Niacin use is limited by cutaneous reactions such as flushing and pruritus of the face and body. The use of aspirin or a nonsteroidal anti-inflammatory drug (NSAID) 30 minutes prior to taking niacin can help alleviate these reactions because they are mediated by an increase in prostaglandin D2.[7,8] In addition, taking niacin with food and avoiding hot liquids or alcohol at the time niacin is taken is helpful in minimizing flushing and pruritus. Lastly, slow titration of the niacin dose to minimize and/or prevent flushing (eg, 500 mg/day to 1000 mg/day over 8 weeks).

In general, niacin reduces LDL cholesterol from 5% to 25%, reduces triglycerides by 11% to 60%, and increases HDL cholesterol by 14% to 39% (Table 13–9). Niacin monotherapy has been shown to reduce CHD events and total mortality, as well as the progression of atherosclerosis when combined with a statin.[29,30] However, a trial that tested the effects of adding niacin ER or placebo in patients with CHD optimally treated (LDL cholesterol approximately 70 mg/dL [1.81 mmol/L]) on a statin was stopped earlier than planned because no apparent benefits by adding niacin ER were found. Moreover, a small and unexplained increase in ischemic stroke in the niacin ER group was seen.[31] Another trial also found no benefit by the addition of niacin ER plus an anti-flush medication (laropiprant).[32] These two trials have resulted in ambiguity in the role of niacin in lipid management. However, niacin is still a useful agent in the management of high triglycerides.

Niacin should be instituted at the lowest dose and gradually titrated to a maximum dose of 2 g daily for ER and SR products and no more than 6 g daily for IR products. FDA-approved niacin products are preferred because of product consistency. Moreover, niacin products labeled as "no flush" do not contain nicotinic acid and therefore have no therapeutic role in the treatment of lipid disorders.[29] The time until maximum effect on lipids for niacins is generally 3 to 5 weeks.

▶ Fibrates

KEY CONCEPT The predominant effects of fibrates are a decrease in triglyceride levels by 20% to 60% and an increase in HDL cholesterol levels by 9% to 30% (Table 13–9). The effect on LDL cholesterol is less predictable. In patients with high triglycerides, however, LDL cholesterol may increase. Fibrates increase the size and reduce the density of LDL particles much like niacin. **KEY CONCEPT** Fibrates are the most effective triglyceride-lowering drugs and are used primarily in patients with elevated triglycerides and low HDL cholesterol.

Fibrates work by activating peroxisome proliferator-activated receptor-alpha (PPAR-α), a nuclear receptor involved in cellular function. This results in a reduction in triglyceride-rich lipoproteins (VLDL and IDL) and an increase in HDL.

Clinical trials of fibrate therapy in patients with elevated cholesterol and no history of CHD demonstrated a reduction in CHD incidence, although less than the reduction attained with statin therapy.[33] In addition, a large study of men with CHD, low HDL cholesterol, low LDL cholesterol, and elevated triglycerides demonstrated a 24% reduction in risk of death from CHD, nonfatal MI, and stroke with gemfibrozil.[33] LDL-lowering therapy with statins should be the primary target if non-HDL and LDL cholesterol are elevated. Evidence of a reduction in CHD risk among patients with established CHD has not been demonstrated with fenofibrate.

The fibric acid derivatives are generally well tolerated. The most common adverse effects include dyspepsia, abdominal pain, diarrhea, flatulence, rash, muscle pain, and fatigue (Table 13–10). Myopathy and rhabdomyolysis can occur, and the risk appears to increase with renal insufficiency or concurrent statin therapy. If a fibrate is used with a statin, fenofibrate is preferred because it appears to inhibit the glucuronidation of the statins less than gemfibrozil.[33] A CK level should be checked before therapy is started and if symptoms occur. Fibrates should be avoided with severe renal dysfunction (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2). Baseline renal function should be assessed and then periodically reassessed in patients with renal dysfunction. Of note, fenofibrate can reversibly increase serum creatinine levels. Liver dysfunction has been reported, and LFTs should be monitored. Fibrates increase cholesterol in the bile and have caused gallbladder and bile duct disorders, such as cholelithiasis and cholecystitis. Unlike niacin, these agents do not increase glucose or uric acid levels. Fibrates are contraindicated in patients with gallbladder disease, liver dysfunction, or severe kidney dysfunction. Risk of bleeding is increased in patients taking both a fibrate and warfarin, specifically with gemfibrozil based on a CYP 2C9 interaction which can result in an increase in a patient's international normalized ratio (INR) if adding gemfibrozil to warfarin therapy. Increased INR monitoring is suggested after initiation of gemfibrozil in patients currently taking warfarin. The time until maximum effect on lipids is generally 2 weeks for fenofibrate and 3 to 4 weeks for gemfibrozil.

▶ Omega-3 Fatty Acids

Omega-3 fatty acids (OM3FA) (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), the predominant long-chain FA in the oil of cold-water fish, lower triglycerides by as much as 45% (Table 13–9) when taken in large amounts (2–4 g). Long-chain OM3FA may be useful for patients with high triglycerides despite diet and weight loss, alcohol restriction, and fibrate therapy. This effect may be modulated through reduction in hepatic synthesis and release of VLDL triglycerides, increased β-oxidation of FA, and enhanced triglyceride clearance from triglyceride-rich lipoproteins. EPA and DHA both have the ability to lower triglycerides, but DHA also leads to increases in LDL cholesterol whereas EPA does not increase. Long-chain OM3FA have other cardiac effects such as reduced platelet aggregation and antiarrhythmic properties. The current AHA Scientific Statement on fish consumption, fish oil, OM3FA, and cardiovascular disease recommends an increased intake of OM3FA in the diet.[34]

Prescription-grade long-chain OM3FA ethyl esters and free FA formulations are FDA approved at a dose of 2 to 4 g daily for the treatment of elevated triglycerides (≥ 500 mg/dL [5.65 mmol/L]). Based on the REDUCE-IT, a multicenter, randomized, double-blind, placebo-controlled trial in patients with clinical ASCVD or with DM and additional CV risk factors, icosapent ethyl has demonstrated the ability to lower CV events in patients on maximum tolerated statins with fasting triglycerides from 135 to 499 mg/dL (1.53–5.64 mmol/L) and an LDL cholesterol from 41 to 100 mg/dL (1.06–2.59 mmol/L).[10] The positive CV outcomes seen with icosapent ethyl have not been demonstrated with other prescription OM3FA products (eg, omega-3 acid ethyl esters). One hypothesis is that icosapent ethyl only contains EPA and thus does not increase LDL cholesterol like the omega-2 acid ethyl ester products which contain both EPA and DHA and can increase LDL cholesterol. As previously stated, the FDA approved icosapent ethyl as adjunct to maximally tolerated statin therapy to reduce the risk of MI, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with triglyceride levels greater than or equal to 150 mg/dL (1.70 mmol/L) and established ASCVD or DM and two or more additional risk factors for CV disease (ie, male > 55 years of age or female > 65 years of age, tobacco smoker, hypertension, low HDL cholesterol, hs-CRP > 3 mg/L, renal dysfunction, retinopathy, albuminuria, ABI < 0.9).

Use of high-quality OM3FA free of contaminants such as mercury and organic pollutants should be encouraged when using these agents. Common side effects associated with long-chain OM3FA are dyspepsia and eructation (Table 13–10). Patients taking anticoagulant or antiplatelet agents should be monitored more closely when consuming these products because excessive amounts of long-chain OM3FA (eg, > 3 g daily) may lead to bleeding and may increase risk of hemorrhagic stroke.

▶ Microsomal Triglyceride Transport Inhibitors

Lomitapide is an oral inhibitor of microsomal triglyceride transfer protein, thereby inhibiting the normal transfer of triglycerides to Apo B in the lumen of the endoplasmic reticulum and preventing the assembly of Apo B–containing lipoproteins in enterocytes and hepatocytes.[7,8] Lomitapide reduces LDL cholesterol levels on average by 40% (Table 13–9) in homozygous FH patients on maximum tolerated lipid-lowering therapy and LDL apheresis. However, given its mechanism of action, GI side effects and elevation in liver enzymes and hepatic fat are common (Table 13–10). Because of the risk of hepatotoxicity, lomitapide is available only through the Risk Evaluation and Mitigation Strategy (REMS) program and is currently FDA approved for the management of patients with homozygous FH. Gastrointestinal side effects are managed by strict adherence to a low-fat diet (< 20% of total calories from fat) and gradual dose escalation based on acceptable safety and tolerability. Lomitapide is primarily metabolized by CYP 3A4. Lomitapide interacts with numerous agents such as strong and moderate CYP 3A4 inhibitors and 3A4 inducers. Lomitapide is classified as pregnancy category X.

▶ *Antisense Oligonucleotide Inhibitor of Apo B-100 Synthesis*

Mipomersen is a once-weekly subcutaneous injectable antisense inhibitor of Apo B synthesis. When given in combination with maximum tolerated doses of lipid-lowering therapy, it can reduce LDL cholesterol by an additional 25% in homozygous FH patients (Table 13–9).[7,8] Injection site reactions, flu-like symptoms, hepatic fat, and liver enzyme elevations are common (Table 13–10). Because of the risk of hepatotoxicity similar to lomitapide, mipomersen is available only through a REMS program. Mipomersen is not a substrate for CYP metabolism and is metabolized by endonucleases and exonucleases. Therefore, mipomersen has minimal clinically relevant drug–drug interactions. Mipomersen is pregnancy category B.

▶ *Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors*

Alirocumab and evolocumab are subcutaneous injectable human monoclonal antibodies that bind to PCSK9. PCSK9 binds to the LDL receptors on hepatocyte surfaces to promote low-density lipoprotein receptor (LDLR) degradation (Figure 13–7). LDLR is the primary receptor that clears circulating LDL; therefore, the decrease in LDLR levels by PCSK9 results in higher blood levels of LDL. By inhibiting the binding of PCSK9 to LDLR, these agents increase the number of LDLRs available to clear LDL, thereby lowering LDL levels. In clinical trials, these agents have produced an additional 48% to 71% decrease in LDL levels when used in combination with statin therapy, compared with statin monotherapy (Table 13–9). Both medications are FDA approved for heterozygous FH or ASCVD as an adjunct to diet and maximally tolerated statin therapy, when additional LDL lowering is required.[4,7,8] Evolocumab is also indicated as an adjunct in homozygous FH.[4,7,8] The results of the CV outcomes study for evolocumab demonstrated CV event lowering.[35] Alirocumab's CV outcome trial demonstrated a reduction in major adverse cardiovascular events in post-acute coronary syndrome patients who were taking maximally tolerated statins compared to placebo.[36,37] Both the evolocumab and alirocumab CV outcome studies demonstrated a reduction in the primary CV composite endpoint on top of statin therapy. These findings drove the 2018 AHA/ACC guidelines to include PCSK9 inhibitors as nonstatin therapy that is recommended to be added to maximum tolerated statin therapy in the very-high-risk ASCVD population (Figure 13–6). The 2018 AHA/ACC guidelines additionally recommend adding ezetimibe to maximum tolerated statin therapy prior to adding PCSK9 inhibitors as a more cost-effective approach.

Combination Pharmacotherapy

A large proportion of the US population remains at high risk for future CV events despite treatment with statin therapy. Reasons for high residual risk include inadequate starting doses, lack of dose escalation, and high baseline risk warranting lower treatment targets. In addition, if lack of response is seen, patient adherence and adverse events should be assessed. Moreover, patients with concomitant elevations in triglycerides may need combination drug therapy to reach their non-HDL cholesterol goal. **KEY CONCEPT** Combination drug therapy is an effective means to achieve greater reductions in non-HDL and LDL cholesterol (statin plus ezetimibe or PCSK9 inhibitor) as well as lowering serum triglycerides (statin plus long-chain OM3FA or fibrate).

▶ *Combination Therapy for Elevated LDL Cholesterol*

For patients who do not achieve their non-HDL and LDL cholesterol goals with statin monotherapy and lifestyle modifications, including those unable to tolerate high doses due to adverse effects, combination therapy may be appropriate. The 2018 AHA/ACC guidelines describe the first-line and second-line add-on therapies to statins for both primary and secondary prevention of

Patient Encounter 2, Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Diagnosed with peripheral artery disease 2 years ago (most recent right ABI = 0.67 and left ABI = 0.60).

FH: Both parents are still living; no known cardiovascular disease in family.

SH: Works in an office setting and exercises three times a week (rides bike about 5 miles each time). Drinks alcohol (three beers about three to four times a week)

Meds: Losartan 100 mg once daily, amlodipine 10 mg once daily, aspirin 81 mg daily, atorvastatin 80 mg once daily

ROS: No chest pain, shortness of breath, or dizziness today in clinic

PE:

VS: BP 140/86 mm Hg, pulse 88 beats/min, RR 18 breaths/min, T 98.8°F (37.1°C)

CV: RRR, normal S_1, S_2; no murmurs, rubs, or gallops

Abd: Soft, nontender, nondistended; positive for bowel sounds, no hepatosplenomegaly or abdominal aortic aneurysm

Exts: Right ABI 0.67 and Left ABI 0.60

Neck: No carotid and basilar bruits

EENT: Within normal limits

Labs: Total cholesterol 220 mg/dL (5.69 mmol/L), triglycerides 230 mg/dL (2.60 mmol/L), HDL cholesterol 42 mg/dL (1.09 mmol/L), non-HDL cholesterol 178 mg/dL (4.60 mmol/L), LDL cholesterol 132 mg/dL (3.41 mmol/L) (baseline pre-statin LDL cholesterol 175 mg/dL [4.53 mmol/l]), and glucose 115 mg/dL (6.4 mmol/L); all other labs within normal limits

Given this additional information, what is your assessment of the patient's ASCVD risk?

Identify your treatment goals for the patient based on the AHA/ACC guidelines.

What nonpharmacologic and pharmacologic alternatives are available for the patient?

Should his children be screened for high cholesterol and why?

Develop a care plan for the patient.

ASCVD (Figure 13–6). First-line add-on therapies include ezetimibe or PCSK9 inhibitors. Second-line add-on therapies include BAS. Bempedoic acid is not mentioned in the guidelines since it was just recently FDA approved. Ezetimibe, PCSK9 inhibitors, and BAS combine effectively with statins to augment further cholesterol reduction, with the largest LDL cholesterol and non-HDL cholesterol reductions seen with PCSK9 inhibitors combined with statins. Adverse events are similar to those of each product taken separately. The time until maximum effect on lipids for the combinations of statins plus ezetimibe, PCSK9 inhibitors, BAS, or bempedoic acid is generally 4 weeks.

Some patients, in particular those with genetic forms of hypercholesterolemia such as FH (Table 13–1), require three or more drugs to manage their disorder. It is recommended that patients with FH obtain a minimum of greater than or equal to 50% reduction in LDL cholesterol.[4,7,8]

▶ Combination Therapy for Elevated Cholesterol and Triglyceridemia with or without Low HDL Cholesterol

Fibrates are the most effective triglyceride-lowering agents and also raise HDL cholesterol levels. Combination therapy with a fibrate, particularly gemfibrozil, and a statin has been found to increase the risk for myopathy. Therefore, more frequent monitoring, thorough patient education, and consideration of factors that increase risk as reviewed previously should be considered.

KEY CONCEPT The evidence of reducing non-HDL and LDL cholesterol while substantially raising HDL cholesterol (statin plus niacin or fibrate) to reduce the risk of CHD-related events to a greater

Patient Care Process

Collect Information:

- Obtain fasting cholesterol profile.
- Obtain vital signs and physical examination findings.
- Obtain a thorough history of prescription, nonprescription, and natural drug product use.
- Obtain history of lipid-lowering therapy use (current and past).
- Obtain a family history for premature heart disease.
- Obtain a smoking history.
- Obtain a medical history for other comorbidities that may increase ASCVD risk or adverse drug reactions to the lipid-lowering therapy.
- Obtain history of current diet and exercise regimen/pattern.

Assess the Information:

- Assess any abnormal lipid levels (Table 13–6).
- Assess lifestyle factors including diet and exercise habits.
- Assess if patient fits any of the groups who would benefit from lipid-lowering therapy (Figures 13–5 and 13–6).
- Assess major risk factors for ASCVD (Table 13–8). Assign patient to risk category based on AHA/ACC patient benefit groups or NLA/AACE risk categories previously described (eg, Figure 13–6 and Tables 13–7 and 13–8).
- Assess if taking any medications that may contribute to abnormal lipid levels or increase risk of adverse drug reactions (eg, drug interactions) (Table 13–2).
- Assess concomitant diseases that may contribute to abnormal lipid levels (Table 13–2).
- Assess treatments for cholesterol the patient has used in the past (if any). If already receiving pharmacotherapy for dyslipidemia, assess efficacy, safety, and adherence. Are there any significant drug interactions?

Develop a Care Plan:

- Determine treatment goal for percent LDL cholesterol lowering, non-HDL cholesterol, and LDL cholesterol based on risk category (Figures 13–5 and 13–6).
- Discuss importance of family screening if patient has FH.
- Select TLCs and educate patient on importance of TLCs and regular physical activity (Table 13–3).
- Consider starting pharmacotherapy in patients based on their risk category for ASCVD (Figures 13–5 and 13–6). Consider potential disease and drug interactions that may affect choice or intensity of pharmacotherapy (Table 13–10).
- For patients with ASCVD or DM, consideration should be given to use of moderate- or high-intensity statin therapy (Table 13–5), irrespective of baseline cholesterol levels.
- Determine patient's prescription coverage.

Implement the Care Plan:

- Provide patient education and address concerns associated with ASCVD, hyperlipidemia, drug therapy, and therapy adherence.
- Educate patient on TLC interventions (eg, exercise, diet modifications).
- Start pharmacotherapy concordant with statin-benefit group or overall ASCVD risk in collaboration with healthcare team.
- Develop a follow-up plan for the patient to assess efficacy and safety.
- Stress the importance of medication adherence to the patient.
- Address any patient concerns about dyslipidemia and its management.

Follow-up: Monitor and Evaluate:

- Follow-up at regular intervals (4–12 weeks after initiation/titration and then every 3–12 months thereafter) to assess cholesterol levels for attaining goals for dyslipidemia and monitoring of side effects (Table 13–10).
- Review medication adherence.
- Review physical examination, laboratory tests, and results of other diagnostic tests to assess changes in clinical status.
- For patients with FH, if it is not possible to attain desirable cholesterol levels, a reduction of at least 50% is recommended.
- Intensify TLC for those patients above cholesterol targets.
- Titrate therapy or add additional drug as needed.

degree than statin monotherapy remains in question. A trial found the combination of fenofibrate and simvastatin did not reduce the overall rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke, as compared with simvastatin alone.[38] However, in a prespecified subgroup analysis, incremental benefits of adding a fenofibrate to simvastatin therapy were noted in patients with triglycerides greater than or equal to 204 mg/dL (2.31 mmol/L) and HDL cholesterol less than or equal to 34 mg/dL (0.88 mmol/L).[38]

Compared with monotherapy, combination therapy may reduce patient adherence through increased side effects and increased costs. When used appropriately and with proper precautions, however, combination therapy is effective in normalizing lipid abnormalities, particularly in patients who cannot tolerate adequate doses of statin therapy for more severe forms of dyslipidemia.

OUTCOME EVALUATION

- **KEY CONCEPT** The successful outcome in cholesterol management is to reduce cholesterol and triglycerides in an effort to alter the natural course of atherosclerosis and decrease future cardiovascular events and pancreatitis.
- Use an adequate trial of TLC in all patients, but institute pharmacotherapy concurrently in higher-risk patients.
- For patients in whom lipid-lowering drug therapy is indicated, statin treatment is the primary modality for reducing ASCVD risk because of its ability to substantially reduce non-HDL and LDL cholesterol, ability to reduce morbidity and mortality from atherosclerotic disease, convenient once-daily dosing, availability of inexpensive generics, and low risk of side effects.
- Use an individualized patient monitoring plan in an effort to promote medication safety, minimize side effects, maintain treatment adherence, and achieve lipid goals.
- Lipid goals should be assessed by determining if the patient has achieved their target LDL cholesterol reduction based on their statin benefit group (eg, clinical ASCVD patient on a high-intensity statin should achieve at least a 50% reduction in LDL cholesterol; if baseline LDL cholesterol values are not available to calculate percent reduction, then achieving an LDL cholesterol of less than 70 mg/dL [1.81 mmol/L] or a non-HDL cholesterol of less than 100 mg/dL [2.59 mmol/L] are additional targets).

Abbreviations Introduced in This Chapter

AACE	American Association of Clinical Endocrinologists
ABI	Ankle-brachial index
ACC	American College of Cardiology
ACE	American College of Endocrinology
ACL	Adenosine triphosphate citrate lyase
AHA	American Heart Association
AIDS	Acquired immunodeficiency syndrome
Apo	Apolipoprotein
ASCVD	Atherosclerotic cardiovascular disease
BAS	Bile acid sequestrant
C	Cholesterol
CAC	Coronary artery calcium
CETP	Cholesterol ester transfer protein
CHD	Coronary heart disease
CK	Creatine kinase
CKD	Chronic kidney disease
CLEAR	Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen
CVD	Cardiovascular disease
CV	Cardiovascular
CYP	Cytochrome P-450
DBP	Diastolic blood pressure
DHA	Docosahexaenoic acid
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
EPA	Eicosapentaenoic acid
ER	Extended-release
FA	Fatty acid
FDA	Food and Drug Administration
FH	Familial hypercholesterolemia
GI	Gastrointestinal
HbA_{1c}	Glycosylated hemoglobin
HDL	High-density lipoprotein
HeFH	Heterozygous familial hypercholesterolemia
HIV	Human immunodeficiency virus
HL	Hepatic lipase
HMG-CoA	3-Hydroxy-3-methylglutaryl coenzyme A
hs-CRP	High-sensitivity C-reactive protein
IDL	Intermediate-density lipoprotein
INR	International normalized ratio
IR	Immediate-release
LDL	Low-density lipoprotein
LDLR	Low-density lipoprotein receptor
LFT	Liver function test
Lp(a)	Lipoprotein (a)
LPL	Lipoprotein lipase
LRP	LDL-related protein
MI	Myocardial infarction
NLA	National Lipid Association
NPC1L1	Niemann-Pick C1 Like 1
NSAID	Nonsteroidal anti-inflammatory drug
OM3FA	Omega-3 fatty acid
PPAR-α	Peroxisome proliferator-activated receptor-alpha
PCE	Pooled cohort equation
PCSK9	Proprotein convertase subtilisin/kexin 9
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
REDUCE-IT	Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial
REMS	Risk evaluation and mitigation strategy
SAMS	Statin-associated muscle symptoms
SBP	Systolic blood pressure
SR	Sustained-release
SR-BI	Scavenger receptor class B type I
TG	Triglycerides
TLC	Therapeutic lifestyle changes
VLDL	Very-low-density lipoprotein

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14 Circulatory Shock Syndromes

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. List the most common conditions resulting in the following circulatory shock syndromes: hypovolemic, cardiogenic, and obstructive.
2. Describe the major hemodynamic and metabolic abnormalities that occur in patients with circulatory shock.
3. Describe the clinical presentation including signs, symptoms, and laboratory test measurements for the typical circulatory shock patient.
4. Prepare a treatment plan with clearly defined outcome criteria for hypovolemic, cardiogenic, and obstructive shock patients, including fluid management, pharmacologic therapy, and/or surgical/mechanical interventions.
5. Compare and contrast relative advantages and disadvantages of crystalloids, colloids, and blood products in treating hypovolemic shock.
6. Formulate a stepwise monitoring strategy for patients with hypovolemic, cardiogenic, and obstructive shock.

INTRODUCTION

The primary function of the circulatory system is to supply oxygen and vital metabolic compounds to cells throughout the body, as well as remove metabolic waste products. Circulatory shock is a life-threatening condition whereby this principal function is compromised, resulting in inadequate cellular oxygen utilization.[1,2] While septic shock also has a cardiovascular component to its manifestation, it will not be addressed in this chapter based on its unique presentation involving the systemic inflammatory response. Instead, this shock state is addressed as a component of Chapter 84, "Sepsis and Septic Shock" within this textbook. Furthermore, less common shock states such as anaphylactic and neurogenic shock will not be addressed in this chapter. **KEY CONCEPT** When circulatory shock is caused by a severe loss of blood volume or body water, it is called hypovolemic shock. Cardiogenic shock can be thought of as "pump failure." It most often follows an acute myocardial infarction and less commonly, end-stage heart failure, advanced valvular disease, or cardiac arrhythmias.[2,3] Obstructive shock limits adequate heart functioning mechanically, usually due to a massive pulmonary embolism, cardiac tamponade, tension pneumothorax, or abdominal compartment syndrome.[4] These three shock states share the commonality of decreased blood flow.[5] Rapid and effective restoration of circulatory homeostasis using fluids and/or blood products, pharmacologic agents, and/or surgical/mechanical interventions is imperative to prevent complications of untreated shock and, ultimately, death following circulatory shock.

ETIOLOGY AND EPIDEMIOLOGY

The most common type of shock is septic shock, accounting for over 60% of cases in a large shock trial. In this same trial, cardiogenic, hypovolemic, and obstructive shock accounted for 16%, 16%, and 2% of enrolled patients, respectively.[6] The prognosis of shock patients depends on several variables, including type, severity, duration, underlying etiology, preexisting organ dysfunction, and reversibility.[5] For example, overall mortality rates may approach 50% in cardiogenic shock patients,[7] while hypovolemic shock due to hemorrhage is a major factor in trauma deaths, with an estimated 1.9 million deaths per year worldwide.[8]

Practitioners must have a good understanding of cardiovascular physiology to diagnose, treat, and monitor circulatory problems in critically ill patients. The interrelationships among the major hemodynamic variables are depicted in Figure 14–1.[9] These variables include mean arterial pressure (MAP), cardiac output (CO), systemic vascular resistance (SVR), heart rate (HR), stroke volume (SV), left ventricular size, afterload, myocardial contractility, and preload. Although an oversimplification, Figure 14–1 is beneficial in conceptualizing where the major abnormalities occur in patients with hypovolemic and cardiogenic shock as well as predicting the body's compensatory responses.

Hypovolemic shock is caused by a loss of intravascular volume either by hemorrhage or fluid loss (eg, dehydration). There is a profound deficit in preload, defined as the volume in the left ventricle at the end of diastole. Decreased preload results in subsequent decreases in SV, CO, and, eventually, MAP. As such, restoration of preload becomes an overarching goal in management of hypovolemic shock. Cardiogenic shock is primarily a result of diminished myocardial contractility leading to decreased SV and CO with an increase in preload due to inadequate left ventricular emptying. Obstructive shock interferes mechanically with the heart's capacity to function resembling heart failure resulting in a lowered CO and MAP.[4] This is due to decreased left ventricular filling secondary to these mechanical forces resulting in a reduction in preload, SV, and CO.

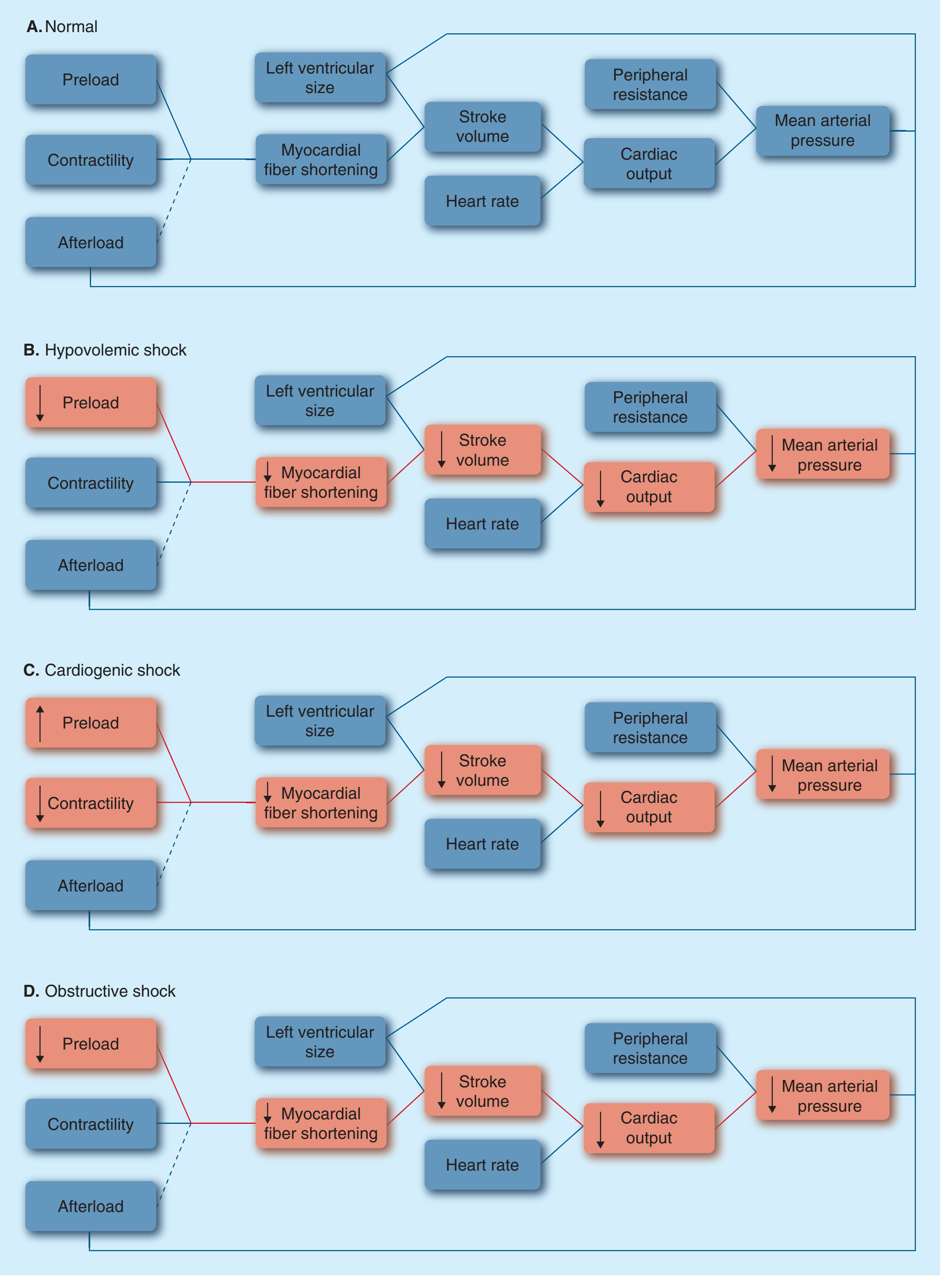
A. Normal
Preload
Contractility
Afterload
Left ventricular size
Myocardial fiber shortening
Stroke volume
Heart rate
Peripheral resistance
Cardiac output
Mean arterial pressure
B. Hypovolemic shock
↓ Preload
Contractility
Afterload
Left ventricular size
↓ Myocardial fiber shortening
↓ Stroke volume
Heart rate
Peripheral resistance
↓ Cardiac output
↓ Mean arterial pressure
C. Cardiogenic shock
↑ Preload
↓ Contractility
Afterload
Left ventricular size
↓ Myocardial fiber shortening
↓ Stroke volume
Heart rate
Peripheral resistance
↓ Cardiac output
↓ Mean arterial pressure
D. Obstructive shock
↓ Preload
Contractility
Afterload
Left ventricular size
↓ Myocardial fiber shortening
↓ Stroke volume
Heart rate
Peripheral resistance
↓ Cardiac output
↓ Mean arterial pressure

FIGURE 14–1. Hemodynamic relationships among key cardiovascular parameters (A). Solid lines represent a direct relationship; the broken line represents an inverse relationship. In (B), the alterations typically observed in hypovolemic shock are highlighted with arrows depicting the likely direction of the alteration. The alterations typically observed in cardiogenic shock are highlighted in (C). In (D), the alterations resulting from obstructive shock are highlighted. In this latter instance, the reduction in preload is secondary to mechanical interference with mechanical filling. (Panel A from Braunwald E. Regulation of the circulation. I. N Engl J Med. 1974;290:1124–1129, with permission.)

Table 14–1

Circulatory Shock Manifestations on Major Organs

Heart
- Myocardial ischemia
- Dysrhythmias

Brain
- Restlessness, confusion, obtundation
- Global cerebral ischemia

Liver
- Release of liver enzymes
- Biliary stasis

Lungs
- Pulmonary edema
- ARDS

Kidneys
- **Oliguria**
- Decreased glomerular filtration
- Acute kidney injury

GI tract
- Stress-related mucosal disease
- Bacterial translocation

Hematologic
- Thrombocytopenia
- Coagulopathies

ARDS, acute respiratory distress syndrome; GI, gastrointestinal.

PATHOPHYSIOLOGY

KEY CONCEPT Regardless of etiology, the most distinctive clinical manifestations of circulatory shock are arterial hypotension, clinical signs of hypoperfusion, and metabolic acidosis.[2] Metabolic acidosis is a consequence of an accumulation of lactic acid resulting from tissue hypoxia and anaerobic metabolism. Prolonged tissue hypoxia sets in motion a downward spiral of events leading to organ dysfunction and eventual failure if untreated. Table 14–1 describes the effects of shock on the body's major organs. Relative failure of more than one organ is referred to as multiple organ dysfunction syndrome (MODS). Primary or secondary involvement of the heart is particularly devastating considering its central role in oxygen delivery and the potential for myocardial dysfunction to perpetuate the shock state. Preexisting organ dysfunction and buildup of inflammatory mediators can also exacerbate effects of circulatory shock to the point of irreversibility.[7] For example, heart failure can lead to pulmonary edema, further aggravating gas exchange in the lungs, and, ultimately, tissue hypoxia. Thus, circulatory shock must be treated aggressively to avoid MODS.

Hypovolemic Shock

The total amount of water in a typical 70 kg (154 lb) adult is approximately 42 L (Figure 14–2). About 28 of the 42 L are inside the cells of the body (intracellular fluid); the remaining 14 L are in the extracellular fluid space (fluid outside of cells, ie, interstitial fluid and plasma). Circulating blood volume for a normal adult is roughly 5 L (70 mL/kg) and composed of 2 L of red blood cell fluid (intracellular) and 3 L of plasma (extracellular). Diminished intravascular volume results from severe external or internal bleeding, profound fluid losses from gastrointestinal (GI) sources such as diarrhea or vomiting, or urinary losses such as diuretic use, diabetic ketoacidosis, or diabetes insipidus (Table 14–2).[1,10] Other sources of intravascular fluid loss can occur through damaged skin, as seen with burns, or via capillary leak into the interstitial space or peritoneal cavity, as seen with peripheral edema or ascites. This latter phenomenon is often referred to as "third spacing" because fluid accumulates in the interstitial space disproportionately to the intracellular and extracellular fluid spaces. Regional ischemia may also develop as blood flow is naturally shunted from organs such as the GI tract or the kidneys to vital organs such as the heart and brain.

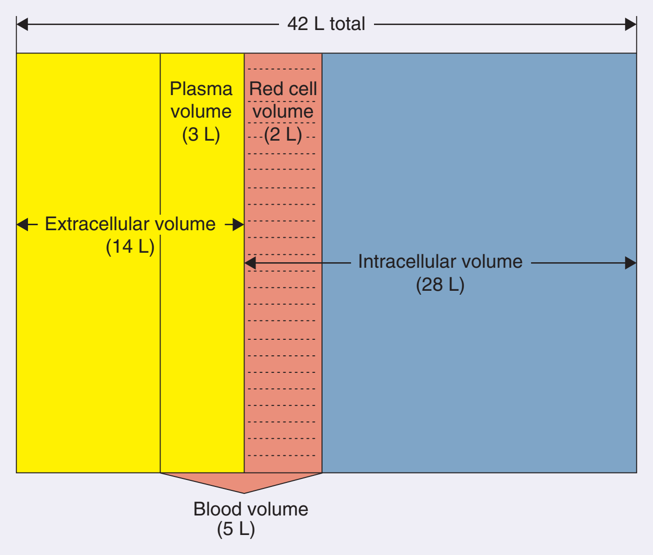

FIGURE 14–2. Distribution of body fluids showing the extracellular fluid volume, intracellular body fluid volume, and total body fluids in a 70 kg (154 lb) adult. Extracellular volume (ECV; yellow section of figure) comprises 14 L of total body fluid (42 L). Plasma volume makes up approximately 3 L of the 14 L of ECV. Intracellular volume (blue section of figure) accounts for the remaining 28 L of total body fluids, with roughly 2 L located within the red blood cells. Blood volume (~5 L) is also depicted and made up of primarily red blood cells and plasma (red section of figure). (From Guyton AC, Hall JE. Textbook of Medical Physiology, 8th ed. Philadelphia, PA: Saunders, 1991:275, with permission.)

Hypovolemic shock symptoms begin to occur with decreases in intravascular volume in excess of 1500 to 2000 mL (about 3–4 pints), or 30% to 40% of the circulating blood volume in adults.[8] Decreases in preload result in decreases in SV. Initially, CO may be partially maintained by compensatory tachycardia. Similarly, reflex increases in SVR, and myocardial contractility may diminish arterial hypotension. Regardless, rapid losses (eg, minutes) undoubtedly have more profound effects than losses

Table 14–2

Major Hypovolemic Shock Etiologies[1,2,10]

- I. Hemorrhagic
  - Trauma
  - Gastrointestinal bleeding
  - Abdominal aortic aneurysm
- II. Nonhemorrhagic
  - Vomiting
  - Diarrhea
  - Third spacing
  - Burns
  - Fistulae

Clinical Presentation and Diagnosis

General

Patients will be in acute distress, although symptoms and signs will vary depending on the severity of the circulatory shock

Symptoms

- Thirst
- Weakness
- Light-headedness
- Substernal chest pain; may be radiating to shoulder, back, jaw*
- Nausea

Signs

- Hypotension, arterial systolic blood pressure (SBP) less than 90 mm Hg or fall in SBP greater than 40 mm Hg
- Tachycardia
- Tachypnea
- Hypothermia
- Oliguria
- Dark, yellow-colored urine
- Skin color: pale to ashen; may be cyanotic in severe cases
- Skin temperature: cool to cold
- Mental status: confusion to coma
- **Pulmonary artery (PA) catheter** measurements: decreased CO, decreased SV, increased SVR, low **pulmonary artery occlusion pressure** (PAOP) (hypovolemic shock), high PAOP (cardiogenic shock, obstructive shock)
- Electrocardiogram (ECG) changes, arrhythmias*
- Pulmonary edema on chest X-ray*
- Bibasilar rales*
- Vomiting
- Diaphoresis*
- Organ dysfunction (see Table 14–2)

Laboratory Tests

- Increased serum lactate
- Decreased arterial pH
- Decreased hemoglobin/hematocrit (hemorrhagic hypovolemic shock)
- Hypernatremia (hypovolemic shock), hyponatremia (cardiogenic shock)
- Elevated serum creatinine (SCr)
- Elevated blood urea nitrogen
- Hyperglycemia
- Elevated troponin*

*Specific to cardiogenic shock.

over a longer period (eg, hours). This neurohumoral response to hypovolemia is mediated by the sympathetic nervous system in an attempt to preserve perfusion to vital organs such as the heart and brain. Two major endpoints of this response are to conserve water to maximize intravascular volume and improve tissue perfusion by increasing MAP and CO (oxygen delivery). The body attempts to maximize its fluid status by decreasing water and sodium excretion through the release of antidiuretic hormone (ADH), aldosterone, and cortisol. MAP is maintained by peripheral vasoconstriction mediated by catecholamine release and the renin–angiotensin system.[1] CO is augmented by catecholamine release and fluid retention.[1] Unfortunately, the increased sympathetic drive may become detrimental as tissue ischemia occurs with inconsistent microcirculatory flow.[1] The decrease in CO results in a diminished delivery of oxygen to tissues within the body and activation of an acute inflammatory response.[4,8] Oxygen delivery can be further compromised by inadequate blood hemoglobin levels due to hemorrhage and/or diminished hemoglobin saturation due to impaired ventilation. Decreased delivery of oxygen and other vital nutrients results in diminished production of the energy substrate adenosine triphosphate (ATP). Lactic acid is then produced as a by-product of anaerobic metabolism within tissues throughout the body. Lactic acidosis is a key indicator that inadequate tissue perfusion has occurred.[2]

Cardiogenic Shock

Cardiogenic shock is primarily a result of ventricular failure most commonly following an acute myocardial infarction or acute decompensated heart failure.[7] Valvular heart diseases and dysrhythmias can also lead to cardiogenic shock.[1] Readers are directed to Chapter 9, "Acute Coronary Syndromes" (ACS), and Chapter 7, "Heart Failure," for a more detailed description of the pathophysiology and postresuscitation management for these two conditions, including mechanical circulatory support and reperfusion therapy for ACS patients.[7,11] While both hypovolemic and cardiogenic shocks share a reduction in CO and MAP, one major difference is the effect on preload. Whereas hypovolemic shock will be associated with decreased preload, cardiogenic shock patients will generally have increased preload due to diminished ventricular emptying. Inappropriate compensatory fluid retention can also occur due to diminished renal blood flow.

Obstructive Shock

In obstructive shock, physical forces result in compression of the heart chambers or the great vessels. This results in diminished contraction of the heart and/or ventricular filling.[2] These compressive forces are generally a consequence of pericardial tamponade, tension pneumothorax, massive pulmonary emboli, or aortic dissection. Management of these conditions is therefore targeted at reducing the compressive forces through surgical intervention in the case of pericardial tamponade,[12] tension pneumothorax,[13] aortic dissection, and potentially thrombolytic therapy following a pulmonary embolus (see Chapter 11, "Venous Thromboembolism").

TREATMENT

Desired Outcomes

KEY CONCEPT The major goals in treating circulatory shock are to restore effective circulating blood volume and manage the underlying cause of shock. By optimizing the delivery of oxygen and metabolic substrates, such as glucose and electrolytes, to the tissues throughout the body, organ function will be restored and the body will return to homeostasis. This is evidenced by a return to the patient's baseline vital signs, relative normalization of laboratory test results, and alleviation of other signs and symptoms of circulatory shock previously summarized.

General Approach to Therapy

Securing an adequate airway and ventilation is imperative in circulatory shock patients consistent with the "VIP Rule" of resuscitation: Ventilate (oxygen administration), Infuse (fluid resuscitation if needed), and Pump (administration of a vasoactive and/or inotropic agent).[2,4] Any compromise in ventilation only exacerbates the tissue hypoxia occurring secondary to inadequate perfusion. Thus, sedation, endotracheal intubation, and mechanical ventilation should occur early in the resuscitation of the patient (see Figures 14–3 and 14–4). Additionally, intravenous (IV) access is essential for administration of fluids and/or medications. A peripheral IV or central venous catheter should be placed. Central venous access may be preferred in patients requiring rapid or large volumes of fluid and/or blood products, especially for hypovolemic shock. Placement of an arterial catheter is advantageous to allow for accurate and continuous monitoring of MAP, as well as arterial blood gas (ABG) sampling. A bladder catheter should be inserted for ongoing monitoring of urine output. Baseline laboratory tests that should be done immediately include complete blood cell count (CBC) with differential, serum chemistry profile, liver enzymes, prothrombin and partial thromboplastin times, serum lactate, and troponin if ACS is suspected. A urinalysis and an ABG should also be obtained, and ongoing ECG monitoring should be performed. In addition to restoring circulating blood volume, it is necessary to prevent further losses from the vascular space. For patients in hemorrhagic hypovolemic shock, identifying the source of bleeding and achievement of hemostasis is imperative to successfully resuscitate the patient. Frequently, surgical intervention is required to achieve hemostasis. A chest X-ray should also be obtained in patients suspected of cardiogenic or obstructive shock, as well as performance of echocardiography of the heart.[3] Ultrasonography may also be beneficial diagnostically in patients in hemorrhagic shock.[8]

Upon stabilization, central venous catheters that typically reside in the superior vena cava may be used to monitor central venous pressure (CVP). Measurement of CVP allows more specific hemodynamic monitoring than is available from noninvasive measurements such as vital signs, cardiac rhythm, and urine output.[7] Alternatively, a pulmonary artery (PA) catheter may be indicated based on the need for even more extensive cardiovascular monitoring. Key measured parameters obtained from a PA catheter are pulmonary artery occlusion pressure (PAOP), a measure of left ventricular preload, and CO. Based on CO values and simultaneous measurement of HR and MAP, left ventricular SV and SVR can be calculated. Placement of a PA catheter should be reserved for patients at high risk of death due to severity of the circulatory shock or patients with cardiogenic shock. Noteworthy, however, is that central venous catheters are less expensive than PA catheters and have been associated with comparable survival in selected critically ill patient subsets.[14]

Patient Encounter Part 1

A 63-year-old woman is admitted to the trauma center after being struck by a car as a pedestrian. She has bilateral open femur fractures and an unstable pelvis, and a bedside sonogram (focused assessment for sonography in trauma or FAST) shows intra-abdominal bleeding. She is awake but confused and not cooperating fully with her care due to pain. Her initial blood pressure (BP) is 68/40 mm Hg and HR is 112. She is tachypneic (RR 23) and oxygen saturation (SaO_2) is 90% (0.90).

Is this patient in shock? If so, what type of shock does the patient have and what is the cause?

Describe ways the patient can be stabilized for a full assessment.

Describe the first nonpharmacologic steps in treating the patient.

▶ *Fluid Therapy*

The use of fluids is the cornerstone of managing hypovolemic shock.[1,5] KEY CONCEPT Three major therapeutic options are available to clinicians for restoring circulating blood volume: crystalloids (electrolyte-based solutions), colloids (large molecular weight solutions), and blood products.[15] Crystalloid and colloid fluids are first-line therapy in all types of hypovolemic shock. Blood products should be reserved for patients in hemorrhagic shock or in patients with severe preexisting anemia. Vasopressors may be required in patients who are not initially responsive to IV fluids or blood products alone. The aggressiveness of fluid resuscitation (rate and volume) is driven by the severity of the hypovolemic shock and the underlying cause. Warming of all fluids to 37°C (98.6°F) prior to administration is an important consideration to prevent hypothermia, arrhythmias, and coagulopathy because these complications will have a negative impact on resuscitation effort success.[16]

Crystalloids Isotonic crystalloid solutions are fluids with (a) electrolyte composition that approximates plasma known as balanced solutions (eg, lactated Ringer's [LR] solution or Plasma-Lyte) or (b) a total calculated osmolality similar to that of plasma (280–295 mOsm/kg or mmol/kg), such as 0.9% sodium chloride (also known as normal saline [NS] or 0.9% NaCl) (Table 14–3).[15,17] Thus, conventional crystalloids distribute in normal proportions throughout the extracellular fluid space upon administration. In other words, expansion of the intravascular space only increases by roughly 200 to 250 mL for every liter of isotonic crystalloid fluid administered.[18] Hypertonic crystalloid solutions such as 3% NaCl or 7.5% NaCl have osmolalities substantially higher than plasma. Hypertonic sodium solutions increase the osmolality of the intravascular and interstitial fluid compared with the intracellular fluid. Therefore, hypertonic crystalloid fluids result in a relatively larger volume expansion of the intravascular space due to the volume of fluid administered and osmotic drawing of intracellular fluid into the intravascular and interstitial spaces. By comparison with conventional crystalloids, administration of 250 mL of 7.5% sodium chloride results in an intravascular space increase of 500 mL.[18] Crystalloids are generally advocated as the initial resuscitation fluid in hypovolemic shock because of their availability, low cost, and equivalent outcomes compared with colloids. A reasonable initial volume of an isotonic crystalloid (0.9% NaCl, LR, or Plasma-Lyte) in adult patients is 1000 to 2000 mL administered over the first hour of therapy.[4] Ongoing external or internal bleeding requires more aggressive resuscitation with fluid and blood products. KEY CONCEPT In the absence of ongoing blood loss, administration of 4000 to 6000 mL of isotonic crystalloid normally reestablishes baseline vital signs in adult hypovolemic shock patients.[19] Selected populations with high

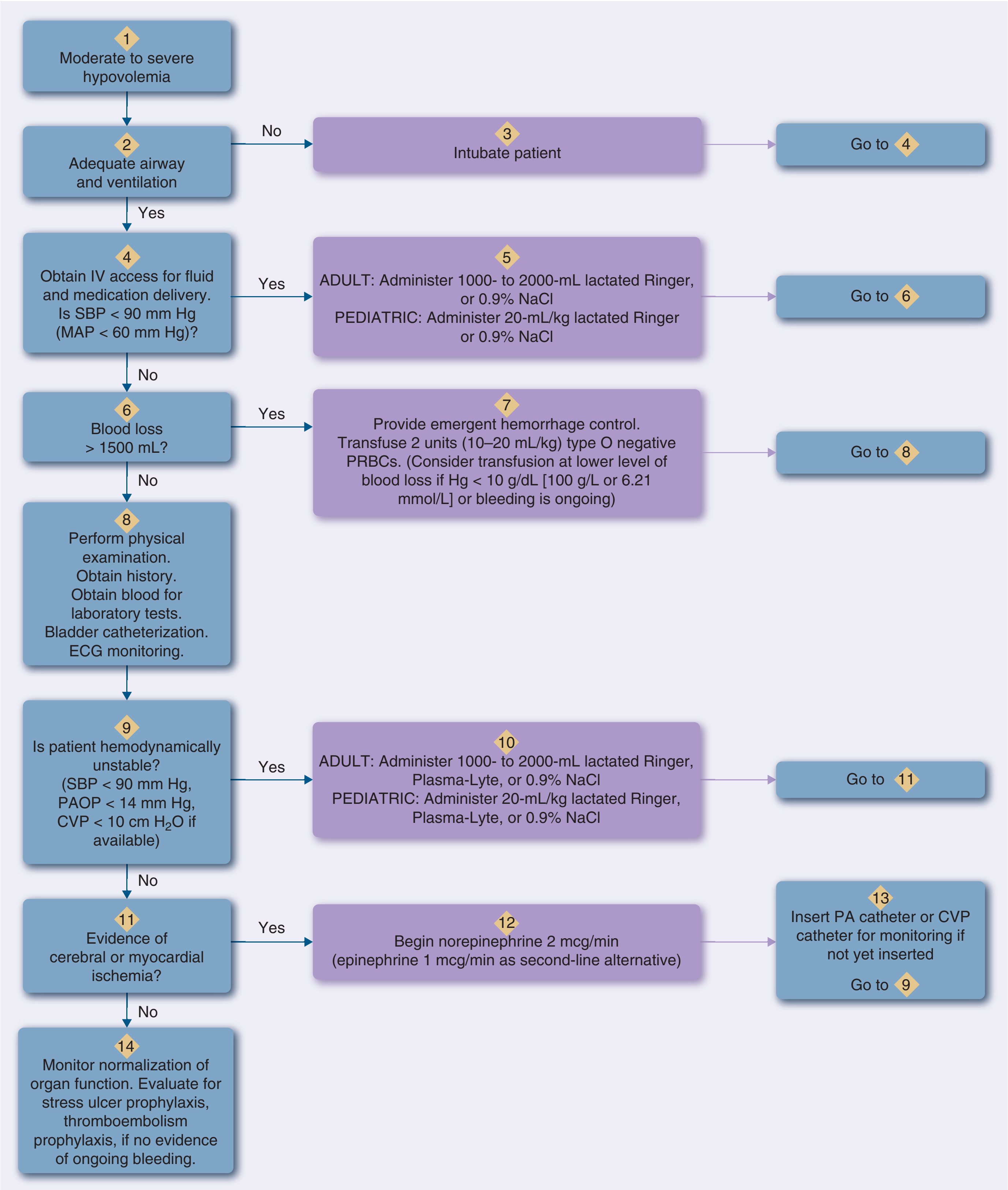
1
Moderate to severe hypovolemia
2
Adequate airway and ventilation
No
3
Intubate patient
Go to 4
Yes
4
Obtain IV access for fluid and medication delivery. Is SBP < 90 mm Hg (MAP < 60 mm Hg)?
Yes
5
ADULT: Administer 1000- to 2000-mL lactated Ringer, or 0.9% NaCl
PEDIATRIC: Administer 20-mL/kg lactated Ringer or 0.9% NaCl
Go to 6
No
6
Blood loss > 1500 mL?
Yes
7
Provide emergent hemorrhage control. Transfuse 2 units (10–20 mL/kg) type O negative PRBCs. (Consider transfusion at lower level of blood loss if Hg < 10 g/dL [100 g/L or 6.21 mmol/L] or bleeding is ongoing)
Go to 8
No
8
Perform physical examination. Obtain history. Obtain blood for laboratory tests. Bladder catheterization. ECG monitoring.
9
Is patient hemodynamically unstable? (SBP < 90 mm Hg, PAOP < 14 mm Hg, CVP < 10 cm H2O if available)
Yes
10
ADULT: Administer 1000- to 2000-mL lactated Ringer, Plasma-Lyte, or 0.9% NaCl
PEDIATRIC: Administer 20-mL/kg lactated Ringer, Plasma-Lyte, or 0.9% NaCl
Go to 11
No
11
Evidence of cerebral or myocardial ischemia?
Yes
12
Begin norepinephrine 2 mcg/min (epinephrine 1 mcg/min as second-line alternative)
13
Insert PA catheter or CVP catheter for monitoring if not yet inserted
Go to 9
No
14
Monitor normalization of organ function. Evaluate for stress ulcer prophylaxis, thromboembolism prophylaxis, if no evidence of ongoing bleeding.

FIGURE 14–3. Treatment algorithm for the management of moderate-to-severe hypovolemia. (balanced solution: lactated Ringer's solution, Plasma-Lyte. CVP, central venous pressure; ECG, electrocardiogram; Hg, hemoglobin; H_2O, water; IV, intravenous; MAP, mean arterial pressure; NaCl, sodium chloride or normal saline; PA, pulmonary artery; PAOP, pulmonary artery occlusion pressure; PRBCs, packed red blood cells; SBP, systolic blood pressure.) Hemoglobin concentration of 10 g/dL is equivalent to 100 g/L or 6.2 mmol/L.

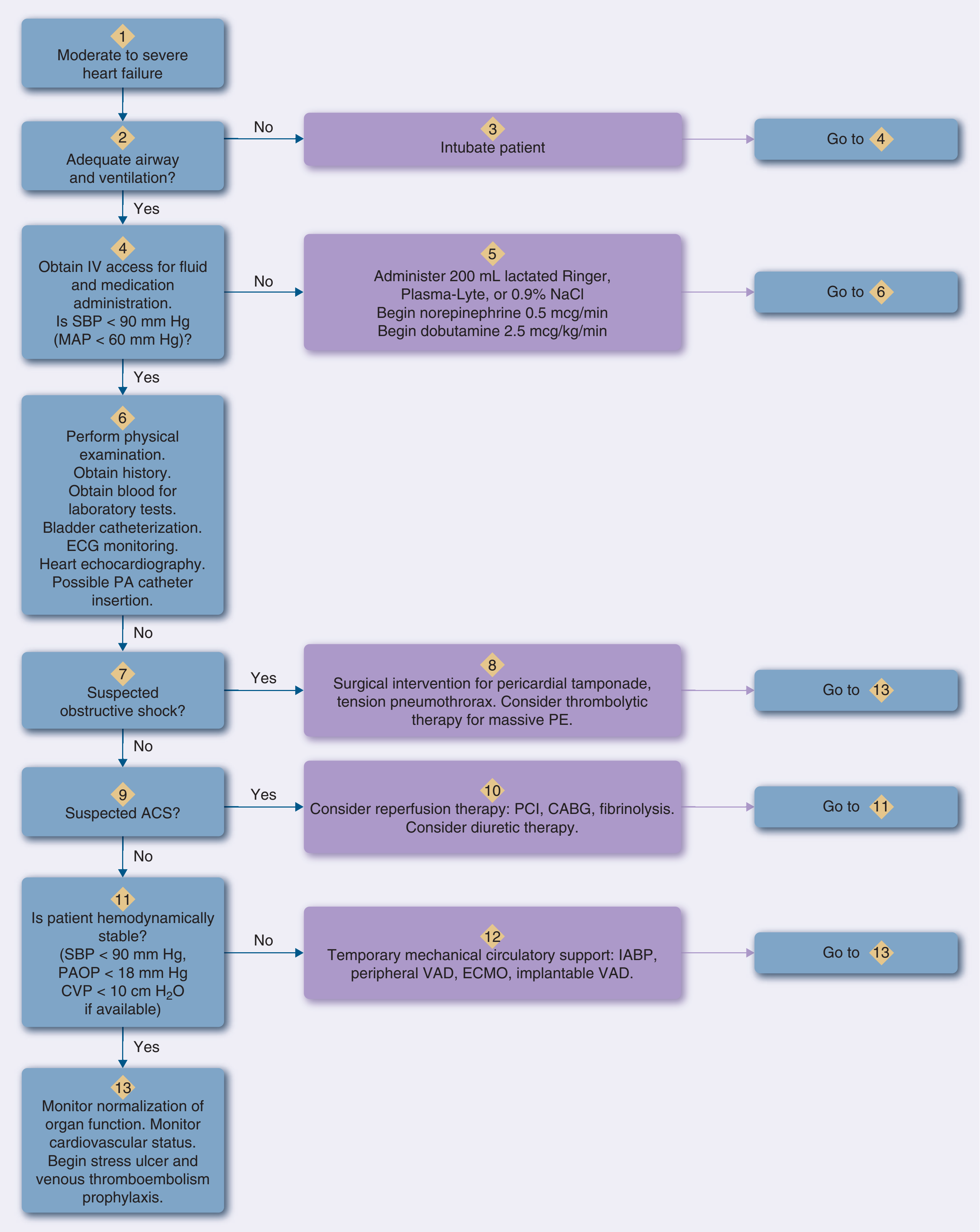
1
Moderate to severe heart failure
2
Adequate airway and ventilation?
No
3
Intubate patient
Go to 4
Yes
4
Obtain IV access for fluid and medication administration.
Is SBP < 90 mm Hg (MAP < 60 mm Hg)?
No
5
Administer 200 mL lactated Ringer, Plasma-Lyte, or 0.9% NaCl
Begin norepinephrine 0.5 mcg/min
Begin dobutamine 2.5 mcg/kg/min
Go to 6
Yes
6
Perform physical examination.
Obtain history.
Obtain blood for laboratory tests.
Bladder catheterization.
ECG monitoring.
Heart echocardiography.
Possible PA catheter insertion.
No
7
Suspected obstructive shock?
Yes
8
Surgical intervention for pericardial tamponade, tension pneumothrorax. Consider thrombolytic therapy for massive PE.
Go to 13
No
9
Suspected ACS?
Yes
10
Consider reperfusion therapy: PCI, CABG, fibrinolysis.
Consider diuretic therapy.
Go to 11
No
11
Is patient hemodynamically stable?
(SBP < 90 mm Hg,
PAOP < 18 mm Hg
CVP < 10 cm H2O
if available)
No
12
Temporary mechanical circulatory support: IABP, peripheral VAD, ECMO, implantable VAD.
Go to 13
Yes
13
Monitor normalization of organ function. Monitor cardiovascular status.
Begin stress ulcer and venous thromboembolism prophylaxis.

FIGURE 14–4. Treatment algorithm for the management of moderate-to-severe heart failure in the setting of cardiogenic shock. (ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CVP, central venous pressure; ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; H_2O, water; IABP, intra-aortic balloon pump; IV, intravenous; MAP, mean arterial pressure; NaCl, sodium chloride or normal saline; PA, pulmonary artery; PAOP, pulmonary artery occlusion pressure; PCI, percutaneous coronary intervention; PE, pulmonary embolism; SBP, systolic blood pressure; VAD, ventricular assist device.)

Table 14–3

Composition of Common Resuscitation Fluids[15,17]

Fluid	Na (mEq/L)[a]	Cl (mEq/L)[a]	K (mEq/L)[a]	Mg (mEq/L)[b]	Ca (mEq/L)[b]	Lactate (mEq/L)[a]	Other	pH	Osmolality (mOsm/kg)[c]
0.9% NaCl	154	154						5.0	308
3% NaCl	513	513						5.0	1027
7.5% NaCl	1283	1283						5.0	2567
Lactated Ringer	130	109	4		3	28		6.7	275
Plasma-Lyte A	140	98	5	3			27 mEq/L (27 mmol/L) Acetate 23 mEq/L (23 mmol/L) Gluconate	7.4	294
Plasma-Lyte 148	140	98	5	3			27 mEq/L (27 mmol/L) Acetate	5.5	294
Hetastarch (Hextend)	143	124	3	0.9	5	28	Hetastarch 6 g/dL (60 g/L)	5.9	307
Hetastarch (Hespan)	154	154					Hetastarch 6 g/dL (60 g/L)	5.5	310
Pentastarch	154	154					Pentastarch 10 g/dL (100 g/L)	5.0	326
5% Albumin	145	145					Albumin 5 g/dL (50 g/L)	6.9	300
25% Albumin	145	145					Albumin 25 g/dL (250 g/L)	6.9	258
5% PPF	130–160	130–160	0.25				Plasma proteins 5 g/dL (50 g/L) (88% albumin)	6.7–7.3	294
Dextran 40	154	154					Dextran 10 g/dL (100 g/L) (avg molecular weight 40 kDa)	5–5.5	310
Dextran 70	154	154					Dextran 6 g/dL (60 g/L) (avg molecular weight 70 kDa)	3.5–7	287
Dextran 75	154	154					Dextran 6 g/dL (60 g/L) (avg molecular weight 75 kDa)	5.5	308

[a] For these values, mEq/L = mmol/L (eg, 154 mEq/L Na = 154 mmol/L).

[b] For these values, mEq/L × 0.5 = mmol/L (eg, 0.9 mEq/L Mg = 0.45 mmol/L Mg).

[c] For this value, mOsm/kg = mmol/kg (eg, 308 mOsm/kg = 308 mmol/kg).

avg, average; Ca, calcium; Cl, chloride; K, potassium; kDa, kilodalton; Mg, magnesium; Na, sodium; NaCl, sodium chloride or normal saline; PPF, plasma protein fraction.

insensible losses of volume, such as burn patients, may require more aggressive fluid resuscitation.[4] In hemorrhagic shock patients, approximately three to four times the shed blood volume of isotonic crystalloids is needed for effective resuscitation. Nevertheless, individualization of therapy is critical with well-defined endpoints to avoid excessive administration of crystalloids based on studies in trauma patients.[20]

Side effects from crystalloids primarily involve fluid overload and electrolyte disturbances of sodium, potassium, and chloride.[1] Dilution of coagulation factors can also occur with overzealous administration of crystalloids resulting in a dilutional coagulopathy, especially in patients with active bleeding.[8] The combination of coagulopathy, hypothermia, and acidosis is a particularly deadly combination known as the "lethal triad."[8] Two clinically significant differences between LR solution and NS are that the former contains potassium and has a lower sodium content (130 vs 154 mEq/L or mmol/L). Therefore, LR solution has a greater potential than NS to cause hyponatremia and/or hyperkalemia. Alternatively, NS can cause hypernatremia, hypokalemia, metabolic acidosis, and hyperchloremia. Hyperchloremia is a particularly concerning adverse effect due to the potential risk for acute kidney injury in critically ill patients.[21] Thus, based on the buffering capacity, lower chloride content, and respective side-effect profiles, balanced crystalloid solutions may be preferred compared with NS by some authorities.[22–24] However, improvements in outcomes have not been consistently documented with balanced crystalloid solutions compared to NS. Additionally, there is no clear association between NS containing a higher chloride content and acute kidney injury.[21,25] Nevertheless, there is a growing consensus in selecting balanced crystalloid solutions over NS.

Colloids Administration of exogenous colloids increases the intravascular colloid osmotic pressure (also referred to as oncotic pressure; see Figure 14–5). The effects of colloids on intravascular volume are a consequence of their relatively large molecular size (> 30 kDa), limiting their passage across the capillary membrane in large amounts. Alternately stated, colloids can be

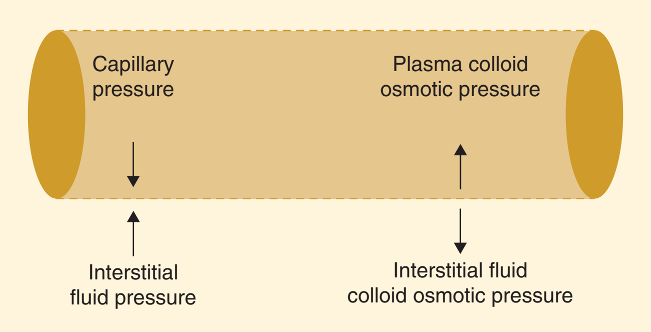
Capillary pressure
Plasma colloid osmotic pressure
Interstitial fluid pressure
Interstitial fluid colloid osmotic pressure

FIGURE 14–5. Operative forces at the capillary membrane tend to move fluid either outward or inward through the capillary membrane. In hypovolemic shock, one therapeutic strategy is the administration of colloids that can sustain and/or draw fluid from the interstitial space by increasing the plasma colloid osmotic pressure. (From Guyton AC, Hall JE. Textbook of Medical Physiology, 8th ed. Philadelphia, PA: Saunders, 1991:174, with permission.)

conceptualized as "sponges" drawing fluid into the intravascular space from the interstitial space. In the case of isooncotic colloids (5% albumin, 6% hetastarch, and dextran products), initial expansion of the intravascular space is approximately 50% of the volume of colloid administered, accounting for some "leakage" of the colloid from the intravascular space.[18]

KEY CONCEPT Thus, in contrast to isotonic crystalloid solutions that distribute throughout the extracellular fluid space, the volume of isooncotic colloids administered remains relatively confined to the intravascular space. In the case of hyperoncotic solutions such as 25% albumin, fluid is pulled from the interstitial space into the vasculature, resulting in an increase in the intravascular volume that is much greater than the original volume of the 25% albumin that was administered. Although theoretically attractive, hyperoncotic solutions should not be used for hypovolemic shock because the expansion of the intravascular space is at the expense of depleting the interstitial space. Exogenous colloids available in the United States include 5% albumin, 25% albumin, 5% plasma protein fraction (PPF), 6% hetastarch, 10% pentastarch, 10% dextran 40, 6% dextran 70, and 6% dextran 75 (see Table 14–3). The first three products are derived from pooled human plasma. Hetastarch and pentastarch are semisynthetic hydroxyethyl starches derived from amylopectin. The dextran products are semisynthetic glucose polymers that vary in terms of the average molecular weight of the polymers. Superiority of one colloid solution over another in terms of efficacy has not been clearly established.[26]

For decades within the critical care literature, a controversy known as the "colloid versus crystalloid debate" raged over the relative merits of these two types of resuscitation fluids. Based on previous data, there does not appear to be a clear-cut overall advantage relative to mortality for either crystalloids or colloids in critically ill patients.[27] This was confirmed in a large study known as the CRISTAL (Colloids Versus Crystalloids for the Resuscitation of the Critically Ill) Randomized Trial published in 2013.[28] Thus, most clinicians today prefer using crystalloids based on their availability and inexpensive cost compared with colloids. However, in addition to these factors, a shift in this debate has recently taken place focused on adverse events.

Generally, the major adverse effects associated with colloids are fluid overload, dilutional coagulopathy, and anaphylactoid/anaphylactic reactions.[18] Because of direct effects on the coagulation system with the hydroxyethyl starch and dextran products, they should be avoided in hemorrhagic shock patients. Further, hetastarch has been associated with an increased risk of acute kidney injury in several recent clinical trials. As such, hydroxyethyl starch products are no longer recommended.[29] Despite these general limitations, there is a paradigm shift in a subset of hypovolemic shock patients, that is, traumatic hemorrhagic shock, to minimize crystalloids, increase the use of blood products and plasma, and accept lower MAP values (permissive hypotension). Collectively, this approach is referred to as damage control resuscitation (DCR).[16,30]

Blood Products **KEY CONCEPT** Blood products are indicated in hypovolemic shock patients who have sustained blood losses from hemorrhage exceeding 1500 mL. This, in fact, is the only setting in which freshly procured whole blood is administered. In virtually all other settings, blood products are given as the individual components of whole blood units, such as packed red blood cells (PRBCs), fresh-frozen plasma (FFP), platelets, cryoprecipitate, and prothrombin complex concentrates (PCC). This includes ongoing resuscitation of hemorrhagic shock. In patients with documented coagulopathies, FFP should be administered to replace lost or diluted clotting factors. Platelets are indicated for patients with severe thrombocytopenia ($< 20–50 \times 10^3/\text{mm}^3$ or $20–50 \times 10^9/\text{L}$).[19] Use of viscoelastic testing may also be a valuable tool for assessing coagulation defects and guiding blood product administration.[31] Type O negative blood or "universal donor blood" is given in emergent cases of hemorrhagic shock. Thereafter, blood that has been typed and cross-matched with the recipient's blood is given.

▶ *Pharmacologic Therapy*

Inotropes Positive inotropes are medications that increase the contractility of the heart and the cornerstone of therapy for patients in cardiogenic shock.[32] A detailed discussion of these agents can be found in Chapter 7, "Heart Failure." Dobutamine and dopamine are inotropes that stimulate the β_1 adrenergic receptors in the heart (see Table 14–4). This stimulation activates cyclic adenosine monophosphate (cAMP), thereby enhancing calcium influx into the myocardial cells resulting in increased contractility. Dobutamine is the gold standard of therapy in cardiogenic shock following an acute myocardial infarction or in patients with decompensated heart failure. Dopamine is less commonly used due to its variable effects on contractility and vasoconstriction depending on dose. Milrinone is a phosphodiesterase inhibitor that also increases cAMP, resulting in increased contractility. While milrinone has utility in the management of heart failure patients, in general, it is rarely used for cardiogenic shock because its vasodilating properties may exacerbate hypotension present in these patients.

Vasopressors Vasopressor is the term used to describe any pharmacologic agent that can induce arterial vasoconstriction through stimulation of the α_1-adrenergic receptors or vasopressin receptors (V_1).[33] **KEY CONCEPT** Use of vasopressors may be warranted as a temporary measure in patients with profound hypotension or evidence of organ dysfunction in the early stages of circulatory shock.[2,7,34] Vasopressors are typically used concurrently with fluid administration in hypovolemic shock if fluids alone have not resulted in adequate restoration of MAP and/or tissue perfusion.[35] Vasopressors are also commonly used with inotropes to support BP and CO in patients with cardiogenic shock. The risk of using vasopressors in cardiogenic shock patients is diminishing CO secondary to impeding ventricular emptying, that is,

Table 14–4

Inotropic and Vasopressor Drugs[1,7]

		Adrenergic Effects			
Drug	**Usual IV Dose**	**α1**	**β1**	**Dopaminergic**	**Potential to Cause Arrhythmias**
Dobutamine[a]	2.5–20 mcg/kg/min	+	+++	0	+++
Dopamine	5–10 mcg/kg/min	+	++	++	++
	10–20 mcg/kg/min[b]	+++	++	++	+++
Norepinephrine	0.01–0.4 mcg/kg/min	+++	++	0	++
Epinephrine	0.01–0.5 mcg/kg/min	++	+++	0	+++
Phenylephrine	0.1–10 mcg/kg/min	++++	0	0	0
Vasopressin[c]	0.02–0.04 U/min	0	0	0	0

[a] Mild vasodilation may occur as a result of β_2 adrenergic receptor stimulation.

[b] Adrenergic effects dose dependent with β_1 effects predominating at lower dosages (1–3 mcg/min) with α_1 effects at higher dosages.

[c] Stimulate vasopressin (V_1) receptors in vascular smooth muscle.

IV, intravenous

0 = No effect

+ = Low

++ = Moderate

+++ = High

++++ = Very high

increased arterial resistance. Table 14–4 lists those vasopressors recommended for use in the management of hypovolemic shock.[1] Although vasopressor therapy may improve the hemodynamic profile in shock patients, data are lacking that they improve mortality.[7,35] Regardless, norepinephrine is considered preferable to dopamine secondary to increased incidence of arrhythmias associated with dopamine in treatment of shock patients if vasopressors are required.[35,36] As such, norepinephrine is generally considered the first-line vasopressor therapy for patients.[2,7,36] Epinephrine should be considered a second-line vasopressor in patients with shock because of its association with tachyarrhythmias, impaired abdominal organ (splanchnic) circulation, and hypoglycemia.[2] Vasopressin is yet another second-line agent. Its mechanism of action is through stimulation of the V_1 within the vascular smooth muscle. If used, generally vasopressin is combined with norepinephrine at a fixed rate, although limited data is available relative to its role in circulatory shock.[7,11] Another vasopressor, angiotensin II, is an active form of the endogenous

Patient Encounter Part 2

PMH: (Per family member) Diabetes, hypertension, hyperlipidemia, heart failure, atrial fibrillation

Meds: (Per family member) "Blood thinner," "heart meds," and insulin

SH: None

FH: Father died of myocardial infarction, mother has diabetes

PE:

VS: BP 65/42 mm Hg, P 125 beats/min, RR 25 breaths/min, T 36.0°C (96.8°F), Ht 5′5″ (165 cm), Wt 80 kg (176 lb), urine output: none since bladder catheterization 10 minutes ago

Neuro: Was in pain upon entering the trauma center. Now calmer but still confused after one-time doses of hydromorphone and midazolam.

Cardiovascular: Heart sounds and ECG normal except for tachycardia

Pulmonary: Normal breath sounds

Abd: Tender, negative bowel sounds

Extremities: Open fractures of both femurs with soft tissue damage and moderate bleeding.

Pertinent labs: pH 7.19, partial pressure of arterial carbon dioxide ($PaCO_2$) 34 mm Hg (4.52 kPa), partial pressure of arterial oxygen (PaO_2) 70 mm Hg (9.31 kPa), Na 145 mEq/L (mmol/L), Cl 104 mEq/L (mmol/L), bicarbonate (HCO_3) 16 mEq/L (mmol/L), K 5.0 mEq/L (mmol/L), Mg 2.8 mg/dL (1.15 mmol/L), lactate 6 mEq/L (mmol/L), serum glucose 218 mg/dL (12.1 mmol/L), SCr 1.5 mg/dL (133 mcmol/L), Hct 28% (0.28), Hgb 9.3 g/dL (93 g/L; 5.8 mmol/L), International Normalized Ratio (INR) 2.78

What signs and symptoms of hypovolemic shock are present in this patient?

What laboratory abnormalities related to hypovolemic shock are present in this patient and why?

Describe treatment goals for the patient in the next hour.

Develop a pharmacologic and fluid therapy plan for initial therapy. Defend your selections compared to alternative agents.

Discuss the role in therapy for blood products, sodium bicarbonate, and hemostatic agents in the patient at this time.

Describe treatment goals for the patient in the next 24 hours.

vasoconstrictor angiotensin and became available in 2017.[33] However, its use to date has been almost exclusively in patients with septic shock refractory to first-line therapies.

Vasopressors are almost exclusively administered as continuous infusions because of their very short duration of action and the need for close titration of their dose-related effects. Starting doses should be at the lower end of the dosing range followed by rapid titration upward if needed to maintain adequate MAP. Monitoring of end-organ function such as adequate urine output should also be used to monitor therapy. Once MAP is restored, vasopressors should be weaned and discontinued as soon as possible to avoid any adverse effects.[2] The most significant systemic adverse events associated with vasopressors are excessive vasoconstriction resulting in decreased organ perfusion and tachyarrhythmias as well as extremity ischemia (see Table 14–4). Vasopressors should be administered via central venous catheter to minimize the risk of local tissue necrosis that can occur with extravasation.

Hemostatic Agents Several systemic pharmacologic agents have been used historically in patients with severe bleeding, such as the prothrombin complex concentrates and recombinant activated factor VII. Off-label use of this latter drug has fallen into disfavor due to uncertain efficacy, safety concerns, and high acquisition cost. In recent years, the greatest interest has shifted instead to use of the antifibrinolytic drug, tranexamic acid. Two large studies of tranexamic acid in trauma patients with or at risk of significant bleeding as well as patients with traumatic brain injury demonstrated a decrease in mortality compared with placebo.[37,38] As such, several guidelines recommend use of tranexamic acid within 3 hours of injury (1 g IV over 10 minutes, then 1 g over 8 hours) as an adjunctive agent in the management of bleeding trauma patients.[39]

Patient Encounter Part 3

Twenty-four hours after the initial fluid bolus, the patient's vital signs are BP 92/64 mm Hg, P 95 beats/min, RR 22 breaths/min, urine output: averaging 35 mL/hour for the last 24 hours. Pertinent new data: lactate 3.0 mEq/L (mmol/L), SCr 1.9 mg/dL (168 mcmol/L), serum glucose 197 mg/dL (10.9 mmol/L), SaO_2 92% (0.92; on mechanical ventilation), INR 1.9. Pulmonary artery catheter readings: Cardiac index (CI) 1.9 L/min/m^2 (0.032 L/s/m^2), PAOP 23 mm Hg.

Assess the patient's condition compared to 24 hours ago.

Develop a plan for additional therapy, if any, that you recommend at this time.

Outline a plan for monitoring the patient over the next 24 hours.

What cultural beliefs, norms, or values should be considered when treating patients with hemorrhagic shock?

Supportive Care Measures

Lactic acidosis, which typically accompanies hypovolemic shock as a consequence of tissue hypoxia, is best treated by reversal of the underlying cause. Administration of alkalizing agents such as sodium bicarbonate has not been demonstrated to have any beneficial effects and may actually worsen intracellular acidosis.[40,41] However, this is based on limited retrospective data in a variety of patients with lactic acidosis. Because GI ischemia is a common complication of circulatory shock, most patients with circulatory shock will meet criteria for initiation of stress ulcer prophylaxis to begin once the patient is stabilized.[42] The most common agents

Patient Care Process

Collect Information

- Conduct medical history to determine the cause of shock to guide pharmacologic and nonpharmacologic therapy.
- Obtain pertinent laboratory tests (electrolytes, CBC, coagulation tests, ABG, serum lactate, liver function tests, and possibly troponin) to help determine circulatory shock etiology, severity, and organ dysfunction.

Assess the Information:

- Assess airway/ventilation status to determine the need for supplemental oxygen/mechanical ventilation.
- Assess vital signs and urine output at least every 15 minutes (continuously if possible) to determine shock severity and response to therapy.
- Determine adequacy of current blood product therapy (if applicable).
- Determine adequacy of current vasopressor/inotropic therapy (if applicable).

Develop a Care Plan

- Assure venous access to deliver fluid resuscitation.
- Determine fluid to be used including rate of administration in hypovolemic shock patients.
- Determine if blood products are needed.
- Ascertain need for continued vasopressor therapy and/or inotropic therapy.
- Consider using tranexamic acid within 3 hours of injury in bleeding trauma patients.

Implement the Care Plan

- Start aggressive crystalloid IV fluid therapy if SBP is less than 90 mm Hg (MAP < 60 mm Hg) in hypovolemic shock patients.
- If required (see Figure 14–3), transfuse PRBCs and provide emergent control of ongoing hemorrhaging.
- Begin vasopressor and/or inotropic therapy if there is evidence of cerebral or myocardial insufficiency.
- Use the resulting data to optimize therapy if a PA catheter is placed.
- Avoid electrolyte disturbances and adverse drug events.

Follow-Up: Monitor and Evaluate:

- Determine if appropriate treatment goals for the first hour and first 24 hours of therapy have been met (see Outcome Evaluation).
- Determine if the underlying cause of circulatory shock has been addressed (eg, control of bleeding or GI fluid losses, etc).
- Ascertain if supportive care measures such as prophylaxis for stress ulcers and venous thromboembolism are indicated.

used for stress ulcer prophylaxis are the histamine$_2$-receptor antagonists and proton pump inhibitors. Prevention of thromboembolic events is another secondary consideration in hypovolemic shock patients. This can be accomplished with the use of external devices such as sequential compression devices and/or antithrombotic therapy such as the low molecular weight heparin products or unfractionated heparin. Sequential compression devices are preferred in any hypovolemic shock patient at risk of ongoing bleeding.

OUTCOME EVALUATION

KEY CONCEPT Successful treatment of circulatory shock is measured by the restoration of MAP to baseline values and reversal of associated organ dysfunction. The likelihood of a successful resuscitation is directly related to the expediency of treatment. Therapy goals include:

- Arterial SBP greater than 90 mm Hg (MAP > 60–75 mm Hg) within 1 hour.
- Organ dysfunction reversal evident by increased urine output to greater than 0.5 mL/kg/hour (1.0 mL/kg/hour in pediatrics), return of mental status to baseline, and normalization of skin color and temperature over the first 24 hours.
- HR should begin to decrease reciprocally to increases in the MAP restoration within minutes to hours.
- Normalization of most laboratory measurements expected within hours to days following fluid resuscitation. Specifically, normalization of base deficit and serum lactate is recommended within 24 hours and may be associated with decreased mortality.
- Achievement of PAOP to a goal pressure of 14 to 18 mm Hg occurs (alternatively, CVP 8–12 mm Hg).

Abbreviations Introduced in this Chapter

ABG	Arterial blood gas
ACS	Acute coronary syndrome
ADH	Antidiuretic hormone
ARDS	Acute respiratory distress syndrome
ATP	Adenosine triphosphate
BP	Blood pressure
Ca	Calcium
cAMP	Cyclic adenosine monophosphate
CBC	Complete blood count
CI	Cardiac index
Cl	Chloride
CO	Cardiac output
CRISTAL	Colloids Versus Crystalloids for the Resuscitation of the Critically Ill trial
CVP	Central venous pressure
DCR	Damage control resuscitation
ECG	Electrocardiogram
FAST	Focused assessment for sonography in trauma
FFP	Fresh-frozen plasma
GI	Gastrointestinal
HCO_3	Bicarbonate
Hct	Hematocrit
HR	Heart rate
INR	International normalized ratio
IV	Intravenous
K	Potassium
kDa	Kilodalton
LR	Lactated Ringer
MAP	Mean arterial pressure
Mg	Magnesium
MODS	Multiple organ dysfunction syndrome
Na	Sodium
NaCl	Sodium chloride (normal saline)
NS	Normal saline
PA	Pulmonary artery
$PaCO_2$	Partial pressure of arterial carbon dioxide
PaO_2	Partial pressure of arterial oxygen
PAOP	Pulmonary artery occlusion pressure
PCC	Prothrombin complex concentrate
PPF	Plasma protein fraction
PRBCs	Packed red blood cells
SaO_2	Oxygen saturation
SBP	Systolic blood pressure
SCr	Serum creatinine
SV	Stroke volume
SVR	Systemic vascular resistance
V_1	Vasopressin receptor
VIP	Ventilate, infuse, pump

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Asthma

Lori Wilken and Amanda Eades

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the pathophysiology and clinical presentation of acute and chronic asthma.
2. List the treatment goals for asthma.
3. Identify environmental factors associated with worsening asthma control.
4. Discuss the factors to consider when choosing an inhaled drug delivery device for a patient.
5. Recommend an asthma medication regimen for an adult patient based on symptoms.
6. Compare the preferred asthma reliever and controller regimens for children, adolescents, and adults.
7. Describe the purpose of an individualized asthma action plan.

INTRODUCTION

KEY CONCEPT Asthma is a disorder of the airways characterized by chronic airway inflammation, bronchial hyperresponsiveness, and airflow obstruction. Patients with asthma typically present with respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough. These symptoms vary over time and in intensity, and worsening is often triggered by factors such as exercise, allergen exposure, change in weather, or respiratory infections.[1] Severity of chronic asthma ranges from mild intermittent symptoms to severe and disabling disease. Despite variability in the severity of chronic asthma, all patients with asthma are at risk of acute severe exacerbations that may be life threatening. International guidelines emphasize the importance of treating underlying airway inflammation to control asthma and reduce asthma-associated risks.[1–5]

EPIDEMIOLOGY AND ETIOLOGY

KEY CONCEPT Asthma is the most prevalent chronic disease of childhood, and it causes significant morbidity and mortality in both adults and children. About 262 million adults and children worldwide have asthma.[6] In the United States, asthma affects 8% of adults (20 million) and 7% of children (5.1 million).[7] Asthma is the primary diagnosis for 9.8 million physician office visits, 1.6 million emergency department visits, and 3524 deaths annually.[7] In 2019, 41.2% of persons with asthma reported having one or more asthma attacks, indicating that nearly half of patients with asthma are not optimally controlled.[8]

Asthma is also a significant economic burden. Annual per-person medical costs have been estimated to exceed $3000, with cost of medications amounting for about 56% of total medical expenditures. The total cost of asthma is estimated to be $81.9 billion, with 61% for medical costs and nearly 39% attributable to absenteeism and mortality.[9]

It is believed that asthma originates primarily early in life and involves a complex interaction of genetic and environmental factors such as allergens, occupational sensitizers, infections, exposure to tobacco smoke, air pollution, diet, and stress.[10] Host factors that increase risk of developing asthma include genes, obesity, sex, and early growth characteristics including younger gestational age, lower birth weight, and greater infant weight gain.

PATHOPHYSIOLOGY

KEY CONCEPT Asthma is characterized by airway narrowing and inflammation primarily in medium-sized bronchi. A key pathophysiologic feature is airway hyperresponsiveness, which is exaggerated narrowing of the airways in response to a trigger or allergen such as cold air, strong odors, pollen, or dust. Airway narrowing results from contraction of airway smooth muscle, increased mucus secretion, airway edema, and remodeling.[1]

In recent years, the discovery of various asthma endotypes, or subtypes of asthma defined by a distinct pathobiological mechanism, has helped clinicians individualize treatment regimens to address a patient's specific pathophysiology within a very heterogeneous disease.[1] Two distinct molecular endotypes have emerged involving a $CD4^+$ T helper 2 (Th2) cell response: Th2 high and Th2 low inflammations.

Th2 high inflammation asthma includes early-onset allergic asthma, adult-onset eosinophilic nonallergic asthma, and exercise-induced asthma.[11] In early-onset allergic asthma, environmental allergens trigger the asthma; it commonly presents in childhood and is associated with family history of allergic disease such as eczema, allergic rhinitis, or food or drug allergy.[1] Airway inflammation is initiated by an inhaled allergen or trigger such as dust, pollen, or animal dander inducing a Th2 response. This leads to B-cell production of antigen-specific immunoglobulin E (IgE), proinflammatory cytokines (eg, interleukin-5), and chemokines that recruit and activate eosinophils, neutrophils, and alveolar macrophages.[2] Further exposure to the antigen results in cross-linking of cell-bound IgE in mast cells and basophils, causing release of preformed inflammatory mediators such as histamine, cysteinyl leukotrienes, and prostaglandin D_2.[1] Patients with Th2 high asthma typically respond well to inhaled corticosteroids (ICS), monoclonal antibodies to IgE, and Th2-targeted therapeutics.

Adult-onset eosinophilic nonallergic asthma develops in adulthood and has a severe onset with high levels of eosinophils in sputum and peripheral blood. These patients often have chronic sinusitis, nasal polyps, and asthma that is exacerbated by aspirin (aspirin-exacerbated respiratory disease, AERD). ICS and IL-5 monoclonal antibodies are used to treat this endotype.

Patients with nonallergic, Th2 low asthma have severe, adult-onset asthma. The sputum shows a high percentage of neutrophils instead of eosinophils. Th2 low asthma is commonly triggered by viral respiratory infections, air pollution, and cigarette smoke. Obesity is also thought to worsen this type of asthma. Patients in this subset of asthma often demonstrate severe disease with a poor response to ICS therapy.

CLINICAL PRESENTATION AND DIAGNOSIS

See accompanying box for the clinical presentation and diagnosis of asthma. Diagnosis is based on a detailed medical history, physical examination of the upper respiratory tract and skin, and measurement of expiratory airflow. The clinician determines if episodic symptoms of airflow obstruction are present, whether airflow obstruction is at least partially reversible, and that alternative diagnoses are excluded. Full pulmonary function tests should be performed at baseline in patients 5 years or older to rule out

Clinical Presentation and Diagnosis of Asthma

General Findings

Asthma presentation ranges from normal pulmonary function with symptoms only during acute exacerbations to significantly decreased pulmonary function with continuous symptoms of daily coughing, wheezing, and shortness of breath.

- Acute asthma can present rapidly (within 3–6 hours), but deterioration more commonly occurs over a longer period, even days or weeks. Acute asthma can be life threatening.
- Family history, social history, precipitating factors, history of exacerbations, and development of symptoms are important components of an asthma diagnosis.

Symptoms

- Patients usually complain of wheezing, shortness of breath, coughing (usually worse at night), and chest tightness.
- Patients may be anxious and agitated. In acute severe asthma, patients may be unable to communicate in complete sentences.
- Mental status changes (eg, confusion, irritability, agitation) may indicate impending respiratory failure.
- The presence of precipitating factors (eg, smoke, mold, or viral illness) worsens symptoms.
- Symptoms usually have a pattern (eg, worse at night, seasonal symptoms).

Physical Exam

Vital signs may reflect **tachypnea**, **tachycardia**, and **hypoxemia**.

- On inspection, there may be hyperexpansion of the thorax and use of accessory muscles.
- Auscultation of the lungs may detect end-expiratory **wheezes** in mild exacerbations or wheezing throughout inspiration and expiration in severe exacerbations.
- **Bradycardia** and absence of wheezing may indicate impending respiratory failure.
- In acute asthma, patients may present with **pulsus paradoxus**, diaphoresis, and cyanosis.

Laboratory Tests

- Spirometry may demonstrate airway limitation and excessive airway variability.
  - Airway limitation is demonstrated by a decrease in the FEV_1/FVC (**forced expiratory volume in the first second**/forced vital capacity) less than 80% (0.80) and a decrease in the FEV_1 to less than 80% (0.80) of the predicted value.
  - Excessive airway variability is seen with:
    a. A positive bronchodilator test, defined as an increase in greater than 200 mL and 12% (0.12) in the FEV_1 from baseline, 10 to 15 minutes after 200 to 400 mcg inhaled albuterol or equivalent. For children, a positive test is defined as increase in the FEV_1 greater than 12% (0.12) of the predicted value.
    b. Excessive variability in twice-daily PEF over 2 weeks: average daily diurnal PEF variability >10% (0.10) for adults and >13% (0.13) for children.
    c. Significant increase in lung function after 4 weeks of anti-inflammatory treatment.
    d. Positive exercise challenge test: fall in FEV_1 greater than 10% (0.10) and more than 200 mL from baseline for adults, and greater than 12% (0.12) predicted for children.
    e. Positive bronchial challenge test: after administration of methacholine or histamine, a decrease in the FEV_1 of 20% (0.20) at specified doses.
- A white blood cell count with differential may show an elevated absolute eosinophil count.
- Elevated serum immunoglobulin E (IgE) levels may be present.
- **Immunoassays** are serologic tests used to detect allergies in patients that may have sensitivities to molds, dust mites, pollen, and other triggers that worsen asthma control. The test is used when skin testing is not available or cannot be used because it is a less sensitive test than skin testing.

Other Diagnostic Tests

- Arterial blood gases (to evaluate PCo_2) should be obtained for patients in severe distress, suspected hypoventilation, or when PEF or FEV_1 is at least 30% less than the percent predicted after initial treatment.
- **Pulse oximetry** is performed at each visit to assess for hypoxemia.
- FeNO changes from baseline may indicate inflammation or a response to an ICS. A normal value in adults is less than 25 parts per billion (ppb).

other disorders. Spirometry is the preferred method of measuring expiratory airflow for diagnosing asthma in persons older than 5 years; however, peak expiratory flow (PEF) meters may be used in the absence of a spirometer. The medical history and physical examination alone are not reliable for characterizing the status of lung impairment or excluding other diagnoses. Spirometry may be normal when the patient is asymptomatic. In this situation, methacholine bronchoprovocation test is used to clinically evaluate airway hyperresponsiveness. Diagnostic tests to confirm allergic asthma include allergy testing for environmental allergens, a white blood cell count to look for increased eosinophils, blood IgE antibody level, and occasionally measurements of fractional concentration of exhaled nitric oxide (FeNO).

Chronic Asthma

KEY CONCEPT Patients with chronic asthma should be assessed based on current symptom control as well as future risk of adverse outcomes. Asthma control considers the frequency and severity of symptoms, use of short-acting β_2-agonists (SABA) for quick relief of symptoms, and impact on normal activity and quality of life. Future risk refers to the potential for future severe exacerbations and asthma-related death, progressive loss of lung function (adults) or reduced lung growth (children), and the occurrence of drug-related adverse effects.[4] Asthma severity is determined by the level of treatment needed to achieve control of asthma symptoms.

Acute Asthma

In acute asthma, symptoms of wheezing, coughing, and shortness of breath increase. Most exacerbations can be treated at home, while some require hospitalization. The severity of the asthma exacerbation does not depend upon the classification of the patient's chronic asthma. Patients with intermittent asthma can have life-threatening acute exacerbations.

TREATMENT

Desired Outcomes

The goals of treatment for asthma are directed at maintaining long-term control of symptoms while minimizing adverse effects.[1–5] Treatment goals are to: (a) achieve good control of asthma symptoms, (b) maintain normal or near-normal pulmonary function, (c) maintain normal activity levels, (d) meet patients' and families' expectations of satisfaction with asthma care, (e) prevent exacerbations of asthma and the need for emergency department visits or hospitalizations, (f) prevent progressive loss of lung function, (g) provide optimal medications with minimal or no adverse effects, and (h) minimize risk of asthma-related death.

Nonpharmacologic Therapy

Incorporating nonpharmacologic care and education is important for patients with asthma. Patient education begins at the time of diagnosis and should meet the individual patient's needs. Asthma management improves when patients are empowered to assume an active role in their asthma management and provided with the knowledge and skills to do so.[1] It is also vital that all individuals with asthma be assessed for sensitivity to common allergens known to worsen asthma. This assessment should include a detailed history of symptoms when exposed to allergens and/or skin testing for sensitivity. For those who are proven to have sensitivity to allergens or other environmental triggers, mitigation interventions may improve asthma control[12] (Table 15–1).

Table 15–1

Nonpharmacologic Interventions to Improve Symptom Control in Patients With Asthma

Tobacco use[1]
- Strongly encourage smokers to quit
- Advise parents/caregivers of children with asthma to not smoke and not allow smoking in rooms or cars that children use

Physical activity[1]
- If EIB, use a SABA or ICS–formoterol 5–20 minutes prior to physical activity
- Encourage stretching and warm-up exercises prior to physical activity

Occupational exposures[1]
- Ask patients with adult-onset asthma about work history and other exposures
- Record when work-related exposures and symptoms occur, when bronchodilator is needed, and peak airflow at work vs. home
- Use respiratory protective devices such as air-purifying masks to help protect against noxious occupational inhalants
- Identify and eliminate occupational sensitizers and remove sensitized patients from further exposure, if possible

Medications[1]
- Ask about asthma before prescribing NSAIDs and advise patients to stop NSAIDs if asthma worsens after use
- If β-blockers are indicated, choose cardioselective agents (eg, atenolol). Asthma is not an absolute contraindication to β-blocker use, but consider the risk vs. benefit

Indoor allergens[12]
- Mold: Dehumidifiers, removal of dampness in homes, and mold abatement
- Rodents and/or cockroaches: Abatement and measures to block infestation
- Dust mites: Dust-mite impermeable pillow and mattress covers, HEPA filter-equipped vacuum cleaner, carpet and curtain removal, and cleaning products

Diet[1]
- Avoid foods for which there is a confirmed allergy
- Encourage weight reduction if overweight or obese
- Avoid foods containing sulfites if they cause symptoms (eg, beer, wine, shrimp, dried fruit, processed potatoes)

Vaccinations[13,14]
- Administer yearly influenza vaccine to patients with moderate-to-severe asthma
- Follow CDC recommendations for administering the pneumococcal and COVID-19 vaccines

Emotional stress[1]
- Identify goals and strategies (eg, relaxation, breathing exercises) to deal with emotional stress if it worsens asthma

Weather conditions[1]
- Avoid strenuous outdoor activities during unfavorable weather conditions
- Cover the nose and mouth with a scarf on cold or windy days

Outdoor allergens[1]
- When pollen counts are high, remain indoors and keep windows and doors closed
- If time is spent outdoors, shower afterward to remove allergens on the skin
- Avoid being outdoors in areas of high pollution

CDC, Centers for Disease Control and Prevention; EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; NSAID, nonsteroidal anti-inflammatory drug; SABA, short-acting β_2 agonist.

Patient Encounter Part 1

HPI: A 36-year-old woman presents to the clinic for a yearly check-up. She has no acute health complaints other than symptoms of seasonal allergies (sneezing, runny nose, watery eyes). She takes loratadine 10 mg as needed for allergy symptoms and fluticasone nasal spray as needed for rhinitis. She reports having mild allergy symptoms year around, but symptoms are worst in the spring months. The patient has a history of asthma and has been prescribed an albuterol inhaler to use as needed for asthma symptoms. She cannot recall exactly how often she has used her albuterol inhaler in the past month but estimates "maybe 4 or 5 times. I usually need it about once a week." She remembers needing it after she participated in a walkathon event stating, "I finished the walk, but I thought I was going to pass-out afterwards." She also recalls needing to use albuterol when she was helping her mother clean out her basement and states, "That day I thought I was going to end up in the emergency room again." She says she self-treated with several puffs of albuterol and took some prednisone she had in her cabinet. Otherwise, she attributes the need for her inhaler to outdoor allergens. She denies any nighttime awakenings due to asthma symptoms.

PMH:

- Mild, intermittent asthma diagnosed during childhood; has never been hospitalized or intubated. She has had one emergency department visit in the past year for an asthma exacerbation. She was treated with albuterol/ipratropium inhalation solution and discharged with a prednisone burst.
- Allergic rhinitis
- Nasal polyps
- Obesity

Family History: Has a sister who also has asthma. No other notable family history

Social History: Denies tobacco use; socially drinks (1–2 glasses of wine on the weekends); lives in a smoke-free home, but her mother smokes heavily; denies having any pets; patient is self-employed (owns a pastry shop in her town); home has hardwood floors throughout. She enjoys walking when it is nice outside, but it aggravates her asthma.

Allergies: Pollen, ragweed, trees, grass, roaches, mold, sulfites, dogs, and cats. No known medication allergies.

What environmental factors may affect the patient's asthma control?

What nonpharmacologic recommendations might decrease the patient's risk of future exacerbations?

What aspects of the patient's past medical history are relevant?

Pharmacologic Therapy

Treatment of chronic asthma involves avoidance of triggers known to precipitate or worsen asthma and use of long-term control and quick-relief medications. Long-term control medications include ICS, inhaled long-acting β_2-agonists (LABAs), oral leukotriene receptor antagonists (LTRAs), inhaled long-acting muscarinic antagonists (LAMA), and biologic agents. Quick-relief medications include SABAs, ICS–formoterol, short-acting muscarinic antagonists (SAMAs), and short bursts of systemic corticosteroids.

▶ *Drug Delivery Devices*

KEY CONCEPT Direct airway administration of asthma medications through inhalation is the most efficient route and minimizes systemic adverse effects. Inhaled asthma medications are available in metered-dose inhalers (MDIs), dry powder inhalers (DPIs), slow mist inhalers (SMIs), breath-actuated inhalers (BAI), and inhalation solutions for nebulization. Poor inhaler technique is common with inhaler devices and results in increased oropharyngeal deposition, leading to decreased efficacy and increased adverse effects. Use of a spacer is recommended with an MDI inhaler to decrease the need for coordination of actuation with inhalation, decrease oropharyngeal deposition, and increase pulmonary drug delivery.[15,16] A spacer with a face mask may be used in younger patients who are unable to hold their breath after inhalation. A spacer with a face mask is not recommended for most adults because the mask results in fewer drug particles being delivered to the lungs. Using an MDI with a spacer also has faster medication delivery and is as effective as administration by nebulization. Although DPIs and BAIs have the benefit of not requiring coordination of breath with the actuation of the inhaler, patients must demonstrate the ability to breathe quickly and deeply for the drug particles to deposit in the lungs rather than in the mouth and throat. This technique for DPI and BAI limits their use in younger patients. Selection of the appropriate inhalation device depends on patient characteristics and medication accessibility.

▶ *Maintenance Medications*

Inhaled Corticosteroids KEY CONCEPT All adults and adolescents with persistent asthma should receive an ICS-containing treatment to control symptoms and reduce future risk of severe exacerbations.[1] It is recommended that patients who present with asthma symptoms at least 2 days each month be initiated on either daily low-dose ICS therapy along with a SABA as needed, or low-dose ICS–formoterol to use as needed.

Corticosteroids are the most potent anti-inflammatory agents available for asthma treatment and are available in inhaled, oral, and injectable dosage forms. They decrease airway inflammation, attenuate airway hyperresponsiveness, and minimize mucus production and secretion. Corticosteroids also improve the response to β_2-agonists. ICS are more effective than LTRAs in improving lung function and preventing emergency department visits and hospitalizations due to asthma exacerbations.[1,4] The primary advantage of using ICS instead of systemic corticosteroids is targeted drug delivery to the lungs, which decreases the risk of systemic adverse effects. Product selection is based on preference for dosage form, delivery device, and cost.

Recommended doses of ICS are provided in Tables 15–2 and 15–3. ICS have a flat dose–response curve; doubling the dose has a limited additional effect on asthma control.[17] Cigarette smoking decreases the response to ICS, and smokers require higher doses of ICS than nonsmokers.[18] Although some beneficial effect is seen within 12 hours of administration of an ICS, 2 weeks of therapy is necessary to see significant clinical effects.

Table 15–2

Estimated Comparative Daily Dosages for Inhaled Corticosteroids and Inhaled Corticosteroid–Long-Acting β_2-Agonist Combinations for Asthma in Ages 12 Years and Older[1]

Medication	Low Dose	Medium Dose	High Dose
Beclomethasone HFA Redihaler 80 mcg/inhalation	80 mcg: 1 inhalation twice daily	80 mcg: 2 inhalations twice daily	80 mcg: > 2 inhalations twice daily
Budesonide DPI Flexhaler 90 or 180 mcg/inhalation	90 mcg: 2 inhalations twice daily 180 mcg: 1 inhalation twice daily	180 mcg: 2 inhalations twice daily	180 mcg: > 2 inhalations twice daily
Ciclesonide HFA MDI 80 or 160 mcg/inhalation	80 mcg: 1 inhalation twice daily	160 mcg: 1 inhalation twice daily	160 mcg: > 1 inhalation twice daily
Fluticasone furoate DPI Ellipta 100 or 200 mcg/inhalation	100 mcg: 1 inhalation daily		200 mcg: 1 inhalation daily
Fluticasone propionate DPI Respiclick and Digihaler 55, 113, or 232 mcg/inhalation	55 mcg: 1 inhalation twice daily	113 mcg: 1 inhalation twice daily	232 mcg: 1 inhalation twice daily
Fluticasone propionate HFA MDI 110 or 220 mcg/inhalation	110 mcg: 1 inhalation twice daily	110 mcg: 2 inhalations twice daily 220 mcg: 1 inhalation twice daily	220 mcg: 2 inhalations twice daily
Fluticasone propionate DPI Diskus 100 or 250 mcg/inhalation	100 mcg: 1 inhalation twice daily	100 mcg: 2 inhalations twice daily 250 mcg: 1 inhalation twice daily	250 mcg: 2 inhalations twice daily
Mometasone DPI Twisthaler 220 mcg/inhalation	220 mcg: 1 inhalation twice daily	220 mcg: 2 inhalations daily in the evening or 1 inhalation twice daily	220 mcg: 2 inhalations twice daily
Mometasone HFA MDI 100 or 200 mcg/inhalation	100 mcg: 1 inhalation twice daily	200 mcg: 1 inhalation twice daily	200 mcg: 2 inhalations twice daily
Combined ICS/LABA			
Fluticasone/Salmeterol DPI Diskus and Inhub 100/50 mcg, 250/50 mcg, 500/50 mcg	100/50 mcg: 1 inhalation twice daily	250/50 mcg: 1 inhalation twice daily	500/50 mcg: 1 inhalation twice daily
Fluticasone/Salmeterol DPI Respiclick and Digihaler 55/14 mcg, 113/14 mcg, 232/14 mcg	55/14 mcg: 1 inhalation twice daily	113/14 mcg: 1 inhalation twice daily	232/14 mcg: 1 inhalation twice daily
Fluticasone/Salmeterol HFA MDI 45/21 mcg, 115/21 mcg, 230/21 mcg	45/21 mcg: 2 inhalations twice daily	115/21 mcg: 2 inhalations twice daily	230/21 mcg: 2 inhalations twice daily
Budesonide/Formoterol HFA MDI 80/4.5 mcg, 160/4.5 mcg	80/4.5 mcg: 1 inhalation twice daily	160/4.5 mcg: 1 inhalation twice daily	160/4.5 mcg: 2 inhalations twice daily
Mometasone/Formoterol HFA MDI 100/5 mcg, 200/5 mcg	100/5 mcg: 1 inhalation twice daily	200/5 mcg: 1 inhalation twice daily	200/5 mcg: 2 inhalations twice daily
Fluticasone furoate/Vilanterol DPI Ellipta 100/25 mcg, 200/25 mcg	100/25 mcg: 1 inhalation daily		200/25 mcg: 1 inhalation daily

DPI, dry powder inhaler; HFA, hydrofluoroalkane; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; MDI, metered-dose inhaler.

Longer treatment may be necessary to realize the full effects on airway inflammation.

Local adverse effects associated with ICS therapy include oral candidiasis, cough, and dysphonia. For most delivery devices, the majority of the drug is deposited in the mouth and throat and swallowed. The incidence of local adverse effects can be reduced by using an MDI with a spacer and by having the patient rinse the mouth with water and expectorate after use. Decreasing the dose reduces the incidence of hoarseness. Systemic adverse effects, such as adrenal suppression and decreased bone mineral density, may also occur with long-term high doses of ICS. Growth suppression is a concern of some parents whose children are prescribed an ICS. However, final adult height is not thought to be affected by ICS use, but growth velocity is slightly reduced (by less than half a centimeter per year), and height after 1 year of treatment is decreased by less than 1 cm in children treated with low- and medium-dose ICS.[19,20] Risk of pneumonia is increased with higher ICS doses in adults.[21] An important drug interaction causing Cushing syndrome and adrenal insufficiency occurs when potent inhibitors of CYP3A4 (eg, ritonavir, itraconazole, ketoconazole) are administered with high doses of ICS; therefore, coadministration should be avoided whenever possible.[22] Poor adherence to ICS treatment is common and contributes to uncontrolled asthma.[23] The cost, slow onset of action and concerns about side effects are major deterrents to using these highly effective medications.

Considerable variability in response to ICS exists, with up to 40% of patients not responding to ICS. This lack of response may be related to functional glucocorticoid-induced transcript 1 gene (*GLCCI1*) variant in some patients with asthma.[24]

Systemic Corticosteroids Add-on low-dose oral corticosteroids (prednisone, prednisolone, methylprednisolone) are considered a last-line option for patients with severe, uncontrolled asthma when all other add-on treatment options have been

Table15–3

Estimated Comparative Daily Dosages for Inhaled Corticosteroids and Inhaled Corticosteroid—Long-Acting β_2-Agonist Combinations for Asthma in Children < 12 Years Old[1]

Medication	Low Dose	Medium Dose	High Dose
Beclomethasone HFA BAI 40 or 80 mcg/inhalation	5 years of age: 40 mcg: 1 inhalation twice daily 6–11 years of age: 40 mcg: 1–2 inhalations twice daily 80 mcg: 1 inhalation twice daily	6–11 years of age: 80 mcg: 2 inhalations twice daily	6–11 years of age: 80 mcg: > 2 inhalations twice daily
Budesonide DPI 90 or 180 mcg/inhalation	6–11 years of age: 90 mcg: 1 inhalation twice daily	6–11 years of age: 180 mcg: 1 inhalation twice daily	6–11 years of age 180 mcg: > 2 inhalations twice daily
Budesonide inhalation suspension for nebulization 0.25 mg/2 mL, 0.5 mg/2 mL, 1 mg/2 mL	0–4 years of age: 0.25 mg once or twice daily 5–11 years of age: 0.25 mg twice daily or 0.5 mg once daily	0–4 years of age: 0.25–0.5 mg twice daily 5–11 years of age: 0.5 mg twice daily	0–4 years of age: > 0.5 mg twice daily 5–11 years of age: 1 mg twice daily
Fluticasone propionate HFA MDI 44, 110, or 220 mcg/inhalation	4–11 years of age: 44 mcg: 1 inhalation twice daily	4–11 years of age: 44 mcg: 2 inhalations twice daily	6–11 years of age: 110 mcg: ≥ 1 inhalation twice daily[1]
Fluticasone propionate DPI 50 or 100 mcg/inhalation	4–11 years of age: 50 mcg: 1 inhalation twice daily	4–11 years of age: 100 mcg: 1 inhalation twice daily	4–11 years of age: 100 mcg: 1 inhalation twice daily
Fluticasone furoate DPI 50 mcg/inhalation	5–11 years of age: 50 mcg: 1 inhalation daily		
Mometasone HFA MDI 50 mcg/inhalation	5–11 years of age: 50 mcg: 1 inhalation twice daily	5–11 years old: 50 mcg: 1 inhalation twice daily	5–11 years old 50 mcg: 2 inhalations twice daily
Mometasone DPI 110 mcg/inhalation	4–11 years of age: 110 mcg: 1 inhalation daily in the evening		
Combined ICS/LABA			
Fluticasone/Salmeterol DPI 100/50 mcg	4–11 years of age: 100/50 mcg: 1 inhalation twice daily		
Budesonide/Formoterol HFA MDI 80/4.5 mcg	6–11 years of age: 80/4.5 mcg: 2 inhalations twice daily		
Mometasone/Formoterol HFA MDI 50/5 mcg	5–11 years of age: 50/5 mcg: 2 inhalations twice daily		

BAI, breath-actuated inhaler; DPI, dry powder inhaler; HFA, hydrofluoroalkane; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; MDI, metered-dose inhaler.

expended. Prior to considering addition of oral corticosteroids, barriers to asthma control should be assessed (eg, poor inhaler technique, nonadherence to inhaled treatments, exposure to environmental triggers). If systemic therapy is necessary, once-daily or every-other-day therapy is used with repeated attempts to decrease the dose or discontinue the drug. Patients must be counseled on potential adverse effects including weight gain, mood disturbances, hypertension, impaired wound healing, adrenal suppression, and decreased bone mineral density.

Long-Acting Inhaled β_2-Agonists LABAs are frequently used as add-on maintenance therapy for asthma that is not controlled on an ICS alone. Class benefits of LABAs when used as maintenance therapy in combination with an ICS include improved pulmonary function, increased symptom-free days, and decreased need for SABA use. Adding a LABA to a low-dose ICS is at least as effective in improving symptoms and decreasing asthma exacerbations as doubling the dose of an ICS or adding an LTRA to ICS.[25] Adding a LABA to ICS therapy also reduces the amount of ICS necessary for asthma control.[5] LABAs should not be used as monotherapy for chronic asthma because there may be an increased risk of severe asthma exacerbations and asthma-related deaths when LABAs are used alone.[26] Labeling for all drugs containing LABAs includes a box warning against their use without an ICS. The risk of increased severe asthma exacerbations does not appear to be increased in adults receiving both a LABA and ICS.[27]

Salmeterol is available as a single-ingredient product and as a fixed-ratio combination product containing an ICS. Formoterol is available in combination with ICS for asthma and as an inhalation solution for nebulization for COPD. Vilanterol is available only in combination with ICS. Combination products may increase adherence because of the need for fewer inhalers and inhalations. The individual LABAs vary both in their onset and duration of action. Vilanterol has the longest duration of action, allowing for once-daily dosing, while salmeterol and formoterol must be dosed every 12 hours. Salmeterol has a delayed onset of action compared to the other LABAs; both vilanterol and formoterol have an onset of action of around 5 minutes, whereas salmeterol onset is around 15 minutes.

Long-Acting Muscarinic Antagonists (LAMAs) Muscarinic antagonists inhibit the effects of acetylcholine on muscarinic receptors in the airways and protect against cholinergic-mediated bronchoconstriction. Tiotropium bromide is an inhaled LAMA available as a slow-mist inhaler for asthma. It has an onset in approximately 30 minutes and a duration longer than 24 hours. Tiotropium is used as a long-term controller medication in patients at least 6 years of age with uncontrolled asthma already taking an ICS or an ICS and LABA combination.[28,29] Addition of a LABA is preferred over adding a LAMA to patients who are not adequately controlled on an ICS alone.[12] Addition of tiotropium to combined ICS-LABA therapy has been associated with improved asthma control and quality of life with no change in exacerbations.

Umeclidinium is another LAMA available as a three-drug combination with fluticasone and vilanterol for treatment of asthma in patients at least 18 years of age. This is currently the only once-daily single inhaler with triple therapy available for treatment of asthma. In clinical trials, combination umeclidinium–fluticasone–vilanterol showed statistically significant improvements in FEV_1 when compared to combination fluticasone–vilanterol.[30] Muscarinic-antagonists may cause adverse effects such as urinary retention, dry mouth, headache, and upper respiratory tract infections. Refer to Table 15–4 for LAMA dosing recommendations.

Leukotriene Receptor Antagonists The LTRAs are anti-inflammatory medications that either inhibit 5-lipoxygenase (zileuton) or competitively antagonize the effects of leukotriene D_4 (montelukast, zafirlukast). These agents improve FEV_1 and decrease asthma symptoms, SABA use, and asthma exacerbations. Although they offer the convenience of oral administration, they are significantly less effective than ICS.[4,31] Combining an LTRA with an ICS is not as effective as an ICS plus a LABA but is considered steroid sparing.[1,4] LTRAs are beneficial for asthma patients with allergic rhinitis, aspirin sensitivity, or exercise-induced bronchospasm (EIB).[1]

Montelukast has a boxed warning about serious mental health side effects. All three LTRAs have reports of neuropsychiatric events, such as sleep disorders, aggressive behavior, and suicide. Zileuton and zafirlukast are less commonly used because of the risk of hepatotoxicity. Zileuton use requires liver function tests prior to use, monthly for 3 months, every 3 months for the first year, and periodically thereafter. Zileuton and zafirlukast are metabolized through the CYP 2C9 hepatic pathway and have significant drug interactions. Refer to Table 15–4 for LTRA dosing recommendations.

Biologic Agents About 3.7% of patients with asthma have severe, difficult to treat asthma requiring high doses of ICS and at least one other controller medication along with frequent bursts of oral corticosteroids or daily use of oral corticosteroids.[32,33] These patients have poor symptom control despite good adherence to medications and appropriate inhaler technique. Biologic agents target Th2 inflammation, allowing for reduction or discontinuation in corticosteroid use, fewer asthma exacerbations, and improved lung function. Assessing inflammatory markers such as IgE, blood eosinophils, and FeNO help identify the appropriateness of an individual biologic agent.

Anti-IgE Monoclonal Antibody Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that inhibits binding of IgE to receptors on mast cells and basophils, resulting in inhibition of inflammatory mediator release and attenuation of the early- and late-phase allergic response. Omalizumab is indicated for patients with moderate-to-severe persistent asthma whose symptoms are not controlled by ICS and who have a positive skin test or in vitro reactivity to aeroallergens and elevated IgE (30–700 IU/mL [kIU/L] for patients age 12 and older or 30–1300 IU/mL [kIU/L] for ages 6–11 years). Omalizumab significantly decreases ICS use, reduces the number and length of exacerbations, and increases asthma-related quality of life.[34] The initial dose is based on the patient's weight and baseline total serum IgE concentration. See Table 15–4 for dosing recommendations. Subsequent IgE levels are not monitored.

The most common adverse effects of omalizumab are injection-site reactions (bruising, redness, pain, stinging, itching, and burning). Anaphylactic reactions are rare but may occur at any time after medication administration. Monitoring the patient for an anaphylactic reaction for 2 hours after medication administration is recommended for the first 3 months; thereafter, monitoring time can be reduced to 30 minutes.[35] It is also important to issue a prescription for subcutaneous epinephrine and educate the patient on its use for anaphylactic reactions to omalizumab.

Interleukin-5 (IL-5) and IL-5R (Receptor) Antagonist Monoclonal Antibody For patients with severe asthma exacerbations in the past year and high blood eosinophil counts, starting a medication that decreases eosinophils improves asthma outcomes. Mepolizumab and reslizumab are monoclonal antibodies that block the cytokine IL-5 from recruiting eosinophils. Benralizumab is a monoclonal antibody that binds directly to the IL-5 receptor alpha on eosinophils and destroys the cells. All three medications decrease asthma exacerbations and symptoms.[36–38] Common side effects include nasopharyngitis, headache, hypersensitivity reactions, and worsening asthma or upper respiratory tract infections. Long-term side effects are unknown. See Table 15–4 for dosing.

Interleukin-4 (IL-4) Receptor Alpha Antagonist Monoclonal Antibody Dupilumab improves the symptoms of patients with high IgE and eosinophil counts by inhibiting IL-4 and IL-13 signaling in Th2 inflammation. Dupilumab decreases asthma exacerbations, oral corticosteroid dosing, and asthma symptoms.[39] The most common side effects are injection site pain and transient blood eosinophilia.

Macrolides Recent evidence indicates that azithromycin 500 mg orally three times weekly decreases asthma exacerbations and improves quality of life for adults with asthma not controlled with a medium-to-high dose ICS and LABA.[40] Results were similar in patients with both eosinophilic and noneosinophilic asthma. Potential benefits result from anti-inflammatory and not antimicrobial properties. Screening for hearing impairment, cardiac arrhythmias, and drug interactions is recommended prior to initiating treatment. There is no clear evidence on how long azithromycin should be continued, but a clear benefit was not seen until after 3 months of treatment. Treatment for at least 6 months is recommended.[1]

▶ *Reliever Medications*

Short-Acting Inhaled B_2-Agonists SABAs such as albuterol (known as salbutamol outside the United States) reverse acute airway obstruction caused by bronchoconstriction and block the early-phase response to antigen in an asthma exacerbation. They also increase mucociliary clearance and stabilize mast-cell membranes. Due to their rapid onset of action for reversing bronchoconstriction, inhaled SABAs have been considered the cornerstone of therapy for acute asthma exacerbations. More recent evidence shows that SABA use without an ICS increases the risk of asthma-related death, urgent asthma-related healthcare, and reduced lung function.[41] Based on these findings, SABAs may still be used to manage acute asthma symptoms, but guidelines recommend that an ICS be given concomitantly in patients age 6 years and older.[1] Scheduled SABA use decreases the duration of bronchodilation provided by the SABA and is not recommended.

Table 15–4

Usual Doses of Long-Term Control Medications in Asthma[a]

Medication	Dosage Form	Ages 0–11 Years	Adults and Children > 12 Years
Inhaled Corticosteroids (see Tables 15–2 and 15–3)			
Inhaled Corticosteroids/Long-Acting β_2-Agonists (see Tables 15–2 and 15–3)			
Long-Acting β_2-Agonists			
Salmeterol	DPI 50 mcg/blister	Ages 0–3 years: N/A Ages 4–11 years: One inhalation every 12 hours	One inhalation every 12 hours
Long-Acting Muscarinic Agents			
Tiotropium	SMI 1.25 mcg/actuation	Ages 0–5: N/A Ages 6–11: Two inhalations of 1.25 mcg once daily	Two inhalations once daily
Inhaled Corticosteroid/Long-Acting β_2-Agonists/Long-Acting Muscarinic			
Fluticasone/Umeclidinium/Vilanterol	DPI 100/62.5/25 mcg/actuation or 200/62.5/25 mcg/actuation	N/A	Age 12-17: N/A Age 18 and older: One inhalation daily
Leukotriene Modifiers			
Montelukast	4 mg or 5 mg chewable tablets 4 mg granule packets 10 mg tablet	Ages 1–5 years: 4 mg at bedtime Ages 6–11 years: 5 mg at bedtime	Ages 12–14 years: 5 mg at bedtime Ages 15 and older: 10 mg at bedtime
Zafirlukast	10 or 20 mg tablets	Ages 0–4 years: N/A Ages 5–11 years: 10 mg twice daily	20 mg twice daily
Zileuton	600 mg extended-release tablet 600 mg immediate-release tablet	N/A: only approved for those 12 years of age and older	Extended-release tablets: 1200 mg twice daily after morning and evening meals Immediate-release tablets: 600 mg four times daily
Anti-IgE Monoclonal Antibody			
Omalizumab	Injection: 75 mg/0.5 mL and 150 mg/mL solution in prefilled syringe and 150 mg powder in single-dose vial for reconstitution	Ages 0–5: N/A Ages 6–11: 75–375 mg SC every 2–4 weeks, depending on body weight and pretreatment serum IgE level; see dosing chart[b]	150–375 mg SC every 2–4 weeks, depending on body weight and pretreatment serum IgE level; see dosing chart[b]
Interleukin-5 and Interleukin-5 Receptor Antagonist Monoclonal Antibodies			
Mepolizumab	Injection: 100 mg/mL, single-dose, prefilled autoinjector or prefilled syringe and 100 mg powder for reconstitution	Age 0-5: N/A Ages 6-11: 40 mg SC once every 4 weeks	100 mg SC once every 4 weeks; suggested AEC ≥150–300 cells/μL (0.15×10^9–0.3×10^9/L)
Reslizumab	Injection: 100 mg/10 mL vial	N/A	Ages 12-17: N/A Ages 18 and older: 3 mg/kg IV infusion over 20–50 minutes every 4 weeks; suggested AEC ≥ 400 cells/μL (0.4×10^9/L)
Benralizumab	Injection, 30 mg/mL prefilled syringe and single-dose autoinjector pen	N/A	30 mg SC every 4 weeks for the first 3 doses, followed by once every 8 weeks; suggested AEC > 300 cells/μL (0.3×10^9/L)
Interleukin-4 Receptor Alpha Antagonist Monoclonal Antibody			
Dupilumab	Injection: 200 mg/1.14 mL and 300 mg/2 mL prefilled syringe; 300 mg/2 mL and 200 mg/1.14 mL solution in a prefilled pen	N/A	400 mg SC, followed by 200 mg SC every other week; suggested AEC >150 cells/μL (0.15×10^9/L) or FeNO ≥ 25 ppb OR 600 mg SC, followed by 300 mg SC every other week for patients on OCS or also having atopic dermatitis and asthma

[a] Dosages are provided for products that have been approved by the US FDA or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.

[b] XOLAIR (omalizumab) Dosing for Allergic Asthma, CIU & Nasal Polyps (xolairhcp.com).

AEC, absolute eosinophil count; DPI, dry powder inhaler; FeNO fraction of exhaled nitric oxide ppb parts per billion; IgE, immunoglobulin E; IV, intravenous; N/A, safety and efficacy not established; OCS, oral corticosteroid; SC, subcutaneous; SMI, slow mist inhaler.

Inhaled SABAs have an onset in less than 5 minutes and a duration of action of 4 to 6 hours. Albuterol is the most commonly used inhaled SABA and is available as an MDI, breath-actuated DPI, and an inhalation solution for nebulization. Levalbuterol, the pure R-enantiomer of albuterol (referred to as R-salbutamol outside the United States), is available as an MDI and an inhalation solution for nebulization. Levalbuterol has similar efficacy to albuterol and is purported to have fewer side effects; however,

Table 15–5

Usual Dosages for Reliever Medications for Asthma in Home Setting[a,b]

Medications	Dosage Form	Children 0–11 Years	Adults and Children 12 Years of Age and Older
Inhaled SABA			
Albuterol HFA	MDI (inhalation suspension) 90 mcg/inhalation, 200 actuations/canister	0–11 years: 2–6 inhalations every 4–6 hours as needed[1]	2 inhalations every 4–6 hours as needed
Albuterol	DPI (inhalation powder) 90 mcg/inhalation, 200 actuations/canister	Not approved for <12 years of age	2 inhalations every 4–6 hours as needed
Albuterol	Inhalation solution 0.63 mg/3 mL, 1.25 mg/3 mL, 2.5 mg/3 mL, 5 mg/mL (0.5%)	0–4 years: 0.63–2.5 mg every 4–6 hours as needed 5–11 years: 1.25–5 mg every 4–8 hours as needed	2.5–5 mg every 6–8 hours as needed
Levalbuterol HFA	MDI (inhalation suspension) 45 mcg/Inhalation, 200 actuations/canister	0–3 years: N/A 4–11 years: 1–2 inhalations every 4–6 hours as needed	2 inhalations every 4–6 hours as needed
Levalbuterol	Inhalation solution 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/0.5 mL, 1.25 mg/3 mL	6–11 years: 0.31–0.63 mg every 8 hours as needed	0.63 mg every 6–8 hours as needed; may titrate to 1.25 mg every 8 hours if inadequate response
Systemic Corticosteroids			
Methylprednisolone	2, 4, 8, 16, 32 mg oral tablets	1–2 mg/kg/day by mouth in 2 divided doses (max 20 mg/day for <2 years; 30 mg/day for <6 years; 40 mg/day for <12 years) for 3–5 days	40–50 mg/day by mouth as single or two divided doses for 5–7 days
Prednisolone	5 mg oral tablets; 5 mg/5 mL and 15 mg/5 mL oral liquid		
Prednisone	1, 2.5, 5, 10, 20, 50 mg oral tablets; 5 mg/mL and 5 mg/5 mL oral liquid		

[a] Dosages are provided for products that have been approved by the US FDA or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.

[b] Doses are increased in the hospital/emergency department setting.

DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; N/A; safety and efficacy not established; SABA, short-acting β_2-agonist.

clinical trials have not demonstrated this benefit.[42] See Table 15–5 for SABA dosing recommendations. During an asthma exacerbation, albuterol doses may be increased to 4 to 10 puffs every 20 minutes for up to 1 hour to gain rapid control of symptoms, and then continued at a higher dose and frequency as determined by treatment response. The dose and frequency of reliever medications should be individualized based on the severity and frequency of the patient's exacerbation history and should be included in the patient's asthma action plan. Repeated SABA use over 1 to 2 days signals a lack of response and the need to contact the healthcare provider. Adverse effects of SABAs include tachycardia, tremor, and hypokalemia, which are usually not troublesome with inhaled dosage forms unless high doses are required to treat an exacerbation.

ICS–formoterol KEY CONCEPT As-needed use of formoterol combined with a low-dose ICS is considered the preferred reliever treatment for adults and adolescents with mild asthma.[1] This combination may be recommended as the sole treatment for patients with intermittent asthma or in combination with a daily maintenance inhaler containing an ICS or ICS–formoterol for patients with more severe asthma. Clinical trials showed decreased severe exacerbations when as-needed budesonide–formoterol was compared to a SABA alone in patients with mild asthma.[43] Furthermore, patients with infrequent asthma symptoms have poor adherence to prescribed maintenance medications, exposing them to the risks of SABA-only treatment.[1] Use of as-needed ICS–formoterol provides the added benefit of ICS therapy to combat airway inflammation while decreasing the burden of daily ICS use.

Although other combinations of ICS–formoterol may be considered, current evidence only exists for the combination of budesonide and formoterol. Patients using budesonide–formoterol as a reliever medication should not exceed 72 mcg of formoterol per day. As-needed ICS–formoterol has not been studied in children 11 years of age and younger, and the recommended reliever treatment is different for this age group.

Short-Acting Muscarinic Antagonists (SAMAs) Ipratropium bromide is available as an MDI and inhalation solution for nebulization. Its onset is approximately 15 minutes, and the duration is 4 to 8 hours. Addition of ipratropium bromide to a SABA during a moderate-to-severe asthma exacerbation improves pulmonary function and decreases hospitalization rates in both adult and pediatric patients.[44] Combining a SABA with ipratropium to increase bronchodilation is only indicated in the emergency department setting. The bronchodilator effects of SAMAs are not as pronounced as SABAs in asthma.[1,4] See Table 15–5 for dosing recommendations of ipratropium.

Systemic Corticosteroids Prednisone, prednisolone, and methylprednisolone are the cornerstone of treatment for acute asthma not responding to a SABA (see Table 15–5 for recommended doses).[1,4] The onset of action for systemic corticosteroids is 4 to 12 hours. For this reason, systemic corticosteroids are started early in the course of severe acute exacerbations (eg, PEF < 60% of personal best, patient not responding to treatment over 48 hours, or patients with history of sudden severe exacerbations). The oral route is preferred in acute asthma; it is less invasive, less costly, and has a quicker onset of action compared to intravenous corticosteroid administration. For children, the liquid formulation is preferred to tablets. Prednisolone sodium phosphate oral solution (15 mg/5 mL) rather than prednisolone base is more palatable for children.[45] The duration of therapy usually ranges from 5 to 7 days. Tapering the corticosteroid dose in patients receiving less than 2 weeks of therapy is usually not necessary because any adrenal suppression is transient and rapidly reversible.[1]

Patient Encounter Part 2

Current Home Medication Regimen:

- Albuterol MDI 2 inhalations every 4 to 6 hours as needed for shortness of breath. Last filled 28 days ago.
- Albuterol 2.5-mg solution for inhalation every 6 hours as needed for wheezing. Last filled 2 weeks ago.
- Loratadine 10 mg orally daily for allergies. Purchases over the counter. She does not buy often because of cost.
- Fluticasone nasal spray 50 mcg/actuation: 1 spray in each nostril twice daily. Last filled 3 months ago.
- Daily multivitamin

Medication History

- Montelukast 10 mg at bedtime. Discontinued ~2 years ago because of nonadherence. Per patient "I just always seemed to fall asleep before taking it."
- Fluticasone DPI 100 mcg twice daily. Discontinued ~3 years ago because of nonadherence. Patient said it didn't seem to help and it gave her oral thrush.
- Prednisone 40 mg 1 tablet daily × 7 days.

Vaccinations: Receives yearly influenza vaccine; unable to recall what other vaccines she has received.

Discuss whether the patient is currently receiving the preferred drug therapy for asthma management.

What motivational interviewing techniques may be used to discuss medication adherence with the patient?

Which vaccines should the patient receive based on her asthma history?

Treatment of Chronic Asthma

KEY CONCEPT Current clinical practice guidelines recommend control-based asthma management, where pharmacologic treatment is adjusted in a continuous cycle that involves assessment, treatment, and review.[1] In this approach, asthma control and future risk are used to determine the initial treatment, and then the response to treatment is evaluated to determine if further adjustment is needed to achieve asthma control. The least amount of medications necessary to meet the therapeutic goals is used.

The first step in asthma management is determining the frequency of asthma symptoms and the risk for future exacerbations. Pharmacologic treatment is then initiated based on the recommendations for that particular risk category (Tables 15–6 and 15–7). From there, a stepwise approach is used to adjust treatment based on patient response. Therapeutic plans must be individualized, and patient/caregiver preferences should be taken into consideration.

Table 15–6

GINA Recommendations for Initial Treatment in Adults and Adolescents

Symptom Presentation	Preferred Option for Adults/Adolescents	Preferred Option for children 6–11 Years of Age
Asthma symptoms < 2×/month; no risk factors for exacerbations	As-needed low-dose ICS–formoterol OR Low-dose ICS whenever SABA is taken	As-needed SABA with low-dose ICS whenever SABA is taken
Asthma symptoms or need for ≥2×/month	Low-dose ICS with a SABA as-needed OR As-needed low-dose ICS–formoterol	Low-dose ICS with a SABA
Asthma symptoms most days or waking up due to asthma at least once/week	Low-dose ICS-formoterol as controller and reliever therapy OR Low-dose ICS-LABA with as-needed SABA OR Medium-dose ICS with SABA	Low-dose ICS-LABA with as-needed SABA OR Medium-dose ICS with as-needed SABA OR Low-dose ICS-formoterol daily and as reliever
Daily symptoms, waking with asthma symptoms once a week or more or FEV1<65%	High-dose ICS with as-needed SABA +/– oral steroid burst OR Medium-dose ICS-formoterol daily and as-needed +/– oral steroid burst	Medium-dose ICS-LABA with as-needed SABA +/– oral steroid burst OR low dose ICS-formoterol daily and as a reliever

GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist, LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting β_2-agonist.

Data from Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. www.ginasthma.org.

Table 15–7

Risk Factors for Asthma Exacerbation

- Uncontrolled asthma symptoms
- Frequent use of SABA
- Inadequate ICS therapy
- Low FEV$_1$ (especially if < 60% predicted)
- Major psychological or socioeconomic problems
- Exposures: smoking, allergen exposure if sensitized
- Comorbidities: Obesity, rhinosinusitis, confirmed food allergy
- Sputum or blood eosinophilia; elevated FeNO (in adults with allergic asthma)
- Pregnancy
- History of intubation or treatment in ICU for asthma
- 1 or more severe exacerbations in the past 12 months

FeNO, fraction of exhaled nitric oxide; FEV$_1$, forced expiratory volume in the first second; ICS, inhaled corticosteroid; ICU, intensive care unit; SABA, short-acting β_2-agonist.

▶ *Intermittent Asthma*

This classification includes patients with EIB, seasonal asthma, or asthma symptoms associated with infrequent trigger exposure. Patients with intermittent asthma continue to have chronic inflammation, and preferred treatment options include ICS–formoterol as needed or as-needed SABA with low-dose ICS.[1] Although a SABA alone is still an option for intermittent asthma, this regimen has been associated with an increased risk of severe exacerbations when compared to treatment regimens that also contain an ICS.[1]

Exercise is one of the most common precipitants of asthma symptoms. Shortness of breath, wheezing, or chest tightness usually occur during or shortly after vigorous exercise, peak 5 to 10 minutes after stopping the activity, and resolve within 20 to 30 minutes. Warming up prior to exercise and covering the mouth and nose with a scarf or mask during cold weather may prevent EIB (Table 15–1). Pretreatment with a SABA or low-dose ICS–formoterol 5 to 20 minutes prior to exercise is the treatment of choice for EIB and will protect against bronchospasm for 2 to 3 hours. Regular treatment with an ICS is recommended if treatment is needed daily before exercise.[46]

▶ *Persistent Chronic Asthma*

ICS are the long-term control medications of choice at all levels of asthma severity (mild, moderate, and severe) and in all age groups.[1,4–6] Single Maintenance and Reliever Therapy (SMART) therapy, which refers to the use of ICS–formoterol as both controller therapy and reliever therapy, is now considered the treatment of choice for adults and adolescents 12 years and older with moderate persistent asthma.[12] SMART therapy has shown superiority to a higher daily dose of an ICS with an as-needed SABA, a daily same-dose ICS plus LABA and an as-needed SABA, and a higher daily dose ICS plus LABA and an as-needed SABA.[12] Addition of a LAMA, biologic agents, and/or oral corticosteroids may be considered for patients who are unable to achieve control on SMART therapy alone. Patients should be assessed 1 to 3 months after changes to their medication regimen to determine whether asthma control has been achieved and a "step up" in therapy should be considered if symptoms persist (Table 15–8 and 15–9). Adherence to the treatment regimen as well as proper inhaler technique should always be assessed prior to making changes in therapy.

Patients with controlled asthma are monitored at 3- to 12-month intervals to ensure that control is maintained. A gradual step-down in long-term controller therapy is attempted once control has been maintained for 3 months.[1] If treatment is stepped down too far or too quickly, exacerbation risk may increase even if symptoms remain controlled.[1] Factors associated with a poor response to step-down therapy include serious exacerbations in the past 12 months and a low baseline FEV$_1$.[1] Controversy exists about how best to taper long-term controller medication. A safe approach seems to be stepping down ICS dose by 25% to 50% at 3-month intervals.[1] Complete cessation of ICS is not recommended because it is associated with a significant risk of exacerbations, and stopping LABA therapy has been shown to result in increased hospitalizations and reduced lung function.[47] Therefore, it is vital to monitor patients closely during step-down therapy, provide them with an asthma

Table 15–8

Assessment of Asthma Control in Adults, Adolescents, and Children

Adults, Adolescents, and Children 6–11 Years		Children ≤ 5 Years	
Asthma Symptoms	**Level of Symptom Control**	**Asthma Symptoms**	**Level of Symptom Control**
In the past 4 weeks, has the patient had: • Daytime asthma symptoms more than twice per week • Nighttime awakening due to asthma • Reliever needed for symptoms more than twice per week • Activity limitation due to asthma	If yes to none of these = well controlled If yes to 1–2 of these = partly controlled If yes to 3–4 of these = uncontrolled	In the past 4 weeks, has the child had: • Daytime asthma symptoms for more than a few minutes, more than once a week • Nighttime awakening or nighttime coughing due to asthma • SABA needed more than once per week • Activity limitation due to asthma	If yes to none of these = well controlled If yes to 1–2 of these = partly controlled If yes to 3–4 of these = uncontrolled

1. If asthma is not well controlled, assess inhaler technique, adherence to therapies, and environmental controls before considering adjustment of therapy.
2. Consider stepping up therapy if uncontrolled symptoms or recent exacerbations or high risk for exacerbations (see Table 15–6 and 15–7). Refer to Table 15–9 for stepwise approach to control asthma symptoms.
3. Consider stepping down therapy if symptoms controlled for 3 months + low risk for exacerbations.

Data from Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. www.ginasthma.org.

Table 15–9

GINA Stepwise Approach to Control Symptoms and Minimize Future Risk

Adolescents and Adults 12 Years and Older

Step	Preferred Controller	Preferred Reliever
1	As-needed low-dose ICS–formoterol	As-needed low-dose ICS–formoterol
2	As-needed low-dose ICS–formoterol	As-needed low-dose ICS–formoterol
3	Daily low-dose ICS-formoterol	As-needed low-dose ICS–formoterol
4	Daily medium-dose ICS-formoterol	As-needed low-dose ICS–formoterol
5	Refer for expert advice. High-dose ICS-formoterol + add-on treatment LAMA, anti-IgE, anti-IL5/5R, OR anti-IL4Rα	As-needed low-dose ICS–formoterol

Children Aged 6-11 Years of Age

Step	Preferred Controller Option	Other Controller Options	Preferred Reliever
1	Low-dose ICS taken when SABA taken	Daily low-dose ICS	SABA
2	Daily low-dose ICS	LTRA OR low-dose ICS taken whenever SABA taken	SABA
3	Daily low-dose ICS-LABA OR medium-dose ICS, OR very low dose ICS-formoterol	Low-dose ICS + LTRA	SABA OR as-needed low-dose ICS-formoterol if patient is on ICS-formoterol as maintenance
4	Medium-dose ICS-LABA OR low dose ICS-formoterol. Refer for expert advice	Medium-dose ICS-LABA + tiotropium OR medium-dose ICS-LABA + LTRA	SABA OR as needed low-dose ICS-formoterol if patient is on ICS-formoterol as maintenance
5	High-dose ICS-LABA + add on treatment LAMA, anti-IgE; Refer for expert advise	Add anti-IL5 (mepolizumab) OR add low-dose OCS	SABA

Children Ages 5 Years and Younger

Step	Preferred Controller Option	Other Controller Options	Preferred Reliever
1	No controller		SABA
2	Low-dose ICS	LTRA Intermittent ICS at symptom onset	SABA
3	Medium-dose ICS; Refer for expert advice	Low-dose ICS + LTRA	SABA
4	Medium-dose ICS; Refer for expert advice	Add LTRA OR increase ICS frequency OR add intermittent ICS	SABA

*If patient is on a LABA other than formoterol, then a SABA should be used as reliever

GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting β_2 agonist.

Data from Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. www.ginasthma.org.

action plan, and ensure that they have a supply of their controller medication at home to resume if necessary.

Treatment of Acute Asthma

KEY CONCEPT In acute asthma, early and appropriate intensification of therapy is important to resolve the exacerbation and prevent relapse and future severe airflow obstruction. Both SABA therapy and as-needed ICS–formoterol are optional reliever medications for self-management of asthma exacerbations. However, use of SABA reliever is less effective in preventing progression to severe exacerbation requiring oral corticosteroids than low-dose ICS–formoterol.[1] If adherence to an ICS is problematic, increasing the ICS dose during acute exacerbations may be acceptable directions to provide in the action plan. Based on the initial response to these self-management strategies, the severity of the exacerbation is assessed, and treatment is appropriately intensified. Patients should add an oral corticosteroid if worsening asthma symptoms persist for 48 hours.[1] Patients deteriorating quickly or not responding to reliever medications should go to the emergency department for assessment and treatment of the exacerbation.

Patients achieving a sustained response in the emergency department are generally discharged home with a 5- to 7-day course of oral corticosteroids, an appropriate long-term controller medication, and a reliever medication. Patients who do not respond adequately to intensive therapy in the emergency department within 3 to 4 hours are admitted to the hospital. Refer to Table 15–10 for treatment recommendations in the emergency setting.

Regardless of the severity of an asthma exacerbation, patients should see their primary healthcare provider within 1 week to identify the potential cause of the exacerbation and adjust pharmacologic and nonpharmacologic therapy as necessary.

Asthma Self-Management

Self-management plans give patients the freedom to adjust therapy based on personal assessment of disease control using predetermined written instructions from the physician. Written asthma action plans (a part of standard care) guide at-home treatment of worsening asthma to potentially prevent hospitalizations and death.

The action plan includes instructions on daily management and how to recognize and manage worsening asthma.[1,4]

Table 15–10

Assessment and Treatment of Asthma Exacerbations in the Urgent or Emergency Care Setting

	Signs and Symptoms		
Severity	**> 5 Years of Age**	**Children ≤ 5 Years of Age**	**Clinical Course**
Mild to Moderate	Talks in sentences Prefers sitting to lying Not agitated Respiratory rate increased Accessory muscles not used Pulse rate 100–120 bpm O_2 saturation (on air) 90%–95% (0.90–0.95) PEF > 50% predicted or personal best	Talks in sentences Breathless Wheezing may be present May be agitated Pulse rate < 100 bpm if mild Pulse rate < 180 bpm (0–3 years) or ≤ 150 bpm (4–5 years) if moderate O_2 saturation ≥ 92% (0.92)	• SABA by nebulizer or MDI + spacer • Ipratropium bromide may decrease need for hospitalization and improve FEV_1 compared to SABA alone • Systemic corticosteroid × 5–7 days for adult; 3–5 days for children • Oxygen (if needed); target saturation 93%–95% (0.93–0.95) for adults; 94%–98% (0.94–0.98) for children; > 95% (0.95) during pregnancy • Epinephrine indicated only if exacerbation is associated with anaphylaxis and angioedema
Severe	Talks in words, not sentences Sits hunched forward Respiratory rate > 30/min Accessory muscles in use Pulse rate > 120 bpm O_2 saturation (on air) < 90% (0.90) PEF < 50% predicted or personal best	Talks in words, not sentences Pulse rate > 180 bpm (0–3 years) or > 150 bpm (4–5 years) O_2 saturation < 92% (0.92) Marked subcostal and/or subglottic retractions	• Requires ED visit and likely hospitalization; immediate transfer to hospital is indicated if child ≤ 5 years of age • Give inhaled SABA + ipratropium bromide in ED setting; no benefit from adding ipratropium to SABA once hospitalized • Oxygen to maintain saturation 93%–95% (0.93–0.95) for adults; 94%–98% (0.94–0.98) for children; > 95% (0.95) during pregnancy • Oral or IV systemic corticosteroids; oral preferred if possible • Consider IV magnesium[a] • Epinephrine indicated only if exacerbation is associated with anaphylaxis and angioedema
Subset: Life Threatening	Too dyspneic to speak Drowsiness Confusion Silent chest Central cyanosis Pulse rate > 200 bpm PEF < 25% predicted or personal best	Unable to speak or drink Central cyanosis Silent chest Confusion	• Transfer to ICU • While waiting, start SABA + ipratropium bromide, IV corticosteroids, and O_2 to maintain saturation 93%–95% (0.93–0.95) for adults; 94%–98% (0.94–0.98) for children; > 95% (0.95) during pregnancy • Prepare patient for intubation • Consider IV magnesium[a] • Epinephrine indicated only if exacerbation is associated with anaphylaxis and angioedema

[a] Intravenous magnesium sulfate is not recommended for routine use in asthma exacerbations; however, it reduces hospital admissions in some patients, including adults with FEV_1 < 25%–30% predicted at presentation; adults and children who fail to respond to initial treatment and have persistent hypoxemia; and children whose FEV_1 fails to reach 60% predicted after 1 hour of care. The role of magnesium sulfate is not established for children ages 5 years and younger but may be considered as an adjuvant to standard treatment in children 2 years or age and older with severe asthma.

bpm, beats per minute; ED, emergency department; FEV_1, forced expiratory volume in first second; ICU, intensive care unit; MDI, metered-dose inhaler; O_2, oxygen; PEF, peak expiratory flow; SABA, short-acting β_2-agonist.

Data obtained from Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. Available from: www.ginasthma.org.

Asthma control is assessed by evaluating symptoms of worsening asthma and/or monitoring PEF. Early signs of deterioration include increasing nocturnal symptoms, increasing use of reliever medication, or symptoms that do not respond to increased use of reliever medication. Providing patients with a prescription for oral corticosteroids to use on an as-needed basis at the onset of an asthma exacerbation is part of asthma self-management.

Measurement of PEF is considered for patients with moderate-to-severe persistent asthma, poor perception of worsening asthma or airflow obstruction, and those with an unexplained response to environmental or occupational exposures.[4] PEF measurements are not necessary for a patient to receive an asthma action plan; the plan can be based on symptoms only. PEF is measured daily in the morning upon waking or when asthma symptoms worsen. For PEF-based action plans, the patient's personal best PEF is established over a 2- to 3-week period when the patient is receiving optimal treatment.[4] Subsequent PEF measurements are evaluated in relation to their variability from the patient's best PEF measurement. PEF measurements in the range of 80% to 100% of personal best (green zone) indicate that current therapy is acceptable. A PEF in the range of 50% to 79% of personal best (yellow zone) indicates an impending exacerbation, and therapy is intensified with reliever therapy, possibly oral corticosteroids, and a call to the physician. A PEF less than 50% (red zone) signals a medical alert; patients use their reliever medications immediately, take oral corticosteroids, and go to the emergency department. PEF measurements alone should not be used to determine the severity of airflow limitation. Measurements can be falsely elevated or decreased with poor technique, such as coughing into the meter or insufficient patient effort. Smaller airways may become inflamed

Patient Encounter Part 3

CC: "One minute I felt fine and then I just couldn't breathe."

HPI: Patient presented to ED with complaints of worsening shortness of breath not relieved by use of albuterol 4 inhalations every 20 minutes. Symptoms began this morning while she was visiting with her mother and worsened despite use of albuterol MDI. It became difficult for her to speak in full sentences, so her husband brought her to the emergency department. She was treated with albuterol–ipratropium inhalation solution and started on oral prednisone 40 mg daily. Supplemental oxygen was given because O$_2$ saturation was 92% (0.92) upon arrival. O$_2$ saturation now improved to 98% (0.98) on room air. Patient is feeling better and is able to speak in full sentences. Patient states that her asthma symptoms have been worse lately because she has been spending a lot of time outside gardening. She's been using her albuterol inhaler 3 to 4 days a week after being outdoors for extended periods.

ROS:

General: no fever/chills, night sweats; + obesity

ENT: + allergic rhinitis, + nasal congestion, + postnasal drip, occasional mouth breathing

Respiratory: + shortness of breath, no cough

The reminder of the ROS is noncontributory.

PE:

VS: Temp 36.3°C, BP 138/84 mm Hg, Pulse 90 bpm, RR 20 breaths/min, Sao$_2$ 98% (0.98), Ht 162 cm, Wt 85 kg, BMI 32.4 kg/m^2

Gen: NAD

Eyes: PERRL, EOMI

HEENT: OP clear, septal spur with deviation to the left noted, TMs clear

Lungs: + slight wheezing at both bases

CV: RRR no m/r/g

Abd: Soft, NT/ND

Skin: No rash/hives, + hyperpigmented cheeks

Neuro/Psych: Grossly normal, normal affect

Asthma Control Test: 15 out of 25 (goal above 20); 3 months prior to today's visit ACT: 23

PEFR: 350 L/min best. 210 L/min in ED today

FeNO: 50 ppb at last visit

Review of RAST testing: Pollen, ragweed, trees, grass, roaches, mold, dogs, and cats

Spirometry from 1 month ago:

	Measured	% Predicted
FVC (L)	3.87	112.73
FEV$_1$ (L)	3.10	75.09
FEV$_1$/FVC (%)	80	–
TLC (L)	5.93	92.47
DLCO (mL/min/mm Hg)	29.31	143.09

Summary: Normal FEV$_1$/FVC. FVC is normal and FEV$_1$ is decreased. There is a response to inhaled bronchodilator (not shown in the table). The TLC and diffusing capacity are normal.

Labs:

Na 141 mEq/L (mmol/L)
K 3.6 mEq/L (mmol/L)
Cl 104 mEq/L (mmol/L)
CO$_2$ 30 mEq/L (mmol/L)
Anion gap 7
Ca 9.3 mg/dL (2.33 mmol/L)
Scr 0.92 mg/dL (81 μmol/L)
eGFR 106 mL/min/1.73 m^2

WBC 9.6 × 103 cells/μL (9.6 × 10^9/L)
Absolute eosinophil count 400 cells/μL (0.4 × 10^9/L)
Hgb 15.4 g/dL (154 g/L; 9.56 mmol/L)
Hct 43.9% (0.439)
Plt 216 × 103 cells/μL (216 ×10^9/L)
IgE 90 IU/mL (kIU/L)
Aspergillus antibody: none detected

What therapeutic regimens are available for this patient?

Provide this patient with an asthma action plan.

Recommend monitoring and follow-up for this patient.

during severe exacerbations, and the PEF is unable to detect this, possibly causing a patient to be discharged from the hospital with an unresolved exacerbation. Use the PEF meter as a tool along with assessing the patient's symptoms for best care. It is important to advise patients who use peak flow meters as a monitoring tool to treat asthma symptoms in accordance with their asthma action plan even if the PEF does not indicate airflow impairment.

OUTCOME EVALUATION

Chronic Asthma

- Assess onset, duration, and timing of subjective symptoms such as wheezing, shortness of breath, chest tightness, cough, nocturnal awakenings, and activity level. Use validated questionnaires (such as the Asthma Control Test, Asthma Therapy Assessment Questionnaire, or Asthma Control Questionnaire) to objectively document control.
- Monitor use of reliever medications to help determine asthma control and if a step-up in therapy is warranted.
- Determine the frequency of patient exacerbations. Frequent exacerbations, unscheduled clinic visits, emergency department visits, and hospitalizations due to asthma may indicate the need to reassess the patient's asthma regimen and environment.
- Measure lung function using office spirometry yearly in patients older than 5 years.
- Identify environmental factors triggering asthma exacerbations and provide trigger avoidance recommendations.
- Perform medication reconciliation to identify discrepancies in medications prescribed and used by the patient and to determine drug and disease state interactions.
- Assess adherence to medications and inhaler technique at every visit and always ensure adherence and proper technique before stepping up therapy.

Patient Care Process: Chronic Asthma

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. Identify allergies to medications and other substances.
- Review previous full pulmonary function tests, RAST, CBC, IgE levels, and chemistry panel.
- Assess patient's peak flow measurement (if applicable).
- Collect current asthma control using validated questionnaire (eg, ACT or c-ACT) results.
- Document current height, weight, blood pressure, heart rate, and pulse oximetry.
- Auscultate the lungs for wheezing. Look in the mouth for signs of oral candidiasis if on ICS.
- Identify asthma exacerbations since the last visit, including emergency room visits or hospitalizations, or use of oral corticosteroid bursts.
- Ask about tobacco use and exposure to secondhand smoke (tobacco or marijuana).
- Ask the patient to demonstrate inhaler use. Ask when the inhaler is used, how many times in the past week the inhaler was used, and when the inhaler was last refilled.
- Identify the number of missed days of school or work because of asthma.
- Ask about patient (or caregiver) goals and satisfaction with asthma control.
- Collect diet and exercise information and use of SABA or reliever before exercise.
- Identify comorbid conditions that may affect asthma control including gastroesophageal reflux disease (GERD), allergic rhinitis, sleep apnea, anxiety, and depression.

Assess the Information:

- Evaluate medication side effects (rapid heart rate, jitteriness, bad taste, cough, dysphonia, lack of efficacy).
- Verify medication adherence. Examine the patient's inhaler for the number of doses remaining. Call the dispensing pharmacy to determine fill history of inhalers.
- Determine whether the patient is taking any medications (including prescription, OTC, or supplements) that may cause cough or worsen asthma control.
- Determine if patient's asthma medications are appropriate based on spirometry results, exacerbation history, and current asthma control.
- Identify changes in home, work, or school environment that may contribute to worsening asthma symptoms.
- Assess for worsening in comorbid conditions that may contribute to worsening asthma symptoms.
- Identify factors that may be affecting medication adherence including side effects, cost issues, formulary issues, and unclear understanding of purpose of inhalers.
- Assess inhaler technique. Identify any barriers that inhibit the patient from using their inhaler correctly.
- Determine if the patient needs the influenza, COVID-19 and pneumococcal vaccines.
- Assess the patient's readiness to stop using tobacco or marijuana.

Develop a Care Plan:

- Document the patient's specific goals for asthma control.
- If the patient is not controlled, before adding medications or increasing dosing, make sure the patient is using the current inhalers correctly and is willing to use the inhalers.
- If asthma is not controlled and patient is adherent to their asthma medications and using them correctly, consider a step up in therapy.
- Identify patient preference, ability to pay, and insurance coverage for MDI, DPI, SMI, BAI, or nebulization.
- If the patient is controlled and has been on the current regimen for 3 months or longer, consider discontinuing or lowering the dose of controller medications.

Implement the Care Plan:

- Educate the patient about changes in drug therapy, medication administration, potential new adverse effects, and how to manage and report adverse effects that may occur.
- Review patient's technique with inhalers. Use physical demonstration with placebo inhalers, standardized checklists, pictures, and videos of inhalers (http://use-inhalers.com/).
- Provide an updated medication list with indication and use of each inhaler device.
- Provide an updated asthma action plan with medication changes.
- Review environmental asthma triggers and avoidance plans.
- Administer and update vaccinations.
- Discuss diet and exercise (using SABA or ICS–formoterol prior to exercise if needed).
- Refill all asthma-related medications, including medications to treat allergic rhinitis and GERD.

Follow-up: Monitor and Evaluate:

- Schedule follow-up physician visits depending on asthma control (3–6 months).
- Check spirometry yearly.
- Review adherence and inhaler technique at every visit.
- Update asthma action plan yearly or with each medication change.
- Monitor ACT quarterly.
- Monitor medication refill history.
- Evaluate asthma-related hospitalizations, emergency department visits, and oral corticosteroid use.

- Assess the patient's understanding of the indication for long-term controller medication and identify adverse events, cost issues, and need for refills.
- Review and update the asthma action plan and provide the patient with a written copy of the plan.
- Update the patient's immunization status and provide an annual influenza vaccination.

Acute Asthma

In addition to the outcomes measured for chronic asthma, acute asthma monitoring also includes the following:

- Assess asthma symptoms and measure the PEF. The goal is improved asthma symptoms and a PEF measurement greater than 70% of the patient's personal best peak flow after the first three doses of an inhaled SABA or reliever. Spirometry is not usually conducted in the emergency department.
- Check respiratory rate and measure oxygenation using pulse oximetry and provide oxygen via nasal cannula if needed. The goal oxygen saturation is 93% to 95% (0.90–0.95) in adults and 94% to 98% (0.94–0.98) in children, pregnant women, and patients with coexisting cardiovascular disease.
- Obtain a pCO_2 measurement via arterial blood gases in patients with severe asthma exacerbations. An increased pCO_2 indicates the potential for respiratory failure.
- Monitor serum potassium for hypokalemia upon admission and periodically throughout the admission in patients receiving high-dose or continuous nebulization of SABA.

Abbreviations Introduced in This Chapter

AERD	Aspirin-exacerbated respiratory disease
BAI	Breath actuated inhaler
DPI	Dry powder inhaler
EIB	Exercised induced bronchospasms
FeNO	Fraction of exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GLCCI1	Glucocorticoid-induced transcript 1 gene
HFA	Hydrofluoroalkane
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
IL-5	Interleukin 5
LABA	Long-acting β_2-agonist
LTRA	Leukotriene receptor antagonist
LAMA	Long-acting muscarinic antagonist
MDI	Metered-dose inhaler
NHLBI	National Heart, Lung, and Blood Institute
pCO_2	Partial pressure of carbon dioxide
PEF	Peak expiratory flow
SABA	Short-acting β_2-agonist
SAMA	Short-acting muscarinic antagonist
SMI	Slow mist inhaler
Th_2	Type 2 T-helper $CD4^+$ cell

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16

Chronic Obstructive Pulmonary Disease

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the pathophysiology of chronic obstructive pulmonary disease (COPD).
2. Assess a patient for signs and symptoms of COPD.
3. List the treatment goals for a patient with COPD.
4. Design an appropriate COPD maintenance treatment regimen based on patient-specific data.
5. Design an appropriate COPD exacerbation treatment regimen based on patient-specific data.
6. Develop a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for COPD.
7. Formulate an appropriate education plan for a patient with COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by airflow limitation that is not fully reversible. Previous definitions of COPD included chronic bronchitis and emphysema. Chronic bronchitis is defined clinically as a chronic productive cough for at least 3 months in each of 2 consecutive years in a patient in whom other causes have been excluded.[1] Emphysema is defined pathologically as destruction of alveoli.[1] The major risk factor for both conditions is cigarette smoking, and many patients share characteristics of each one. Therefore, current guidelines focus instead on chronic airflow limitation.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) is an expert panel of health professionals who developed consensus guidelines for the diagnosis and care of patients with COPD that are updated annually.[1]

EPIDEMIOLOGY AND ETIOLOGY

COPD is a major cause of morbidity and mortality and a significant cause of disability worldwide. In 2017, the estimated prevalence of COPD in the United States was 6.4%.[2] Over 169,000 adults died from COPD, making it the fourth leading cause of death.[2,3] Personal health care spending in the United States on COPD was estimated to be $53.8 billion in 2013.[4] In addition, patients with COPD have a higher prevalence of coronary artery disease and hypertension.[5] Other common comorbidities that can impact disease course and prognosis include lung cancer, heart failure, gastroesophageal reflux disease (GERD), obstructive sleep apnea, osteoporosis, and depression/anxiety.[1,5]

COPD is caused by repeated inhalation of noxious particles or gases, most commonly cigarette smoke. Marijuana and other forms of tobacco, including secondhand smoke, are also risk factors.[1] Not all smokers develop clinically significant COPD, which suggests that genetic susceptibility plays a role. The best documented genetic factor is a rare hereditary deficiency of α_1-antitrypsin (AAT). Severe deficiency of this enzyme results in premature and accelerated development of emphysema. Factors that potentially reduce maximal attained lung function (eg, maternal smoking, preterm birth, early childhood lung infections, air pollution, childhood asthma, and active smoking during adolescence) increase the risk of COPD.[1,6] Other COPD risk factors include occupational exposure to dusts and chemicals (vapors, irritants, and fumes), biomass smoke inhalation, asthma, and bronchial hyperresponsiveness. Outdoor air pollution has been implicated as a cause, but its exact role is unclear.

PATHOPHYSIOLOGY

Repeated exposure to noxious particles and gases causes chronic inflammation, resulting in pathologic changes in the central and peripheral airways, lung **parenchyma**, and pulmonary vasculature that lead to obstruction.[1,7,8] An imbalance between **proteases** and **antiproteases** in the lungs and oxidative stress are also important in the pathogenesis of COPD (**Figure 16–1**).

Inflammation is present in the lungs of all smokers, yet not all smokers develop COPD. In patients with COPD, the inflammatory response is amplified, likely due to a genetic predisposition, although the exact mechanisms are unknown. KEY CONCEPT The inflammation of COPD differs from that seen in asthma, so the use of and response to anti-inflammatory medications is different. The inflammation of asthma is mainly mediated through eosinophils and mast cells. In COPD, the primary inflammatory cells are neutrophils, macrophages, and $CD8^+$ T lymphocytes.[7] A subset of patients with COPD also have increased eosinophils, which appears to predict a more favorable response to bronchodilators and corticosteroids and may indicate coexisting asthma.[7] Activated inflammatory cells release mediators (eg, interleukin-1, interleukin-8 [CXCL8], tumor necrosis factor-α) and secrete proteases (eg, elastase, proteinase-3, matrix metalloproteinase-9) which sustain and amplify inflammation and damage lung structures.[1,7]

Proteases and antiproteases are part of the normal protective and repair mechanisms in the lungs. An imbalance of

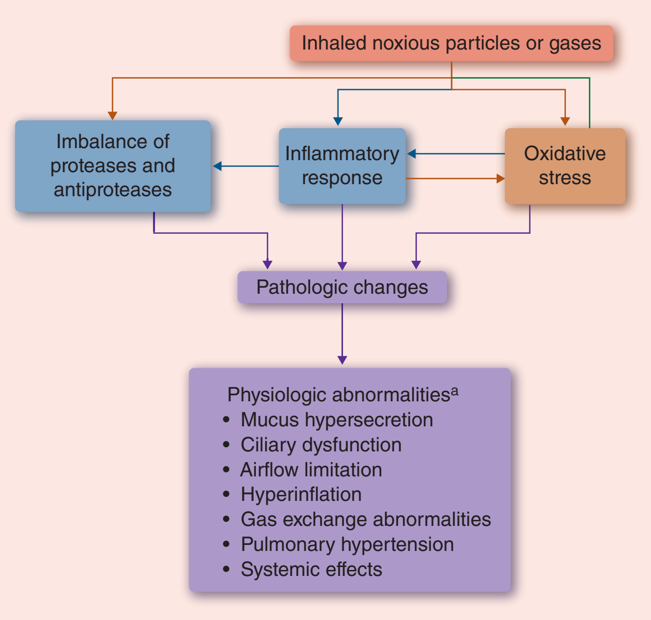

FIGURE 16–1. Pathophysiology of COPD. [a]The physiologic abnormalities usually develop in this order.

protease-antiprotease activity in COPD results from either increased production or activity of destructive proteases or inactivation or reduced production of protective antiproteases. AAT (an antiprotease) inhibits trypsin, elastase, and several other proteolytic enzymes. Deficiency of AAT results in unopposed protease activity, which promotes destruction of alveolar walls and lung parenchyma, leading to emphysema.

Oxidative stress occurs from smoke exposure and an increase in activated neutrophils and macrophages. Oxidative stress promotes inflammation and contributes to the protease-antiprotease imbalance by reducing antiprotease activity. In addition, oxidants constrict airway smooth muscle, contributing to reversible airway narrowing.

In the central airways (the trachea, bronchi, and larger bronchioles), inflammatory cells and mediators stimulate mucus gland hyperplasia and mucus hypersecretion. Mucus hypersecretion and ciliary dysfunction lead to chronic cough and sputum production. The major site of airflow obstruction is the peripheral airways (small bronchi and bronchioles). Narrowing of small airways results from fibrosis, increased mucus, and accumulation of inflammatory debris.[1,7,8] The reduced airway diameter causes increased resistance to airflow. Parenchymal destruction leads to loss of elasticity and structural support resulting in closure of small airways during expiration, further obstructing airflow.

As airflow obstruction worsens, the rate of lung emptying slows and the interval between inspirations does not allow expiration to the relaxation volume of the lungs. This leads to pulmonary hyperinflation, which initially only occurs during exercise but later is also seen at rest. Hyperinflation contributes to the discomfort associated with airflow obstruction by flattening the diaphragm and placing it at a mechanical disadvantage.

In advanced COPD, airflow obstruction, damaged bronchioles and alveoli, and pulmonary vascular abnormalities lead to impaired gas exchange, resulting in hypoxemia and eventually hypercapnia. Hypoxemia is initially present only during exercise but occurs at rest as the disease progresses. Inequality in the ventilation/perfusion ratio (V_A/Q) is the major mechanism underlying hypoxemia. As hypoxemia worsens, the body may increase erythrocyte production in an attempt to increase oxygen delivery to tissues.

Pulmonary hypertension develops late in the course of COPD, usually after development of severe hypoxemia. It is the most common cardiovascular complication of COPD and can result in cor pulmonale, or right-sided heart failure. Progressive loss of skeletal muscle mass in longstanding COPD contributes to exercise limitation and declining health status.

CLINICAL PRESENTATION AND DIAGNOSIS

See accompanying box for the clinical presentation of COPD.

Diagnosis

A suspected diagnosis of COPD should be based on patient symptoms and history of exposure to risk factors. Spirometry is required to confirm the diagnosis, using the ratio of forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC). A postbronchodilator FEV_1/FVC ratio less than 70% (0.70) confirms airflow limitation that is not fully reversible.[1] Spirometry results can further be used to classify severity of airflow limitation in these patients. The GOLD classification categories of severity based on postbronchodilator FEV_1 are as follows: GOLD 1, mild = 80% predicted or greater; GOLD 2, moderate = 50% to

Clinical Presentation of COPD

General

- Patients are initially asymptomatic. COPD is usually not diagnosed until declining lung function leads to significant symptoms and prompts patients to seek medical care.

Symptoms

- Symptom onset is variable and does not correlate well with severity of airflow limitation measured by FEV_1.[1]
- Initial symptoms include chronic cough (for > 3 months) that may be intermittent at first, chronic sputum production, and dyspnea on exertion. Patients may complain of a sensation of chest heaviness or increased effort to breathe.
- As COPD progresses, dyspnea at rest and/or orthopnea develop, and ability to perform activities of daily living declines.

Signs

- Inspection may reveal use of accessory muscles of respiration (paradoxical movements of the chest and abdomen in a seesaw-type motion), pursed-lips breathing, and hyperinflation of the chest with increased anterior–posterior diameter ("barrel chest").
- On lung auscultation, patients may have distant breath sounds, wheezing, a prolonged expiratory phase, and rhonchi.
- In advanced COPD, signs of hypoxemia may include cyanosis and tachycardia.
- Signs of cor pulmonale include increased pulmonic component of the second heart sound, jugular venous distention (JVD), lower extremity edema, and hepatomegaly.

79% predicted; GOLD 3, severe = 30% to 49% predicted; GOLD 4, very severe = less than 30% predicted.[1] Full pulmonary function tests (PFTs) with lung volumes and diffusion capacity and arterial blood gases (ABGs) are not necessary to establish the diagnosis or severity of COPD.

Pulse oximetry should be obtained in patients with signs or symptoms suggestive of cor pulmonale or respiratory failure.[1] If oxygen saturation is less than 92% (0.92), ABGs should be assessed.[1] Patients may exhibit increased arterial carbon dioxide tension ($Paco_2$) and decreased arterial oxygen tension (Pao_2).

A complete blood count (CBC) may reveal an elevated hematocrit that may exceed 55% (0.55; polycythemia). An AAT level is recommended in all COPD patients, especially in areas with a high prevalence of AAT deficiency.[1] Chest radiography may show lung hyperinflation and signs of emphysema.

It is important to distinguish COPD from asthma because treatment and prognosis differ. Differentiating factors include age of onset, symptom variability, smoking history, triggers, occupational history, and coexisting conditions (eg, presence of allergic rhinitis and/or eczema favors asthma). In some patients, a clear distinction between asthma and COPD is not possible. Management of these patients should be like that of asthma.

TREATMENT

Desired Outcomes

The goals of COPD management include (a) smoking cessation if applicable, (b) reducing symptoms, and (c) preventing and treating exacerbations.[1]

General Approach to Treatment

KEY CONCEPT An integrated approach of health maintenance (eg, smoking cessation), vaccinations, pharmacotherapy, and supplemental therapy (eg, oxygen and pulmonary rehabilitation) should be used via an individualized approach. Symptom severity, risk of COPD exacerbations, adverse effects, comorbidities, and the patient's response and/or desires should be used to guide therapy decisions.[1]

Either the modified Medical Research Council (mMRC) Questionnaire or COPD Assessment Test (CAT) is recommended for symptom assessment. The CAT is preferred because it provides a more comprehensive assessment.[1] An mMRC grade of 0 or 1 or a CAT score less than 10 indicates fewer symptoms. Patients with more symptoms will have an mMRC grade of 2 or more or a CAT score of 10 or more. These patients require inhaled long-acting bronchodilators on a scheduled basis.[1]

Risk of future COPD exacerbation is assessed using number of exacerbations per year. Patients with a history of two or more exacerbations per year or one or more exacerbation(s) requiring hospitalization are at high risk for future exacerbations. Patients at high risk of COPD exacerbations also require inhaled long-acting bronchodilators on a scheduled basis to reduce the frequency of exacerbations.[1] Figure 16–2 provides an overview of the management of COPD.

Patient Encounter, Part 1

A 62-year-old woman with a medical history of asthma, type 2 diabetes mellitus, heart failure with reduced ejection fraction (HFrEF), and previous tobacco abuse (35 pack-year history) presents to the clinic complaining of shortness of breath with moderate physical activity, a "heavy" chest, chronic cough, and chronic sputum production for more than 3 years; however, her symptoms have worsened considerably over the last 3 months.

What symptoms and/or risk factors does she have that are suggestive of COPD?

What additional information do you need before creating a treatment plan for this patient?

Nonpharmacologic Therapy

▶ Smoking Cessation

KEY CONCEPT Smoking cessation slows the rate of decline in pulmonary function in patients with COPD.[9,10] Cessation can also reduce cough and sputum production and decrease exacerbations and all-cause mortality.[9,11] Therefore, it is a critical part of any treatment plan and should be encouraged at every visit. The "5 As" can be used as a framework to help guide interventions (Table 16–1). Even brief (< 3 minutes) counseling urging smokers to quit improves smoking cessation rates.[1,11]

Tobacco users who are ready to quit should be treated with a combination of behavioral counseling and pharmacotherapy. Varenicline or dual nicotine replacement therapy (NRT) (eg, nicotine patch plus as needed nicotine gum, lozenge, inhaler, or nasal spray) are the most effective options.[11] Bupropion and other combinations (eg, varenicline plus bupropion or NRT, bupropion plus NRT) are also effective strategies. Refer to the section "Tobacco Cessation" in Chapter 37.

▶ Pulmonary Rehabilitation

Pulmonary rehabilitation results in significant and clinically meaningful improvements in dyspnea, exercise tolerance, health status, health care utilization, and symptoms of anxiety or depression.[1,12] Initiating pulmonary rehabilitation within 2 weeks of hospitalization for an acute exacerbation can reduce readmissions and mortality.[1] Benefits have been observed in all grades of COPD severity but appear greatest in moderate-to-severe COPD.[1,12] An individualized pulmonary rehabilitation program should include at least twice weekly maximally tolerated load or interval and strength training, education, and self-management interventions aimed at behavior change.[1,12]

Rehabilitation programs may be conducted in multiple settings. The most effective length of a program is 6 to 8 weeks; extending the program to more than 12 weeks does not confer additional benefits.[1] It is important for patients to continue with a home exercise program to maintain the benefits gained from the pulmonary rehabilitation program.[1]

▶ Long-Term Oxygen Therapy

Long-term oxygen administration (> 15 hrs/day) in patients with chronic hypoxic respiratory failure has been shown to reduce mortality.[1] Oxygen therapy should be initiated in stable patients with COPD who have Pao_2 at or below 55 mm Hg (7.3 kPa) or oxygen saturation (Sao_2) at or below 88% (0.88), or with evidence of pulmonary hypertension, peripheral edema suggesting heart failure, or polycythemia. Patients should be reassessed with repeat ABG or oxygen saturation after 60 to 90 days.[1]

The goal is to increase baseline oxygen saturation to at least 90% (0.90) and/or Pao_2 to at least 60 mm Hg (8.0 kPa), allowing adequate oxygenation of vital organs. Hypoxemia worsens during

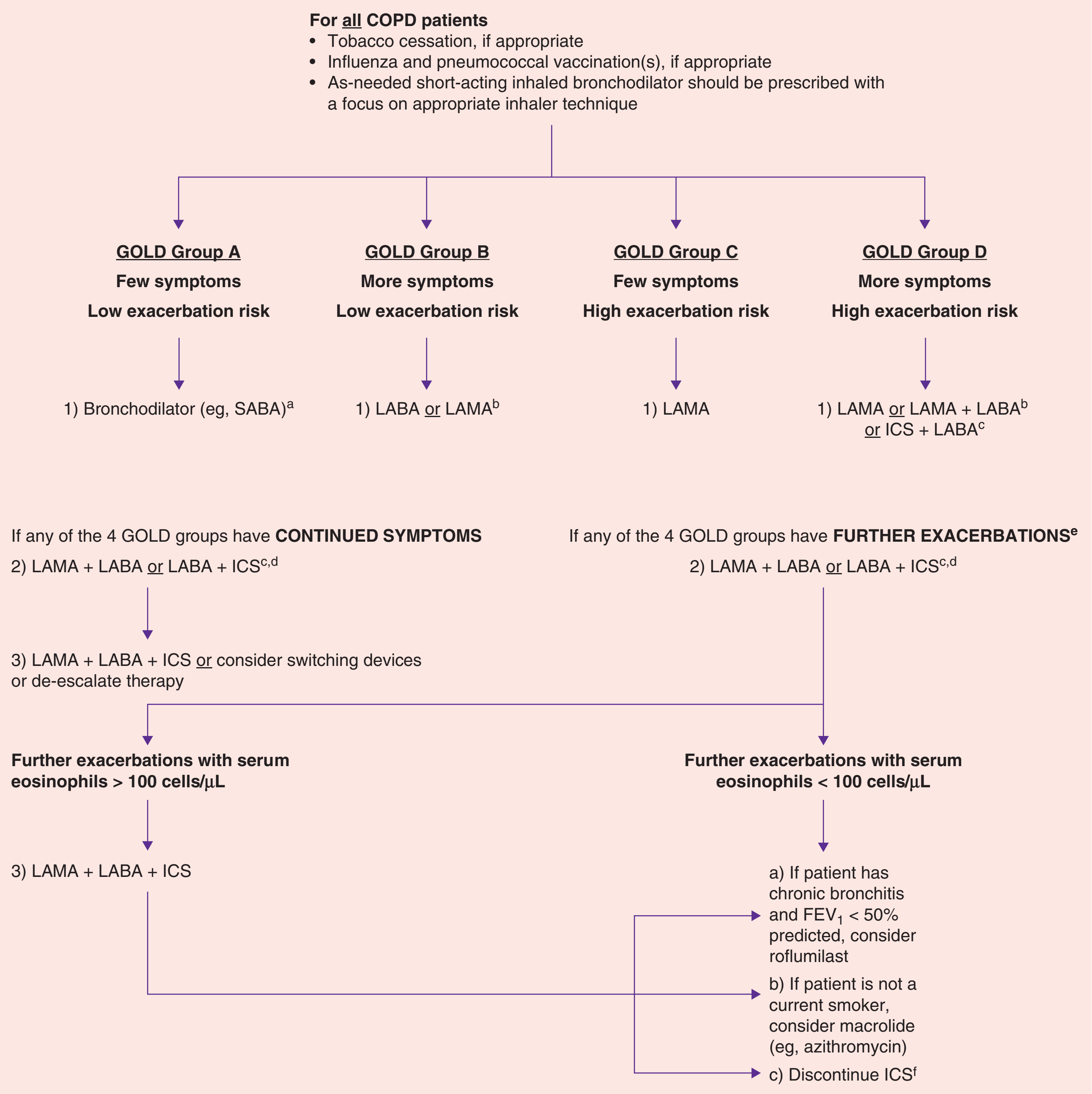
For all COPD patients
• Tobacco cessation, if appropriate
• Influenza and pneumococcal vaccination(s), if appropriate
• As-needed short-acting inhaled bronchodilator should be prescribed with a focus on appropriate inhaler technique
GOLD Group A
Few symptoms
Low exacerbation risk
GOLD Group B
More symptoms
Low exacerbation risk
GOLD Group C
Few symptoms
High exacerbation risk
GOLD Group D
More symptoms
High exacerbation risk
1) Bronchodilator (eg, SABA)[a]
1) LABA or LAMA[b]
1) LAMA
1) LAMA or LAMA + LABA[b] or ICS + LABA[c]
If any of the 4 GOLD groups have CONTINUED SYMPTOMS
2) LAMA + LABA or LABA + ICS[c,d]
3) LAMA + LABA + ICS or consider switching devices or de-escalate therapy
If any of the 4 GOLD groups have FURTHER EXACERBATIONS[e]
2) LAMA + LABA or LABA + ICS[c,d]
Further exacerbations with serum eosinophils > 100 cells/μL
Further exacerbations with serum eosinophils < 100 cells/μL
3) LAMA + LABA + ICS
a) If patient has chronic bronchitis and FEV_1 < 50% predicted, consider roflumilast
b) If patient is not a current smoker, consider macrolide (eg, azithromycin)
c) Discontinue ICS[f]

FIGURE 16–2. Pharmacotherapy Treatment Algorithm for COPD[1]. ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β-agonist. [a]If patient was not placed on a long-acting bronchodilator initially, should be started on either a LABA or LAMA if symptoms continue. [b]GOLD guidelines suggest considering combination LABA/LAMA therapy in highly symptomatic patients. [c]ICS/LABA may be more effective with serum eosinophils > 300 cells/microliter or in patients with concomitant asthma. However, ICS therapy increases the risk of pneumonia. [d]If patient is on ICS/LABA and has continued symptoms or exacerbations, could switch to LABA/LAMA, particularly in those with low serum eosinophil count. [e]If patients are suffering from both continued symptoms and exacerbations, use further exacerbations treatment pathway recommendations. [f]If an ICS is being used at any point and there is a lack of response or development of pneumonia, consider discontinuation of ICS, particularly in those with low serum eosinophil count.

air travel; patients requiring oxygen should generally increase their flow rate by 3 L/min during flight.[1] For patients with chronic hypercapnia and a recent hospitalization for respiratory failure, utilizing noninvasive ventilation (NIV) may improve respiratory acidosis, time to readmission, exacerbation rates, quality of life, and overall mortality.[1,13]

▶ *Surgery*

Bullectomy, lung volume reduction, and lung transplantation are surgical options for very severe COPD refractory to appropriate pharmacologic therapy. These procedures may result in improved lung function, health status, and exercise capacity and

Table 16–1

The 5 As for Brief Intervention for Tobacco Users

Ask: Identify and document tobacco-use status for every patient at every visit
Advise: Strongly urge every tobacco user to quit
Assess: Is the tobacco user willing to make a quit attempt at this time?
Assist: Use counseling and pharmacotherapy to help patients willing to make a quit attempt
Arrange: Schedule follow-up contact, preferably within the first week after the quit date

reduced exacerbations. Patient selection for each of these is critical because not all patients benefit.[1]

▶ *Other Nonpharmacologic Options*

Other treatment considerations include palliative measures in those with end-stage COPD (eg, oxygen in nonhypoxemic patients, fans blowing onto the face, hospice care). Nutritional support, particularly in patients with a low body mass index (BMI), can improve overall health status and respiratory muscle strength. Cognitive behavioral therapy and mind–body interventions can help manage anxiety and depression and may improve lung function and symptoms.[1]

Pharmacologic Therapy of Stable COPD

KEY CONCEPT Medications available for COPD are effective for reducing or relieving symptoms, improving exercise tolerance, reducing the number and severity of exacerbations, and improving health status but have not irrefutably slowed the rate of lung function decline or improved mortality. An individualized evaluation of symptoms, comorbidities, patient preferences, and a patient's future risk for exacerbations should be the guiding principles to determine appropriate pharmacologic management of COPD. Importantly, lung function may continue to worsen even with appropriate therapy.[1]

▶ *Bronchodilators*

KEY CONCEPT Bronchodilators are the mainstay of treatment for symptomatic COPD. They can increase FEV_1, reduce symptoms, reduce frequency and severity of exacerbations and hospitalization rates, and improve exercise tolerance, pulmonary rehabilitation efficacy, and health status.[1,14] They can be used as needed for symptoms or on a scheduled basis to prevent or reduce symptoms. The inhaled route is preferred, but attention must be paid to proper inhaler technique, both on initiation and at each follow-up visit because long-term appropriate adherence rates may be seen in only 23% of patients.[1] Long-acting bronchodilators are more expensive than short-acting bronchodilators but are preferred due to improved clinical outcomes. Toxicity to bronchodilators is dose related, and there is a relatively flat dose–response curve to these agents.[1]

β_2-Agonists These agents cause airway smooth muscle relaxation by stimulating adenyl cyclase to increase formation of cyclic adenosine monophosphate (cAMP). β_2-Agonists are available in inhalation, oral, and parenteral dosage forms; the inhalation route is preferred because of fewer adverse effects.

These drugs are available in short-acting and long-acting formulations (Table 16–2). The short-acting β_2-agonists (SABAs) used in COPD include albuterol (known as salbutamol outside the United States) and levalbuterol (known as R-salbutamol outside the United States). They are used as "rescue" therapy for acute symptom relief or in those with only occasional symptoms.

Long-acting β_2-agonists (LABAs) include salmeterol, formoterol, arformoterol, indacaterol, olodaterol, and vilanterol. Arformoterol and formoterol are both available for nebulization, providing an alternative for patients with poor inhaler technique. Indacaterol, olodaterol, and vilanterol (only available in combination) are long acting, allowing for once-daily dosing. While some studies suggest potential spirometric benefits of one LABA over another (usually indacaterol), definitive data on actual patient outcome differences among agents is lacking.[15] Insurance coverage, patient response, patient preference for type of inhaler device, and prescriber preference are considerations when selecting a LABA. Patients treated with LABAs should also have a SABA such as albuterol for as-needed use ("rescue" medication) but should be advised to avoid excessive use.

Adverse effects of both LABAs and SABAs are dose related and include palpitations, tachycardia, cough, hypokalemia, sleep disturbance, and tremor.

Antimuscarinics Ipratropium, tiotropium, aclidinium, glycopyrrolate (also known as glycopyrronium bromide), revefenacin, and umeclidinium are all available for inhalation treatment of COPD. They produce bronchodilation by competitively blocking muscarinic receptors in bronchial smooth muscle and may also decrease mucus secretion. Tiotropium, revefenacin, and umeclidinium have once-daily dosing while aclidinium and glycopyrrolate, which have shorter half-lives, require twice-daily dosing; each is considered a long-acting muscarinic antagonist (LAMA). While certain studies suggest potential spirometric benefits of one LAMA over another, definitive data on actual patient outcome differences among agents are still lacking.[16] Choice of LAMA should be based on insurance coverage, patient response and preferences, and prescriber preferences.

KEY CONCEPT LAMAs may be more effective than LABAs for reducing exacerbations and decreasing hospitalizations and have fewer adverse effects in patients with moderate-to-very-severe COPD.[1,17] Patients using LAMA maintenance therapy should be prescribed a SABA rather than ipratropium as their rescue therapy to minimize the potential for excessive anticholinergic effects.

Inhaled antimuscarinics are well tolerated with the most common adverse effects being dry mouth, headache, and nasopharyngitis. Occasional metallic taste has also been reported, most commonly with ipratropium. Other anticholinergic adverse effects include constipation, tachycardia, blurred vision, urinary retention, and precipitation of narrow-angle glaucoma symptoms. Increased cardiovascular events in COPD patients who regularly use ipratropium has also been reported.[1,17]

Methylxanthine Theophylline is an oral methylxanthine derivative and nonselective phosphodiesterase inhibitor that increases intracellular cAMP within airway smooth muscle resulting in bronchodilation and may also improve inspiratory function. Its use is limited due to a narrow therapeutic index, multiple drug interactions, questionable efficacy, and adverse effects.[1,18] Theophylline should be reserved for patients who cannot use inhaled medications or who remain symptomatic despite appropriate use of inhaled bronchodilators.[1]

Therapeutic drug monitoring is needed to optimize therapy because of wide interpatient variability. Multiple factors can alter theophylline clearance including concomitant medications (through CYP450 interactions), age, tobacco smoke, and marijuana. Chemicals in tobacco smoke induce theophylline metabolism and increase its clearance. The most common adverse effects of theophylline include headache, heartburn, insomnia, tachycardia, palpitations, and tremor. Dose-related adverse effects include nausea and vomiting, seizures, and arrhythmias.

Table 16–2

Maintenance Medications for COPD

	Medication	Onset	Duration	Usual Dose
Short-Acting β_2-Agonists	**Albuterol**[a]			
	Nebulization	≤ 5 minutes	3–6 hours	2.5 mg every 4–6 hours as needed
	Inhalation	5–8 minutes	2–6 hours	MDI or DPI (90 mcg/puff) two puffs every 4–6 hours as needed
	Levalbuterol[a]			
	Nebulization	10–17 minutes	5–8 hours	0.63–1.25 mg three times/day, 6–8 hours apart as needed
	Inhalation	5–10 minutes	3–6 hours	MDI (45 mcg/puff) two puffs every 4–6 hours as needed
Long-Acting β_2-Agonists	**Formoterol**			
	Inhalation	≤ 3 minutes	12 hours	DPI (12 mcg/inhalation) 12 mcg every 12 hours[b]
	Nebulization	≤ 3 minutes	12 hours	20 mcg every 12 hours
	Salmeterol			
	Inhalation	2 hours	12 hours	DPI (50 mcg/inhalation) one inhalation every 12 hours
	Indacaterol			
	Inhalation	5 minutes	24 hours	DPI (75 mcg/inhalation) one inhalation every 24 hours
	Olodaterol			
	Inhalation	5 minutes	24 hours	MDI (2.5 mcg/inhalation) two inhalations every 24 hours
	Vilanterol			
	Inhalation	15–30 minutes	24 hours	Only in combination inhalers
	Arformoterol			
	Nebulization	7–20 minutes	12 hours	15 mcg every 12 hours
Short-Acting Muscarinic Antagonists	**Ipratropium**			
	Nebulization	≤ 15 minutes	4–8 hours	0.5 mg every 6–8 hours as needed
	Inhalation	≤ 15 minutes	2–4 hours	MDI (17 mcg/puff) two puffs four times/day as needed
Long-Acting Muscarinic Antagonists	**Tiotropium**			
	Inhalation	30–60 minutes	24 hours	DPI (18 mcg/inhalation) one inhalation every 24 hours MDI (2.5 mcg/inhalation) two inhalations every 24 hours
	Aclidinium			
	Inhalation	10 minutes	12 hours	DPI (400 mcg/inhalation) one inhalation every 12 hours
	Umeclidinium			
	Inhalation	≤ 15 minutes	24 hours	DPI (62.5 mcg/inhalation) one inhalation every 24 hours
	Glycopyrrolate			
	Inhalation	5 minutes	24 hours	DPI (15.6 mcg/inhalation) one inhalation every 12 hours
	Nebulization	25 minutes	12 hours	25 mcg every 12 hours
	Revefenacin			
	Nebulization	≤ 45 minutes	24 hours	175 mcg every 24 hours[c]
Phosphodiesterase-4 Inhibitor	**Roflumilast** Oral	4 weeks	–	250 mcg daily for 4 weeks, followed by 500 mcg daily[c]
Inhaled Corticosteroids	**Beclomethasone**	1–14 days		MDI (40, 80 mcg/puff) 50–200 mcg every 12 hours as part of combination therapy
	Budesonide			
	Inhalation	1 day		DPI (90, 180 mcg/inhalation) 100–200 mcg every 12 hours as part of combination therapy
	Nebulization	2–8 days		0.25–0.5 mcg/day as part of combination therapy
	Fluticasone	Variable		MDI (44, 110, 220 mcg/puff) 50–250 mcg every 12 hours as part of combination therapy DPI (50, 100, 250 mcg/inhalation) 50–250 mcg every 12 hours as part of combination therapy

[a] Outside the United States, albuterol is known as salbutamol and levalbuterol is known as levosalbutamol (or R-salbutamol).

[b] Formoterol inhalation (Foradil aerolizer) is no longer available in the United States.

[c] Not recommended in patients with hepatic impairment.

DPI, dry powder inhaler; MDI, metered-dose inhaler.

▶ *Corticosteroids*

Inhaled corticosteroids (ICS) in combination therapy improve symptoms, lung function, health status, and exacerbation rates in patients with moderate-to-very-severe COPD.[1,19] However, there appears to be a limited response of COPD-associated inflammation, and the long-term safety of ICS in COPD patients is unclear.[1]

KEY CONCEPT ICS are recommended in patients with moderate-to-very-severe COPD with increased exacerbation risk who are not adequately controlled by first-line long-acting bronchodilators (eg, LAMA); they appear to be most beneficial in preventing exacerbations in patients with elevated serum eosinophils (> 220–300 cells/μL $0.22–0.3 \times 10^9$/L).[1,19] Monotherapy with an ICS is less

Table 16–3

FDA-Approved Combination Inhalers for Management of COPD

Inhaled Corticosteroid/Long-acting β_2-Agonist (ICS/LABA)

Brand Name	Corticosteroid	β_2-Agonist	Dosage Strengths	Frequency
Advair Diskus	Fluticasone propionate	Salmeterol	250 mcg/50 mcg	Twice daily
Symbicort	Budesonide	Formoterol	160 mcg/4.5 mcg	Twice daily
Breo Ellipta	Fluticasone furoate	Vilanterol	100 mcg/25 mcg	Daily

Long-acting Muscarinic Antagonist/Long-acting β_2-Agonist (LAMA/LABA)

Brand Name	Antimuscarinic	β_2-Agonist	Dosage Strengths	Frequency
Anoro Ellipta	Umeclidinium	Vilanterol	62.5 mcg/25 mcg	Daily
Stiolto Respimat	Tiotropium	Olodaterol	2.5 mcg/2.5 mcg	Daily
Bevespi Aerosphere	Glycopyrrolate	Formoterol	9 mcg/4.8 mcg	Twice daily
Utibron Neohaler	Glycopyrrolate	Indacaterol	15.6 mcg/27.5 mcg	Twice daily
Duaklir Pressair	Aclidinium	Formoterol	400 mcg/12 mcg	Twice daily

Short-acting Muscarinic Antagonist/Short-acting β_2-Agonist (SAMA/SABA)

Brand Name	Antimuscarinic	β_2-Agonist	Dosage Strengths	Frequency
Combivent Respimat	Ipratropium	Albuterol	20 mcg/100 mcg	Four times daily

Long-acting Muscarinic Antagonist/Long-acting β_2-Agonist/Inhaled Corticosteroid (LAMA/LABA/ICS)

Brand Name	Antimuscarinic	β_2-Agonist	Corticosteroid	Dosage Strengths	Frequency
Trelegy Ellipta	Umeclidinium	Vilanterol	Fluticasone furoate	62.5 mcg/25 mcg/100 mcg	Daily
Breztri Aerosphere	Glycopyrrolate	Formoterol	Budesonide	9 mcg/4.8 mcg/160 mcg	Twice daily

effective than combined therapy with a LABA and is therefore not recommended.[1] Combination inhaler devices are convenient and ensure that patients receive both medications (Table 16–3).

The most common adverse effects from ICS include oropharyngeal candidiasis and hoarse voice. These can be minimized by rinsing the mouth after use and by using a spacer device with metered-dose inhalers (MDIs). Increased bruising, decreased bone density, increased risk of diabetes, cataracts, and mycobacterial infections have been reported; an increased pneumonia risk exists with ICS usage, particularly in those using fluticasone, those with a blood eosinophil count less than 2% (0.02), those with more severe COPD, elderly patients, smokers, or underweight patients.[1,14,19,20] Long-term use of systemic corticosteroids should be avoided due to an unfavorable risk-to-benefit ratio.[1]

▸ *Phosphodiesterase-4 (PDE-4) Inhibitor*

Roflumilast is an oral PDE-4 inhibitor approved for improving lung function and preventing moderate and severe COPD exacerbations in patients with severe-to-very-severe COPD associated with chronic bronchitis and a history of exacerbations.[1,21] Roflumilast is believed to reduce inflammation by inhibiting breakdown of cAMP but does not cause direct bronchodilation. Roflumilast has more frequent adverse events than inhaled medications and has little effect on symptoms and quality of life.[21] Adverse effects typically occur early during treatment and include diarrhea, weight loss, nausea, headache, insomnia, decreased appetite, and abdominal pain; neuropsychiatric effects (eg, anxiety, depression, suicidal thoughts) have also been reported.[21] Due to these concerns, it should be avoided in underweight patients or those with depression.[1] Roflumilast can be considered in patients with chronic bronchitis, an FEV_1 less than 50%, and exacerbations while being treated with combination inhaled therapy, particularly LABA/ICS combinations or if they had a hospitalization within the previous year.[1,10]

▸ *Combination Therapy*

For patients who remain symptomatic on monotherapy, a combination of bronchodilators can be used to reduce symptoms and exacerbations.[1,10] Combination therapy should include medications with different mechanisms, which can lower the risk of side effects versus increasing the dose of a single agent.[1] When combination therapy is indicated, multi-ingredient inhalers should be selected over single-ingredient inhalers to reduce medication administration and cost burden to the patient (Table 16–3). Potential benefits and risks of any combination therapy should be considered on a case-by-case basis. While certain studies suggest potential spirometric benefits of one LABA/LAMA combination over another, definitive data on actual patient outcome differences among agents is still lacking.[22] LABA/LAMA combinations have a lower pneumonia risk when compared to LABA/ICS combinations.[1,23,24] LABA/LAMA combinations appear to reduce exacerbations more than LABA/ICS combinations, particularly in patients with normal blood eosinophil counts.[1,20,23]

Triple therapy with ICS, LABA, and LAMA is commonly used in patients who remain symptomatic on dual therapy and reduces symptoms and moderate or severe exacerbations while improving lung function when compared to ICS/LABA or LABA/LAMA combinations.[1,25] Additionally, recent data suggests that triple therapy may reduce mortality rates when compared to LABA/LAMA combination therapy in severe-to-very-severe COPD patients with a history of frequent or severe exacerbations.[26] However, triple therapy appears to increase the incidence of pneumonia when compared to LABA/LAMA combinations.[25]

While spirometry could potentially worsen in the short term, exacerbation rates may not increase when ICS are withdrawn from patients with moderate-to-severe COPD and low blood eosinophil counts.[1,19,27] Based on these results, a step-down in therapy can be considered in the subgroup of nonfrequent exacerbating stable COPD patients with blood eosinophil counts less than 300 cells/μL (0.3×10^9/L).[27]

▶ *Vaccinations*

KEY CONCEPT COPD exacerbations, hospitalizations, and death in COPD patients can be reduced with annual influenza vaccination.[1,28] The optimal time for vaccination is early fall, September through October.

Pneumococcal polysaccharide vaccine (PPSV23) should be administered to all adults with COPD, regardless of age. Patients 65 years old and older should be revaccinated with PPSV23 if it has been more than 5 years since initial vaccination and they were younger than 65 years at the time. Pneumococcal conjugate vaccine (PCV13) can be used in select patients 65 years old and older who have not previously received PCV13 if it is deemed appropriate by shared clinical-decision making. Considerations for giving PCV13 include the individual patient's risk for exposure to PCV13 serotypes and their risk of invasive pneumococcal disease. The risk of exposure is highest in patients living in nursing homes or other long-term care facilities, residing in an area with low pediatric PCV13 uptake, or traveling to an area with no pediatric PCV13 program. Patients with the following risk factors for invasive pneumococcal disease may benefit from PCV13 vaccination: older age; immunocompromising conditions; chronic heart, lung, or liver disease; diabetes; alcoholism; more than one chronic medical condition; and cigarette smoking.[29] If a patient is to receive both pneumococcal vaccines, PCV13 should be administered first, with PPSV23 administered at least 12 months after PCV13.[29]

▶ *α_1-Antitrypsin Augmentation Therapy*

Augmentation therapy consists of weekly intravenous transfusions of pooled human AAT with the goal of maintaining adequate plasma levels (> 11 μmol/L) of the enzyme.[30] Augmentation therapy appears to minimize the progression of lung disease and slow decline in FEV_1, and appears to be most beneficial in never- or ex-smokers with an FEV_1 of 35% to 49% predicted; however, it should be considered in all AAT deficient patients with progressive lung disease.[1,30] The most common adverse effects of augmentation include rash, fatigue, and gastrointestinal upset but are typically mild and self-limiting.[30]

▶ *Other Pharmacologic Therapies*

N-Acetylcysteine has mucolytic activity, and it may reduce exacerbations and improve health status in patients not receiving ICS.[1]

Prophylaxis with macrolides (eg, azithromycin) significantly reduced exacerbations and hospital readmissions in patients susceptible to exacerbations; their benefit was greatest in current nonsmokers.[1,31] Macrolides are associated with cardiovascular adverse effects, hearing loss, and bacterial resistance; electrocardiography should be completed prior to starting therapy to detect a prolonged QTc interval, which may predispose to cardiac arrhythmias with therapy.[32]

Anti-interleukin-5 monoclonal antibodies (eg, mepolizumab) may reduce moderate or severe exacerbations in patients with elevated serum eosinophils and a history of exacerbations while on LABA/LAMA/ICS therapy. While they appear to be well tolerated, their efficacy has not been consistently documented and their current place in therapy warrants further investigation.[1,33]

In patients with low serum vitamin D levels, supplementation may reduce exacerbations.[34]

β-Blockers may reduce mortality and exacerbation rates in COPD patients.[35] Historically, β-blockers were avoided in patients with COPD due to concerns of worsening respiratory status. While much of their benefit may be derived from cardioprotective properties, they may also work via upregulation of β_2-receptors that may have been down-regulated due to long-term adrenergic stimulation. They appear to be safe (particularly β_1-selective agents) and can be continued, particularly when used to treat cardiovascular comorbidities.

Multiple traditional Chinese medicines (eg, Bu Zhong Yi Qi, Bu-Fei Yi-Shen, Yu Ping Feng San) have reduced exacerbations and improved lung function and symptoms when added to standard therapy. However, most trials have been small, flawed studies, and large randomized controlled trials are needed to confirm their efficacy.[36,37]

COPD Exacerbations

An exacerbation is defined as "an acute worsening of respiratory symptoms that results in additional therapy."[1] Exacerbations negatively impact health status, hasten lung function decline, increase rates of hospitalization, and have a reported mortality rate of 10% to 64% when requiring hospitalization and a 5-year mortality rate of roughly 50%.[1,38] While it is often difficult to discern what causes an exacerbation, many precipitating factors have been identified, including air pollution and viral (usually rhinovirus) and bacterial (usually *Haemophilus influenzae*) respiratory tract infections; exacerbations associated with viral infections are often more severe.[1,32,38]

Exacerbations are classified as mild (only short-acting bronchodilators needed), moderate (additional antibiotics and/or corticosteroids needed), or severe (hospitalization or emergency room visit required, often with acute respiratory failure present) and are based on the patient's clinical status.[1] During an exacerbation, patients often have increased inflammation, increased mucus production, increased gas trapping, and reduced expiratory function, which leads to increased dyspnea with symptoms typically lasting 7 to 10 days.[1,38] Factors associated with an increased risk of exacerbation include a history of exacerbation(s), worsening airflow limitation, GERD, the winter months, and old age.[1,38,39]

The treatment goals for exacerbations are to limit the impact of the current exacerbation and to prevent future exacerbations. Patients presenting with signs of a severe COPD exacerbation often use accessory muscles to breathe and are tachypneic, hypoxemic, and hypercarbic. Additionally, patients may be cyanotic and have peripheral edema. Life-threatening signs and symptoms include mental status changes, worsening respiratory status despite ventilatory support, hemodynamic instability, and acidosis. Presence of these signs and symptoms should prompt evaluation for hospital and/or intensive care unit admission.[1,38]

▶ *Nonpharmacologic Management*

Pulse oximetry or blood gases may be useful for determining whether supplemental oxygen therapy is needed during a COPD exacerbation. If necessary, oxygen should be titrated to a saturation of 88% to 92% (0.88–0.92).[1,38] Blood gases should be checked frequently to confirm appropriate oxygenation without compensatory carbon dioxide retention or acidosis.[1]

If mechanical ventilation is required, it can be provided by noninvasive (nasal or face mask) or invasive (orotracheal tube or tracheostomy) methods. NIV decreases acute respiratory acidosis, length of hospital stay, intubation rates, and mortality and should be attempted prior to invasive methods.[1,38,40]

▶ *Pharmacologic Management*

Bronchodilators Administration of a SABA with or without ipratropium is considered standard bronchodilator therapy during a COPD exacerbation.[1,38] Increased doses and/or frequency

Patient Encounter, Part 2: The Medical History, Physical Examination, and Diagnostic Tests

PMH: Asthma × 28 years, HFrEF × 5 years, type 2 diabetes mellitus × 10 years

Allergies: Anaphylaxis to amoxicillin and azithromycin

SH: Smoked one pack per day for 35 years but quit 5 years ago; social intake of alcohol (2–3 drinks per week); no illicit drug use

FH: Noncontributory

Meds: Carvedilol 6.25 mg twice daily, lisinopril 10 mg daily, budesonide DPI 180 mcg every 12 hours, albuterol MDI one puff every 4 to 6 hours as needed, metformin 500 mg twice daily

ROS: (–) fever, chills, or night sweats; (–) nasal congestion, drainage; (–) chest pain, paroxysmal nocturnal dyspnea; (+) orthopnea; (+) shortness of breath, chest heaviness, cough with clear phlegm; (+) mild wheezing; (–) hemoptysis; (–) N/V/D, change in bowel habits; (–) pedal edema

PE:

VS: BP 150/90 mm Hg, P 96 beats/min, RR 24/min, T 36.8°C (98.2°F), Wt 80 kg (176 lb), Ht 65 in. (165 cm), BMI 29.3 kg/m^2

HEENT: EOMI; moist mucous membranes; no JVD; no palpably enlarged cervical lymph nodes

Lungs: Expiratory phase is diminished; mild wheezes bilaterally; no crackles; (+) rhonchi

CV: RRR, normal S_1, S_2; no murmur, gallop, or rub

Abd: Soft, nontender, normoactive bowel sounds, no hepatomegaly

Ext: No cyanosis, edema, or finger clubbing

Pulmonary Function Tests

	Prebronchodilator		Postbronchodilator	
	Actual	% Predicted	Actual	% Predicted
FVC (L)	3.08		3.08	
FEV_1 (L)	1.52	66%	1.76	77%
FEV_1/FVC			57% (0.57)	

CXR: Upper lobe bullous emphysema with hyperexpansion bilaterally; no evidence of pneumonia or pulmonary edema

COPD Assessment Test score: 20

Brain Natriuretic Peptide (BNP): 27 pg/mL (ng/L; 7.8 pmol/L)

History of Exacerbations: No previous exacerbations

Given this additional information, what is your assessment of the patient's condition?

What nonpharmacologic and pharmacologic alternatives are available for managing this patient's COPD?

With the data provided, create a care plan for managing the patient's COPD.

may provide benefit during an exacerbation and an MDI with or without a spacer or a noncontinuous air-driven nebulizer can be used.[1,38,41] Maintenance bronchodilator therapy should be continued during an exacerbation or initiated once stable. However, LAMAs should be discontinued if ipratropium is used as part of the exacerbation bronchodilator regimen to minimize the potential for excessive anticholinergic effects.

Corticosteroids KEY CONCEPT Systemic corticosteroids shorten recovery time, improve lung function, reduce the risk of early relapse, reduce the risk of treatment failure, and reduce length of hospitalization during COPD exacerbations, particularly in patients with higher levels of blood eosinophils (> 2% [0.02]).[1,42] A 5-day course of oral prednisone or prednisolone 40 mg daily is recommended, and patients should be monitored closely for hyperglycemia.[1,38,43] IV corticosteroids should be used only if the oral route is not tolerated because there is no clinical benefit over oral therapy.[1] Nebulized budesonide may be used as an alternative in patients unable to take systemic corticosteroids due to lack of availability or significant systemic adverse effects.[1]

Antibiotics Exacerbations with purulent sputum production have shown increased bacteria, but routine antibiotic use is controversial due to the possibility of nonbacterial causes.[1] Approximately 50% of exacerbations are caused by bacterial infections; antibiotics given for 5 to 7 days reduce risk of treatment failure, hospitalization duration, and mortality when indicated, particularly in ICU patients.[1,32,38,42] Procalcitonin and C-reactive protein (CRP) levels, when low, may have value in determining when to avoid antibiotics in exacerbations specifically in non-ICU patients.[1,38,42,44] Current guidelines recommend antibiotics for patients with increased sputum purulence and either increased sputum volume or increased dyspnea, patients with all three of these symptoms, or patients who require mechanical ventilation.[1] Appropriate antibiotic selections for COPD exacerbations are included in Table 16–4. The oral route is preferred whenever possible, and severity of exacerbation and local resistance patterns should be considered when selecting an antimicrobial regimen.[1]

Other Therapies Hospitalized patients with COPD exacerbations should receive thromboprophylaxis due to increased risk of venous thromboembolism, and their fluid balance should be

Table 16–4

Recommended Antibiotics for Acute Exacerbations of COPD[1,34]

Suspected Pathogens	Commonly Used Antibiotics[a]
Haemophilus influenzae	Amoxicillin ± β-lactamase inhibitor
Streptococcus pneumoniae	Azithromycin or clarithromycin
Moraxella catarrhalis	Doxycycline
Pseudomonas aeruginosa	Ciprofloxacin[b] or levofloxacin Piperacillin–tazobactam Cefepime or ceftazidime Meropenem or doripenem Gentamicin or tobramycin[c]
Methicillin-resistant *Staphylococcus aureus* (MRSA)	Vancomycin[d] Linezolid[d]

[a] Refer to local antibiogram to determine which antibiotic selection is most appropriate.

[b] Limited efficacy against *Streptococcus pneumoniae*.

[c] Aminoglycosides are not effective against *Streptococcus pneumoniae*.

[d] Not effective against *Haemophilus influenzae* or *Moraxella catarrhalis*.

Patient Encounter, Part 3

Two months later, the patient arrives at the local emergency department complaining of significant shortness of breath even while resting, tachypnea, increasing sputum production, and change in sputum color over the last 5 days. Upon examination, she is using accessory muscles and pursed lips to breathe, has an oxygen saturation of 85% (0.85), has a respiratory rate of 28 breaths/min, and is hypercarbic without acidosis. She is diagnosed with a COPD exacerbation and is admitted to the hospital.

What additional signs and symptoms should be evaluated to determine the severity of her exacerbation?

What nonpharmacologic and pharmacologic alternatives are available for this patient?

With the data provided, create a care plan for managing this COPD exacerbation.

closely monitored.[1] Medication reconciliation, proper inhaler technique, vaccination status evaluation, and patient counseling on the importance of smoking cessation are necessary both during the exacerbation and upon hospital discharge. Patients are at a high risk for recurrence during the first 8 weeks after an exacerbation and may also be at increased risk of cardiovascular events within 30 days of an exacerbation if they have cardiovascular disease or are at increased cardiovascular risk.[42,45]

OUTCOME EVALUATION

- Check inhaler technique and adherence at every visit. Make sure that technique is appropriate for the type of inhaler device(s) the patient has.
- Monitor patients for improvement in symptoms. Ask if there is a difference since starting treatment and if so, is it meaningful to them? Are they less breathless? Can they do more activities and/or sleep better? If treatment response was inadequate and the patient was using the medication correctly, consider discontinuing the medication and selecting another agent.
- Changes in FEV_1 should not be the main outcome assessed because FEV_1 changes correlate weakly with symptoms, exacerbations, and health-related quality of life. The GOLD guidelines recommend annual spirometry to identify patients who are declining quickly.[1]
- The CAT is an eight-item questionnaire that can be used to assess for trends and changes in symptoms and disease impact on daily life.[1] Higher CAT scores may also be predictive of future exacerbations, depression, and mortality.[46] The test can be accessed at www.catestonline.org.
- The mMRC dyspnea scale can be used to monitor physical limitation due to breathlessness. The scale is simple to administer, correlates well with health status, and predicts future mortality risk. However, the CAT is preferred because it is more comprehensive.[1]
- A timed walking test (eg, 6-minute walking distance or shuttle-walking test) can be used to monitor functional capacity.
- Monitor theophylline levels with goal serum concentrations of 5 to 15 mcg/mL (mg/L; 28–83 μmol/L). However, bronchodilator effects are small when the serum concentration is below 10 mcg/mL (mg/L; 55 μmol/L).[47] Obtain trough levels 1 to 2 weeks after initiation of treatment and after any dosage adjustment. Routine levels are not necessary unless toxicity is suspected or symptoms have worsened.
- Monitor the patient for adverse effects of the medications selected.
- Monitor the patient for exacerbation frequency and severity.

Patient Care Process

Collect Information:

- Review medical history, physical assessment findings, blood eosinophil count (if available), and PFTs.
- Assess the type, frequency, and severity of the patient's symptoms. Use the CAT to measure symptom impact.
- Ask about disease impact on the patient's life, including limitation of activity, missed work, and feelings of depression or anxiety.
- Obtain a thorough history of prescription, nonprescription, and dietary supplement use.
- Speak with the patient and review records to identify smoking history, exacerbation history (number in the previous 12 months and whether each required hospitalization), immunization status, preferences, health goals, and socioeconomic factors that affect access to medications and/or health care.

Assess the Information:

- Assess efficacy, safety, inhaler technique, and patient adherence.
- Assess appropriateness of each COPD medication based on patient symptoms, blood eosinophil count, and exacerbation risk (Figure 16–2).
- Determine symptom burden using the CAT.
- Identify any significant adverse drug effects or interactions.
- Assess for barriers to medication access. COPD medications can be costly even for patients with insurance.
- Assess immunization records for influenza and pneumococcal vaccinations.
- Determine if current smokers are ready to quit.
- Identify comorbidities that may impact disease course.

(Continued)

Patient Care Process (Continued)

Develop a Care Plan:

- Design a therapeutic plan including lifestyle modifications (eg, smoking cessation) and optimal drug therapy (Figure 16–2). Consider the need for pulmonary rehabilitation, oxygen therapy, and/or surgery.
- Use combination inhalers when appropriate to minimize drug administration burden.
- Review insurance formularies for medication coverage. Use manufacturer patient assistance programs as needed to ensure medication access.
- Write an action plan for the patient. An example COPD action plan is available from the American Lung Association at lung.org/copd.

Implement the Care Plan:

- Provide annual influenza vaccination and pneumococcal vaccination if needed.
- Provide patient education and self-management training:
  - Smoking cessation including behavioral strategies for quitting and proper use of pharmacotherapy.
  - Maintaining or increasing physical activity, ensuring adequate sleep, maintaining a healthy diet.
  - Proper inhaler technique and when to take medications, importance of adherence, adverse effects and how to minimize them.
  - Signs and symptoms of an exacerbation and what to do if one occurs; provide written action plan.
  - Advanced directives and end-of-life issues for patients with severe disease.
- Address any patient concerns about COPD and its management.
- Refer to pulmonary rehabilitation program, if indicated.

Follow-up: Monitor and Evaluate:

- Follow up within 1 month after an acute exacerbation because this can reduce hospital readmissions; additional follow-up at 3 months is also recommended.[1]
- For stable patients, follow up every 3 to 6 months to assess effectiveness and safety of therapy.
- Review smoking status, oxygen saturation, symptoms, exacerbation frequency and severity, recent hospitalizations, and medication regimen (efficacy, adherence, inhaler technique, adverse reactions, drug interactions, issues affecting medication access).
- Obtain spirometry annually to assess disease progression.

List of Abbreviations

AAT	α_1-Antitrypsin
ABG	Arterial blood gas
cAMP	Cyclic adenosine monophosphate
CAT	COPD Assessment Test
COPD	Chronic obstructive pulmonary disease
FEV$_1$	Forced expiratory volume in the first second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	Inhaled corticosteroid
LABA	Long-acting β_2-agonist
LAMA	Long-acting muscarinic antagonist
MDI	Metered-dose inhaler
mMRC	Modified Medical Research Council
NIV	Noninvasive ventilation
NRT	Nicotine replacement therapy
Paco$_2$	Partial pressure of arterial carbon dioxide
Pao$_2$	Partial pressure of arterial oxygen
PCV13	Pneumococcal conjugate vaccine
PDE-4	Phosphodiesterase-4
PFTs	Pulmonary function tests
PPSV23	Pneumococcal polysaccharide vaccine
SABA	Short-acting β_2-agonist
SAMA	Short-acting muscarinic antagonist
Sao$_2$	Arterial oxygen saturation
$V_A/\dot{Q}$	Ventilation/perfusion ratio

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17

Cystic Fibrosis

Kimberly J. Novak

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the pathophysiology of cystic fibrosis (CF) and its multiorgan system involvement.
2. Describe the common clinical presentation and diagnosis of CF.
3. Consider long-term treatment goals with respect to clinical course and prognosis of CF.
4. Identify nonpharmacologic therapies for CF management.
5. Recommend appropriate pharmacologic therapies for chronic CF management.
6. Design appropriate antibiotic regimens for acute pulmonary exacerbations of CF.
7. Apply pharmacokinetic principles when calculating drug doses in CF patients.
8. Formulate monitoring plans for acute and chronic CF pharmacotherapy.

INTRODUCTION

Cystic fibrosis (CF) is an inherited multiorgan system disorder affecting children and, increasingly, adults. It is the most common life-shortening genetic disease among White patients and the major cause of severe chronic lung disease and pancreatic insufficiency in children. Disease generally manifests as mucosal obstruction of exocrine glands caused by defective ion transport within epithelial cells. Due to the array of affected organ systems and complicated medical therapies, appropriate CF treatment necessitates interprofessional team collaboration.

EPIDEMIOLOGY AND ETIOLOGY

In the United States, CF most commonly occurs in White patients, affecting approximately 1 in 3200 individuals. CF is less common in Hispanics (1 in 14,000), African Americans (1 in 15,000), and Asian Americans (1 in 35,000).[1] CF is inherited as an autosomal recessive trait, and approximately 1 in 25 White patients are **heterozygous** carriers. Offspring of a carrier couple (each parent being heterozygous) have a 1 in 4 chance of having the disease (**homozygous**), a 1 in 2 chance of being a carrier (heterozygous), and a 1 in 4 chance of receiving no trait. The *CFTR* gene mutation is found on the long arm of chromosome 7 and encodes for the CF transmembrane regulator (CFTR) protein, which functions as a chloride channel to transport water and electrolytes. Over 2000 mutations have been described in the *CFTR* gene; however, the *Phe508del* mutation (also known as *F508del* or *ΔF508*) is most common and present in about 70% to 90% of CF patients.[1–3]

PATHOPHYSIOLOGY

CF is a disease of exocrine gland epithelial cells where CFTR expression is prevalent. Normally, these cells transport chloride through CFTR chloride channels with sodium and water accompanying this flux across the cell membrane (Figure 17–1). CFTR is regulated by protein kinases in response to varying levels of the intracellular second messenger cyclic-3′,5′-adenosine monophosphate (cAMP). CFTR also downregulates the epithelial sodium channel and regulates calcium-activated chloride and potassium channels, and it may function in exocytosis and formation of plasma membrane molecular complexes and proteins important in inflammatory responses and mucociliary clearance.[3,4] **KEY CONCEPT** In CF, the CFTR chloride channel is dysfunctional and usually results in decreased chloride secretion and increased sodium absorption, leading to altered viscosity of fluid excreted by the exocrine glands and mucosal obstruction. *CFTR* gene mutations are assigned to classes (I–VI) based on degree of residual CFTR protein function (Figure 17–2 for cellular location of the CFTR protein defects). Classes I (absent CFTR synthesis), II (blocked CFTR trafficking), and III (blocked CFTR regulation or gating) mutations result in no CFTR function. Classes IV (altered CFTR conductance), V (reduced CFTR synthesis), and VI (shortened CFTR life span) mutations have some remaining functional protein.[2,3,5]

Pulmonary System

Chronic lung disease leads to death in 90% of patients. **KEY CONCEPT** Pulmonary disease is characterized by thick mucus secretions, impaired mucus clearance, chronic airway infection and colonization, obstruction, and an exaggerated neutrophil-dominated inflammatory response.[1,3] This process leads to air trapping, **atelectasis**, mucus plugging, **bronchiectasis**, cystic lesions, pulmonary hypertension, and eventual respiratory failure. Pulmonary function (measured as FEV_1) declines approximately 1% to 2% per year; an individual's rate of decline depends on severity of CFTR dysfunction and comorbidities, which may cause a more rapid decline (more than 5% per year).[6] Sinusitis and nasal polyps are also common, and microbial colonization is similar to that of the lungs.

Bacterial pathogens are often acquired in age-dependent sequence. Early infection is most often caused by *Staphylococcus aureus*

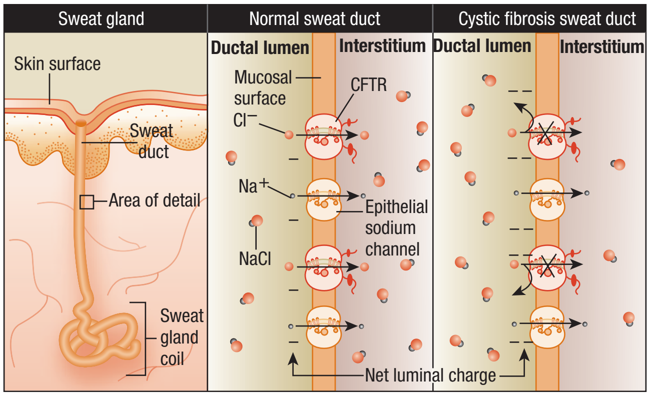

FIGURE 17–1. Pathophysiology of elevated sodium chloride levels in the sweat of patients with CF. Sweat ducts (Section A) in patients with CF have reduced ability to reabsorb chloride before the appearance of sweat on the skin surface. A major pathway for chloride absorption is through CFTR situated within mucosal membranes of cells lining the duct (Section B). In CF, decreased chloride reabsorption in the setting of continued sodium uptake leads to an elevated transepithelial potential difference across the wall of the sweat duct. Due to the failure to reabsorb chloride, the lumen becomes more negatively charged (Section C). Subsequently, sodium chloride flux is markedly decreased, leading to increased sweat chloride content. (Reprinted with permission from Wright CC, Vera YY. Cystic fibrosis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. McGraw-Hill Education; 2017: www.accesspharmacy.com.)

(usually methicillin sensitive) and nontypeable *Haemophilus influenzae*. *Pseudomonas aeruginosa* infection is the most significant pathogen among all age groups. *P. aeruginosa* expresses extracellular toxins that perpetuate lung inflammation. Mucoid strains of *P. aeruginosa* produce an alginate biofilm layer that interferes with antibiotic penetration. Methicillin-resistant *S. aureus* (MRSA) is also a significant CF pathogen, and incidence is increasing in some geographic areas. Respiratory organisms identified later in the disease course include *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Burkholderia cepacia* complex, fungi including *Candida* and *Aspergillus* species, and nontuberculous mycobacteria among others.[1,3] Cultured organisms may represent initial infection, chronic colonization, or microbial overgrowth in an acute exacerbation.

Gastrointestinal System

Gastrointestinal (GI) involvement often presents as **meconium** ileus, small-bowel obstruction shortly after birth due to abnormally thick meconium. Older CF patients may develop distal intestinal obstruction syndrome (DIOS) due to fecal impaction in the terminal ileum and cecum.

Maldigestion due to pancreatic enzyme insufficiency is present in 85% to 90% of CF patients.[1,7] Thick pancreatic secretions and cellular debris obstruct pancreatic ducts and lead to fibrosis. Volume and concentration of pancreatic enzymes and bicarbonate are reduced, leading to maldigestion of fat and protein and subsequent malabsorption of fat-soluble vitamins (A, D, E, and K). Symptoms include abdominal distention, **steatorrhea**, flatulence, and malnourishment despite voracious appetite. Maldigestion is progressive and may develop later in a previously pancreatic-sufficient patient. Other complications may include GI reflux, dysmotility, salivary dysfunction, **intussusception**, **volvulus**, **atresia**, **rectal prolapse**, complications related to corrective surgery for meconium ileus, and increased risk of GI cancers later in life.[7]

Hepatobiliary disease occurs due to bile duct obstruction from abnormal bile composition and flow. Hepatomegaly, splenomegaly, and cholecystitis may be present. Hepatic **steatosis** may be present due to effects of malnutrition. Progression from cholestasis (impaired bile flow) to cirrhosis, esophageal varices, and portal hypertension takes several years. Many patients are compensated and asymptomatic but may be susceptible to acute decompensation in the event of extrinsic hepatic insult from viruses, medications, or other factors.[7]

Endocrine System

CF-related diabetes (CFRD) occurs in approximately 20% of adolescents and 40% to 50% of adults, disproportionally affecting

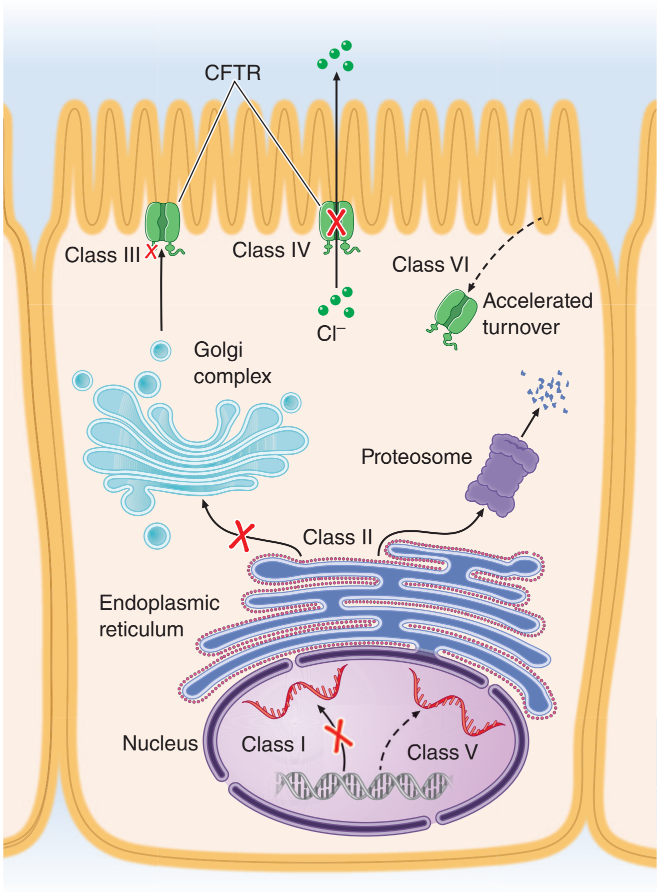

FIGURE 17–2. Categories of CFTR mutations. Classes of defects in the *CFTR gene* include the absence of synthesis (class I); defective protein maturation and premature degradation (class II); disordered gating/regulation, such as diminished adenosine triphosphate (ATP) binding and hydrolysis (class III); defective conductance through the ion channel pore (class IV); a reduced number of CFTR transcripts due to a promoter or splicing abnormality (class V); and accelerated turnover from the cell surface (class VI). (Reprinted with permission from Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. Cystic Fibrosis. In: Harrison's Principles of Internal Medicine, 20e; 2018: www.accesspharmacy.com.)

women. Although it shares characteristics of both type 1 and type 2 diabetes mellitus, CFRD is categorized separately. Reduced functional pancreatic islet cells and increased islet **amyloid** deposition result in insulin insufficiency, the primary cause of CFRD. Insulin secretion is delayed in response to glucose challenge, and absolute insulin secretion over time is reduced. Some insulin resistance may also be present in CFRD and may fluctuate in relation to infection and inflammation.[8,9]

Postprandial hyperglycemia is common, but because some basal insulin secretion is maintained, fasting hyperglycemia is less severe and ketosis is rare. Diet, acute and chronic infection, and corticosteroid use lead to fluctuation in glucose tolerance over time.[8,9] CFRD is associated with greater nutritional failure, increased pulmonary disease, and earlier mortality. Pulmonary function decline and nutritional consequences associated with progressive CFRD have historically overshadowed risks of long-term macrovascular and microvascular complications; however, these complications are now emerging with longer life expectancy.[8,9]

Reproductive System

CF patients often experience delayed puberty. In girls, menarche occurs 18 months later than average; menstrual irregularity is common, and fertility is reduced due to increased cervical mucus viscosity. Due to increasing life expectancy and highly effective therapies, pregnancy is becoming more common; however, outcomes depend on prepartum nutritional and pulmonary status. Almost all males with CF are **azoospermic** due to congenital absence of the vas deferens with resultant obstruction; however, conception still occurs occasionally. Conception can also occur through application of assisted reproductive technologies.[9,10]

Musculoskeletal System

Several factors contribute to development of bone disease in CF: (a) malabsorption of vitamins D and K and calcium, (b) poor nutrition and decreased body mass, (c) physical inactivity, (d) corticosteroid therapy, (e) inflammation, and (f) delayed puberty and hypogonadism. Chronic pulmonary infection, through release of inflammatory cytokines, can increase bone resorption and decrease formation. Osteopenia, osteoporosis, pathological fractures, and **kyphosis** can occur.[9] Episodic or chronic arthritis may occur due to immune complex formation in response to chronic inflammation.[11] Digital **clubbing** is common and a marker for chronic hypoxia.

Clinical Presentation of Cystic Fibrosis

General

- Usually diagnosed in neonates (meconium ileus or newborn screening) or during early childhood. May present later in life due to less severe symptoms or misdiagnosis.

Symptoms

- Pulmonary: Chronic cough, sputum production, decreased exercise tolerance, and recurrent pneumonia and sinusitis. Exacerbations may be marked by increased cough, sputum changes (darker, thicker), hemoptysis, dyspnea, and fever.
- GI: Numerous large, foul-smelling loose stools (steatorrhea), flatulence, and abdominal pain. Intestinal obstruction may present as abdominal pain and distention and/or decreased bowel movements.
- Nutritional: Poor weight gain despite voracious appetite and hunger. Dry skin, skin rash, and visual disturbances may be noted in vitamin deficiency.
- CFRD: Weight loss, increased thirst, and more frequent urination.

Signs

- Obstructive airways disease: Tachypnea, dyspnea, cyanosis, wheezes, crackles, sternal retractions, digital clubbing, and barrel chest.
- Failure to thrive: Below age-based normal of both height and weight in children; adults may be near/below ideal body weight or have a low body mass index (BMI).
- Salty taste to the skin.
- Hepatobiliary disease: Hepatomegaly, splenomegaly, and prolonged bleeding may occur.
- Recurrent pancreatitis (usually in pancreatic-sufficient patients): Episodic epigastric abdominal pain, persistent vomiting, and fever.

Laboratory Tests

- Leukocytosis with increase in polymorphonuclear (PMN) leukocytes and bands may occur in acute pulmonary exacerbations.
- Maldigestion: Decreased serum levels of fat-soluble vitamins (A, D, E, and K). Decreased vitamin K levels may result in elevated prothrombin time (PT) and international normalized ratio (INR). Elevated fecal fat content, reduced pancreatic stool elastase (< 200 mcg/g of feces).
- Glucose intolerance: Blood glucose between 140 and 199 mg/dL (7.8–11 mmol/L) 2 hours after an oral glucose-tolerance test.
- CFRD: Blood glucose 200 mg/dL (11.1 mmol/L) or higher 2 hours after an oral glucose-tolerance test or fasting hyperglycemia (fasting blood glucose 126 mg/dL [7 mmol/L] or more regardless of the postglucose challenge level).
- Hepatobiliary disease: Serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyltransferase, and bilirubin may be elevated.

Other Tests

- Microbial cultures (sputum, throat, bronchoalveolar lavage, or sinus): Isolation of *Pseudomonas aeruginosa, Staphylococcus aureus, Stenotrophomonas maltophilia,* and other CF-related organisms.
- Pulmonary function tests (PFTs): Decreased forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), typically lower during acute pulmonary exacerbations.
- Chest X-ray or CT scan: Infiltrates, atelectasis, bronchiectasis, and mucus plugging.
- Abdominal X-ray or CT scan: Intestinal obstruction may be manifested as meconium ileus, DIOS, or intussusception. Rectal prolapse may be noted on physical examination.

Hematological System

Anemia may be present due to impaired erythropoietin regulation, nutritional factors (vitamin E and iron malabsorption), or chronic inflammation. Increased cytokine production can lead to shortened red blood cell survival, reduced erythropoietin response, and impaired mobilization of iron stores. Additionally, with chronic hypoxia, normal hemoglobin and hematocrit values may represent relative anemia.[12] Increased red blood cell production is a physiological response to hypoxia; however, this response may be blunted in CF and may result in symptoms of anemia despite normal lab values.

Abnormal bleeding or clotting may also be observed as a result of vitamin K malabsorption, antibiotic-associated depletion of GI flora and vitamin K synthesis, reduced coagulation factor synthesis due to liver disease, and/or a procoagulant state due to inflammation.

Integumentary System

Sweat contains abnormally high concentrations of sodium and chloride due to impaired reabsorption within the sweat duct from loss of CFTR channels, a target for CF diagnosis.[1] This may impart a characteristic salty taste to the skin. Patients are usually otherwise asymptomatic. In rare instances such as hot weather or excessive sweating during physical activity, patients may become dehydrated and experience symptoms of hyponatremia (nausea, headache, lethargy, and confusion).

CLINICAL PRESENTATION AND DIAGNOSIS

See the accompanying box for the clinical presentation of CF.

Diagnosis

Testing for CF is part of required newborn screening panels in all US states in an effort to identify patients prior to symptom development, initiate early treatment, and improve long-term outcomes.[13] A positive newborn screen for CF is not diagnostic (due to false-positive results among CF carriers), nor does a negative screen universally exclude the diagnosis. All "positive screens," as well as individuals presenting with signs and symptoms of CF, are referred to a CF care center for sweat chloride test and genetic evaluation. Diagnosis of CF is based on two separate elevated sweat chloride concentrations of 60 mEq/L (mmol/L) or greater obtained through pilocarpine **iontophoresis** ("sweat test"). Genetic testing (*CFTR* mutation analysis) is performed to confirm the diagnosis and determine eligibility for precision medicine therapy, screen in utero, or detect carrier status. More than 70% of diagnoses are made by 12 months of age.[13]

Patient Encounter Part 1

A 4-week-old male term neonate is being evaluated at CF clinic due to an abnormal newborn screen (elevated immunoreactive trypsinogen; gene mutations *G551D* and *Phe508del* on initial testing). Sweat chloride testing is performed on bilateral thighs with results reported as follows:

Sample 1: Sweat chloride 120 mEq/L (mmol/L)

Sample 2: Sweat chloride 116 mEq/L (mmol/L)

Upon parental interview, the neonate is a voracious eater and has 7 to 10 loose stools per day that have a white oily appearance. He is mostly breastfed, with some supplemental 20 kcal/oz (0.67 kcal/mL; 2.8 kJ/mL) infant formula, and he weighs 2.95 kg (birth weight of 3.1 kg). Parents also report that he needed oral laxatives and enemas to help pass his meconium while in the newborn nursery.

What information is consistent with a diagnosis of CF?

What are the next steps in the CF diagnostic process?

The parents are overwhelmed with the diagnosis of CF and are very worried about life expectancy. How would you explain the infant's prognosis?

Clinical Course and Prognosis

Clinical course varies because of multiple genetic mutations and the heterogeneous profile of the *Phe508del* mutation. Some patients develop severe lung disease early in childhood and reach end-stage disease by adolescence, whereas others maintain near-normal lung function into adulthood. Newly diagnosed adults tend to have *CFTR* mutations associated with residual CFTR function and may present with milder respiratory symptoms, pancreatitis, or infertility.[3,5]

Life expectancy has greatly increased from a predicted survival of 16 years of age in 1970 to more than 40 years for patients born in the 1990s.[3,5] According to the Cystic Fibrosis Foundation Registry, 54.6% of patients are over 18 years of age.[14]

TREATMENT

Desired Outcomes

Therapeutic outcomes in CF care relate to chronic and acute treatment goals. With chronic management, the primary goals are to delay disease progression and optimize quality of life. **KEY CONCEPT** Maximizing nutritional status through pancreatic enzyme replacement and vitamin and nutritional supplements is necessary for normal growth and development and for maintaining long-term lung function. Reduction of airway inflammation and infection and aggressive preventive therapies minimize acute pulmonary exacerbations and delay pulmonary decline. In pulmonary exacerbations, therapy is directed toward reducing acute airway inflammation and obstruction through aggressive airway clearance and antibiotic therapy with a goal of returning lung function to preexacerbation levels or greater.

Nonpharmacologic Therapy

▶ *Airway Clearance Therapy*

KEY CONCEPT Airway clearance therapy is a necessary routine for all CF patients to clear secretions and control infection, even at diagnosis prior to becoming symptomatic. Waiting until development of a first pulmonary exacerbation or daily symptoms delays benefits and may accelerate pulmonary decline. The traditional form of chest physiotherapy (CPT) is percussion and postural drainage. Areas of the patient's chest, sides, and back are rapidly "clapped" by hand in different patient positions, followed by cough or forced expiration to mobilize secretions. Patients may also be taught autogenic drainage, which consists of deep breathing exercises followed by forced cough.

Several airway clearance devices are also available. Flutter valve devices use oscillating positive expiratory pressure (OPEP) to cause vibratory airflow obstruction and an internal percussive effect to mobilize secretions. Intrapulmonary percussive ventilation (IPV) provides continuous oscillating pressures during inhalation and exhalation. High-frequency chest compression (HFCC) with an inflatable vest that provides external oscillation is most commonly used and often preferred because patients can perform therapy independently from an early age. Exercise may be an adjunctive modality for airway clearance.[15]

Effective cough and expectoration of mucus are essential for good clearance technique. Airway clearance therapy is typically performed once or twice daily for maintenance care and increased to three or four times per day during acute exacerbations.

▶ *Nutrition*

Most CF patients have increased caloric needs due to increased energy expenditure through increased work of breathing, increased basal metabolism, and maldigestion. Prevention of malnutrition requires early patient-specific nutritional intervention. Caloric requirements to promote age-appropriate weight gain or maintenance are typically 110% to 200% of the recommended daily allowance (RDA) for age, gender, and size and increase as disease progresses. Diets in CF patients should comprise 35% to 40% of calories from fat, 15% to 20% of calories from protein, and no more than 50% calories from carbohydrates. Historically recommended low-fat high-carbohydrate diets are no longer recommended.[16]

Nutrition in malnourished patients consists of baseline required calories plus additional calories for weight gain via a high-calorie high-fat diet. Even with aggressive diet and oral supplements, placement of a gastrostomy or jejunostomy tube for nighttime supplemental feeds may be necessary.[16,17] Patients with refractory malabsorption, CFRD, and/or tube feedings have unique caloric needs. Collaboration with dieticians specially trained in CF nutrition is essential.

Pharmacologic Therapy

▶ *Airway Clearance Therapy*

Airway clearance therapy is often accompanied by bronchodilator treatment with albuterol (known as salbutamol outside the United States) to stimulate mucociliary clearance and prevent bronchospasm associated with other inhaled therapies (Table 17–1).

A mucolytic agent is administered subsequently to reduce sputum viscosity and enhance clearance. Dornase alfa (Pulmozyme) is a recombinant human (rh) DNase that selectively cleaves extracellular DNA released during neutrophil degradation in viscous CF sputum. Nebulization of dornase alfa improves daily pulmonary symptoms and function, reduces pulmonary exacerbations, and improves quality of life.[15,18] Daily dosing is most common, but some patients benefit from twice daily administration. Hypertonic saline for inhalation (HyperSal) 7% or 3.5% is often used as an alternative or add-on mucolytic agent for osmotic effects in airway surface liquid or sputum. It must be preceded by a bronchodilator due to greater incidence of bronchospasm and may not be tolerated by some patients.[18] *N*-acetylcysteine is another mucolytic agent, but its unpleasant odor and taste limit patient acceptance.

CF guidelines do not recommend β_2-agonists or inhaled corticosteroids in patients without asthma or allergic bronchopulmonary aspergillosis (ABPA).[18] Inhaled corticosteroids may attenuate reactive airways and reduce airway inflammation in some patients; however, clear benefit in CF has not been established.[15,18] Patients with asthma or recurrent wheezing or dyspnea who improve with albuterol (salbutamol) should be considered for maintenance asthma therapy, as should patients with bronchodilator-responsive PFTs. Drug delivery to the site of inflammation is limited by mucus plugging, which may limit efficacy. Patients on asthma therapies should administer these medications after airway clearance to optimize drug delivery.

Montelukast, antihistamines, and/or intranasal steroids are used for CF patients with allergic or rhinosinusitis symptoms.

Long-term systemic corticosteroids reduce airway inflammation and improve lung function. However, beneficial effects diminish upon discontinuation, and concern for long-term adverse effects limits use as maintenance therapy.[18,19] Systemic corticosteroids may be used short term in acute exacerbations

Table 17–1

Common Medications Used in Cystic Fibrosis

Medication	Pediatric Dose	Adult Dose
Albuterol (salbutamol)	2.5 mg nebulized with chest physiotherapy two to four times daily; alternatively, two puffs via metered-dose inhaler may be substituted	2.5 mg nebulized with chest physiotherapy two to four times daily; alternatively, two puffs via metered-dose inhaler may be substituted
Dornase alfa	2.5 mg nebulized once or twice daily	2.5 mg nebulized once or twice daily
Hypertonic saline 7%, 3.5%, or 3%	4 mL nebulized one to four times per day	4 mL nebulized one to four times per day
Ibuprofen[a]	20–30 mg/kg/dose given twice daily	20–30 mg/kg/dose given twice daily
Azithromycin	Body weight 25–39 kg: 250 mg on Mondays, Wednesdays, and Fridays	Body weight 40 kg or more: 500 mg on Mondays, Wednesdays, and Fridays
Ivacaftor[b]	25–150 mg every 12 hours (minimum age 4 months)	150 mg every 12 hours
Lumacaftor/ivacaftor[c]	100–400 mg/125–250 mg every 12 hours (minimum age 2 years)	400 mg/250 mg every 12 hours
Tezacaftor/ivacaftor[b]	50–100 mg/75–150 mg in the morning and 0 mg/75–150 mg in the evening (minimum age 6 years)	100 mg/150 mg in the morning and 0 mg/150 mg in the evening
Elexacaftor/tezacaftor/ivacaftor[b]	100–200 mg/50–100 mg/75–150 mg in the morning and 0 mg/0 mg/75–150 mg in the evening (minimum age 6 years)	200 mg/100 mg/150 mg in the morning and 0 mg/0 mg/150 mg in the evening

[a] Adjusted to achieve peak serum concentrations of 50 to 100 mcg/mL (243–485 μmol/L). Maintain chronic dosing with same dosage form and manufacturer. Note that therapy is not always continued into adulthood.

[b] Dose may require adjustment in patients with moderate or severe hepatic impairment and/or when coadministered with moderate or strong CYP3A inhibitors.

[c] Dose may require adjustment in patients with moderate or severe hepatic impairment and/or when coadministered with strong CYP3A inhibitors. Other medication dosages may need increased due to multienzyme CYP induction by lumacaftor.

or for treatment of allergic response to *Aspergillus* colonization (ABPA); however, dose and duration of therapy should be minimized.

High-dose ibuprofen targeting peak concentrations of 50 to 100 mcg/mL (243–485 μmol/L) has been shown to slow disease progression, particularly in children 6 to 17 years of age with mild lung disease ($FEV_1 > 60\%$ predicted). At high doses, ibuprofen inhibits the lipoxygenase pathway, reducing neutrophil migration and function as well as release of lysosomal enzymes. At lower concentrations achieved with analgesic dosing, neutrophil migration increases, potentially increasing inflammation. A dose of 20 to 30 mg/kg given twice daily is usually needed to attain target levels, but interpatient variability necessitates serum concentration monitoring.[18,20] Due to monitoring requirements and concerns regarding long-term safety and tolerability, only a few CF centers prescribe high-dose ibuprofen.

Azithromycin is a macrolide antibiotic commonly used in CF as an anti-inflammatory agent to improve overall lung function and reduce exacerbations in patients colonized with *Pseudomonas* and to reduce exacerbations in those without *Pseudomonas*.[18,21] Proposed mechanisms include interference with *Pseudomonas* alginate biofilm production, bactericidal activity during stationary *Pseudomonas* growth, neutrophil inhibition, cytokine inhibition, and reduction in sputum viscosity.[21] Due to its long tissue half-life, azithromycin is typically dosed 3 days/week (Monday, Wednesday, and Friday). Alternatively, patients may take 500 or 250 mg either daily or only Monday through Friday, based on the same weight parameters.[21] Patients should have a screening acid-fast bacillus sputum culture prior to initiation and then every 6 to 12 months, because isolation of nontuberculous mycobacteria is a contraindication to chronic azithromycin therapy.[18]

▶ *Antibiotic Therapy*

KEY CONCEPT Antibiotic therapy is used in three distinct situations: (a) eradication and delay of colonization in early lung disease (treatment of positive cultures regardless of symptoms), (b) suppression of bacterial growth once colonization is present, and (c) reduction of bacterial load in acute exacerbations in an attempt to return lung function to preexacerbation levels or greater.[22] **KEY CONCEPT** Antibiotic selection is based on periodic culture and sensitivity data, typically covering all organisms identified during the preceding year. If no culture data are available, empirical antibiotics should cover the most likely organisms for the patient's age group. Due to altered pharmacokinetics and microorganism resistance, dose optimization is key (Table 17–2).

Table 17–2

Selected Antibiotic Dosing in Cystic Fibrosis[a]

Antibiotic	Pediatric Dose (mg/kg/day)	Adult Maximum Daily Dose	Interval (hours)
Intravenous			
Tobramycin, gentamicin[b]	10–15	None	8–24
Amikacin[b]	30–45	None	8–24
Ceftazidime	150–400	8–12 g	6–8
Cefepime	150–200	6–8 g	8
Ceftolozane–tazobactam[c]	120	6 g	8
Ceftazidime–avibactam[c]	150–200	6–8	6–8
Piperacillin–tazobactam[c]	400–600	18–24 g	6
Ticarcillin–clavulanate[c]	400–600	12–18 g	4–6
Meropenem	120	6 g	8
Meropenem–vaborbactam[c]	120	6 g	8
Imipenem–cilastatin[c]	100	2–4 g	6
Aztreonam	200–300	8–12 g	6
Ciprofloxacin	30	1.2 g	8–12
Levofloxacin	10–20	750 mg	12–24
Nafcillin	200	12 g	4–6
Vancomycin[b]	60–80	None	6–12
Linezolid	30	1.8 g	8–12
Colistin	5–8	480 mg	8–12
Chloramphenicol[b]	60–80	4 g	6
Oral			
Amoxicillin ± clavulanic acid[c]	90	4 g	12
Dicloxacillin	100	2 g	6
Cephalexin	50–100	4 g	6–8
Trimethoprim–sulfamethoxazole[d]	12–20	1280 mg	6–12
Clindamycin	30	1.8 g	6–8
Ciprofloxacin	40	2 g	12
Levofloxacin	10–20	750 mg	12–24
Doxycycline[e]	4	200 mg	12–24
Minocycline[e]	4	400 mg	12
Linezolid	30	1.8 g	8–12
Inhaled			
Tobramycin	160–600 mg/day	600 mg	12
Aztreonam lysine	225 mg/day	225 mg	8
Colistin	75–150 mg/day	300 mg	12

[a] All doses assume normal renal and hepatic function. Consult a specialized drug reference for dosage adjustment if function is impaired. Dose and/or interval may require adjustment.

[b] Empirical starting doses only. Adjust dose per therapeutic drug monitoring.

[c] Dose based on β-lactam component.

[d] Dose based on trimethoprim component.

[e] Children older than 8 years.

Oral Antibiotic Therapy Severity of pulmonary symptoms also guides antibiotic selection. For recent-onset or mild symptoms, patients may be treated with outpatient oral and inhaled antibiotics for 10 to 14 days. Oral fluoroquinolones are a mainstay for *P. aeruginosa* treatment in CF, even in children.[22] Despite concerns regarding cartilage and tendon toxicity in young animals, clinical practice has not shown an increased risk in human children.[23] Inhaled tobramycin, aztreonam, or colistin is usually continued or added for double coverage if the patient is not on suppressive inhaled antibiotics. Methicillin-sensitive *S. aureus* (MSSA) may be treated with oral amoxicillin–clavulanic acid, dicloxacillin, first- or second-generation cephalosporins, trimethoprim–sulfamethoxazole, clindamycin, doxycycline, or minocycline, depending on sensitivity. MRSA may be treated with oral trimethoprim–sulfamethoxazole, clindamycin, doxycycline, minocycline, or linezolid. *H. influenzae* often produces β-lactamases but can usually be treated with amoxicillin–clavulanic acid, a cephalosporin, or trimethoprim–sulfamethoxazole. Oral trimethoprim–sulfamethoxazole, minocycline, or doxycycline may be used to treat *S. maltophilia*. Delafloxacin, a novel fluroquinolone with activity against both *P. aeruginosa* and MRSA, should be avoided at this time until pharmacokinetic data are known in CF patients to avoid potential underdosing and risk for development of resistance.

Intravenous Antibiotic Therapy For severe infections or patients failing outpatient therapy, IV antibiotic therapy is often prescribed for 10 to 14 days as inpatient therapy. Some patients may be discharged to finish their IV course or even receive their entire IV course at home. **KEY CONCEPT** Typical regimens for severe infections include an antipseudomonal β-lactam plus an aminoglycoside for added synergy and delay of resistance development.[24,25] Cephalosporins tend to be better tolerated and offer the benefit of less frequent administration. Extended-spectrum penicillins have been associated with a higher incidence of allergy. Aztreonam offers little cross-reactivity in penicillin- or cephalosporin-allergic patients; however, it has no gram-positive coverage. Meropenem should be reserved for organisms resistant to all other antibiotics to minimize development of resistance in the carbapenem drug class. Newer agents targeting highly resistant organism (ie, ceftolozane/tazobactam, ceftazidime/avibactam, and meropenem/vaborbactam) should also be restricted.

Tobramycin IV is generally the first-line aminoglycoside. Isolates are usually resistant to gentamicin, and amikacin is reserved for tobramycin-resistant strains. Pharmacokinetic targets are listed in Table 17–3. Higher peak serum concentrations are desired to maximize efficacy, whereas lower trough levels reduce risk of toxicity. Once-daily dosing targets higher peaks and lower troughs, optimizing the concentration-dependent killing of aminoglycosides (eg, tobramycin 10–15 mg/kg/day or amikacin 30–45 mg/kg/day) and is preferred over three times daily dosing.[25] However, time below the minimum inhibitory concentration (MIC) is prolonged with once-daily administration in some children, possibly leading to loss of synergy for a substantial portion of the dosing interval or development of resistance. Traditional dosing may be used in these patients. Incorporation of patient-specific pharmacokinetic history is essential for optimal aminoglycoside dosing. Long-term studies are needed to examine the efficacy and resistance patterns associated with once-daily aminoglycosides in CF patients.[24,25]

As with *Pseudomonas* infections, most other serious gram-negative infections are also treated with combination therapy. *S. maltophilia* is highly resistant and most often treated with trimethoprim–sulfamethoxazole, minocycline, doxycycline, or ticarcillin–clavulanate (not currently available in the United States). There are few options for *A. xylosoxidans* and *B. cepacia*, and multidrug therapy is often used.

An oral fluoroquinolone may be substituted for an IV aminoglycoside based on sensitivity data or presence of renal dysfunction and/or ototoxicity. Due to excellent bioavailability, fluoroquinolones, trimethoprim–sulfamethoxazole, doxycycline, minocycline, and linezolid should be used orally for most patients able to take enteral medications. Due to toxicity risk, colistin IV and chloramphenicol IV are reserved for life-threatening or highly resistant infections.

Inpatient treatment of MRSA can consist of IV vancomycin or oral agents as previously described, depending on the severity of infection and concomitant organisms.[26]

Inhaled Antibiotic Therapy Chronic or rotating inhaled antibiotic maintenance therapy may be used to suppress *P. aeruginosa* colonization in CF patients of all ages; however, long-term systemic antibiotics are not recommended due to emergence of resistance.[18,19,27,28] Inhaled antibiotic therapy is also recommended for eradication of initial *P. aeruginosa* infection.[29] Inhaled tobramycin (TOBI, Bethkis) is typically administered to patients 6 years of age and older in alternating 28-day cycles of 300 mg nebulized twice daily, followed by a 28-day washout period to minimize development of resistance. Long-term cyclical administration improves pulmonary function, decreases microbial burden, and reduces hospitalization for IV therapy.[18] A dry powder formulation of tobramycin (TOBI Podhaler, 112 mg inhaled twice daily) can also be used in 28-day on/off cycles with reduced administration time. Due to minimal systemic absorption, pharmacokinetic monitoring is not necessary with normal renal function. Lower doses of nebulized tobramycin solution for injection have been used in younger children, and *Pseudomonas* eradication studies used 300 mg twice daily in children as young as 6 months.[29]

Aztreonam lysine for inhalation (Cayston) is also used for *P. aeruginosa* suppression in 28-day on/off cycles for CF patients 6 years of age and older.[18] It has been used in children as young as 3 months of age for *P. aeruginosa* eradication.[29] A dose of 75 mg three times daily is given via the Altera nebulizer system, a high-efficiency drug delivery device with shorter administration time.

Nebulized colistin using the IV formulation may be an option in patients with tobramycin-resistant strains or intolerance to

Table 17–3

Target Intravenous Antibiotic Serum Concentrations in Cystic Fibrosis

	Traditional Units of Measurement		SI Units of Measurement	
Antibiotic	**Goal Peak[a] (mcg/mL)**	**Goal Trough[b] (mcg/mL)**	**Goal Peak[a] (μmol/L)**	**Goal Trough[b] (μmol/L)**
Tobramycin, gentamicin	10–12[c]	< 1.5[c]	21–26[c]	< 3.2[c]
	20–40[d]	< 1[d]	42–84[d]	< 2.1[d]
Amikacin	30–40[c]	< 5[c]	51–68[c]	< 8.6[c]
	60–120[d]	< 3[d]	103–206[d]	< 5.1[d]
Vancomycin	–[e]	15–20	–[e]	10–14

Note: Values reported in mcg/mL are numerically equivalent to mg/L.

[a] Peaks calculated 30 minutes after end of infusion for aminoglycosides.

[b] Troughs calculated immediately prior to the time the dose is due.

[c] Goals refer to traditional dosing (every 8 or 12 hours). Higher peaks may be targeted with corresponding lower trough concentrations for aminoglycosides based on center practice.

[d] Goals refer to once-daily (high-dose extended interval) dosing (preferred).

[e] Not routinely measured unless obtained for basis of AUC calculations targeting an AUC:MIC of > 400 for MRSA.

inhaled tobramycin or aztreonam lysine.[30] Pretreatment with albuterol is necessary due to increased risk of bronchoconstriction.

Selection of inhaled antibiotics is based on culture data and patient preference. Alternating inhaled antibiotic regimens are sometimes used in patients with more advanced lung disease.[19] Inhaled antibiotics are typically stopped during acute exacerbations requiring IV therapy because drug delivery is reduced with increased sputum production, and concomitant use of IV aminoglycosides may increase risk of toxicity.[24]

Pharmacokinetic Considerations KEY CONCEPT CF patients have larger volumes of distribution for many antibiotics due to an increased ratio of lean body mass to total body mass and lower fat stores. CF patients also have enhanced total body clearance, although the exact mechanism has not been determined; both renal and extrarenal processes have been proposed.[25]

Because of these pharmacokinetic changes, higher doses of aminoglycosides are needed to achieve target serum levels and adequate tissue penetration.[25] Higher doses of β-lactam antibiotics are also needed to achieve and sustain levels above the MIC.[25] Trimethoprim–sulfamethoxazole displays enhanced renal clearance and hepatic metabolism in the CF population. Higher doses of fluoroquinolones, vancomycin, and linezolid may also be needed to attain inhibitory serum and tissue concentrations against CF pathogens.[25,26]

Although most CF patients have shorter drug half-lives and larger volumes of distribution than non-CF patients, some patients exhibit decreased renal clearance because of concomitant nephrotoxic medications, diabetic nephropathy, or other reasons. Chronic kidney disease is an emerging complication of older adults with CF.[5]

► *Gastrointestinal Therapy*

Pancreatic Enzyme Replacement Therapy (PERT) This is the mainstay of GI therapy. Most enzyme products available in the United States are formulated as capsules containing enteric-coated microspheres or microtablets that escape enzyme inactivation by gastric acid and promote dissolution in the more alkaline duodenum (Table 17–4). Capsules may be opened and the microbeads swallowed with food (for infants and young children), as long as they are not chewed or mixed with alkaline or hot foods (which denature enzymes). Although products may contain similar enzyme ratios, they are not bioequivalent and cannot be interchanged.

PERT is initiated at 1000 units/kg/meal of lipase component (because fats are most difficult to digest) with half-doses given for snacks. Enzymes should be taken at the beginning or divided throughout the meal and must be given with any fat-containing snack. Infants are typically started at 1500 to 2500 units of lipase/120 mL of formula or breast milk and may require division of capsule contents via visual estimation to obtain appropriate doses. Pancreatic enzymes cannot be placed in formula bottles due to inability to pass consistently through the nipple slit. Instead, enzyme microbeads are placed on a small dot of infant applesauce (or moistened infant rice cereal) and administered via infant spoon with subsequent nursing or bottle-feeding to facilitate swallowing. The oral mucosa must be examined afterward to ensure that all enzymes are swallowed because remnant microbeads can cause oral erosions (ulcers).

KEY CONCEPT Titration of PERT dosage is based on control of steatorrhea, stool output, and abdominal symptoms. Infants should have no more than three to four stools per day, whereas older patients should have no more than two to three (children) or one to two (adolescents/adults) well-formed stools per day. Doses are titrated at 2- to 3-week intervals in increments of 150 to 250 units of lipase/kg/meal (or the next easily administered capsule or half-capsule) up to 2500 units/kg/meal. Maximum infant doses are typically 4000 units of lipase/120 mL of formula. Higher doses should be used cautiously due to risk of fibrosing colonopathy observed with doses above 6000 units of lipase/kg/meal for more than 6 months.[16,17] Patients receiving enteral formulas via feeding tubes (either at nighttime or continuously) may receive intermittent doses of oral enzymes. They may also receive enzymes that are administered directly through the feeding tube using a vehicle such as an applesauce bolus, or they may receive crushed enzymes that are given as either intermittent doses via the feeding tube or added to the enteral formula bags in the actual feedings. An *ex vivo* cartridge device containing immobilized lipase (RELiZORB) may also be used with some enteral formulas to predigest fat within the tube feeding apparatus prior to the formula reaching the patient.[17]

Table 17–4

Common Pancreatic Enzyme Replacement Products

Trade Name[a]	Lipase (Units)	Amylase (Units)	Protease (Units)
CREON 3000	3000	15,000	9500
CREON 6000	6000	30,000	19,000
CREON 12,000	12,000	60,000	38,000
CREON 24,000	24,000	120,000	76,000
CREON 36,000	36,000	180,000	114,000
Pancreaze MT 2	2600	10,850	6200
Pancreaze MT 4	4200	24,600	14,200
Pancreaze MT 10	10,500	61,500	35,500
Pancreaze MT 16	16,800	98,400	56,800
Pancreaze MT 20	21,000	83,900	54,700
Pertzye 4000	4000	15,125	14,375
Pertzye 8000	8000	30,250	28,750
Pertzye 16,000	16,000	60,500	57,500
Pertzye 24,000	24,000	90,750	86,250
Viokace[b]	10,440	39,150	39,150
Viokace[b]	20,880	78,300	78,300
Zenpep 3000	3000	14,000	10,000
Zenpep 5000	5000	24,000	17,000
Zenpep 10,000	10,000	42,000	32,000
Zenpep 15,000	15,000	63,000	47,000
Zenpep 20,000	20,000	84,000	63,000
Zenpep 25,000	25,000	105,000	79,000
Zenpep 40,000	40,000	168,000	126,000

[a] The number after a trade name refers to the approximate number of thousands of units of lipase contained per dosage form.

[b] Nonenteric-coated enzyme. Must be given with a gastric acid suppressant. Often administered via feeding tube.

Patients responding poorly to maximal doses of one product may benefit from changing to another product and/or addition of a histamine H_2-receptor antagonist or proton pump inhibitor. Acid suppression may boost the effective enzyme dose if duodenal pH is not alkaline enough to neutralize residual gastric acid and dissolve enteric coating. Acid suppression also treats concomitant gastroesophageal reflux disease, which is common in CF.[16,17]

Fat-Soluble Vitamin Supplementation This is usually required in pancreatic insufficiency. Specially formulated products for CF patients (AquADEKs, DEKAs, MVW Complete Formulation, Choiceful) are usually sufficient to attain normal serum vitamin levels at a dose of 1 mL daily for infants, 1 tablet daily for younger children, and 1 tablet/capsule twice daily for teenagers and adults taken with food and pancreatic enzymes. Additional supplementation (calcium, iron, zinc) may be needed in uncontrolled malabsorption or for replacement of severe vitamin deficiency based on serum vitamin levels, and sodium supplementation is needed in infants.[16,17] Sodium supplementation is usually provided as table salt (1/8 teaspoonful per day if under 6 months of age and 1/4 teaspoonful per day if 6–12 months of age) divided among feedings in infants. Older children will transition to liberally salting their food once eating table food. Appetite stimulants such as cyproheptadine, dronabinol, mirtazapine, or megestrol may be an option for promoting nutrition and weight gain but must be balanced with potential side effects, which can range from drowsiness (cyproheptadine, dronabinol, mirtazapine) to adrenal suppression (megestrol).

Liver Disease Ursodiol 20 mg/kg/day in two divided doses is often used to slow progression of liver disease; however, efficacy data are lacking. It improves bile flow and may displace toxic bile acids that accumulate in a cholestatic liver, stimulate bicarbonate secretion into the bile, and reduce elevated liver enzymes.[7]

Intestinal Obstruction and Constipation Treatment of DIOS consists of enteral administration of polyethylene glycol (PEG) electrolyte solutions. Severe presentations may require surgical resection. Enemas may also be used to facilitate stool clearance. IV fluids are often required to correct dehydration due to vomiting or decreased oral intake. Reevaluation of enzyme adherence and dosing is essential to prevent recurrence, and some patients may require daily PEG administration (MiraLAX) or stimulant laxatives. Oral mineral oil should be avoided due to risk for aspiration.[7]

▶ CF-Related Diabetes

Patients with mild CFRD may be managed with carbohydrate modification if nutritional status is optimal. However, most patients present with poor nutrition and weight loss and require more aggressive treatment. **KEY CONCEPT** Because CFRD results from insulin insufficiency, exogenous insulin replacement is usually required. Many patients can be successfully managed by meal coverage with short- or rapid-acting insulin (regular, lispro, or aspart) dosed per carbohydrate counting. Patients with fasting hyperglycemia or patients receiving nighttime tube feedings typically also require longer acting basal insulin. Regular home glucose monitoring is essential to appropriate therapy. Insulin pump therapy and continuous glucose monitoring offer patients flexibility and reduced frequency of injections and finger sticks. Oral antidiabetic agents have not been studied adequately in CFRD, and routine use is not recommended.[8,9]

▶ Bone Disease and Arthritis

CF patients with low bone mineral density and low serum vitamin D levels may improve bone health through supplemental vitamin D analogs beyond those found in standard CF vitamins. The CF Foundation recommends 25-hydroxyvitamin D levels of at least 30 ng/mL (75 nmol/L) for all patients. For cholecalciferol (or ergocalciferol), a minimum of 400 to 500 IU and 800 to 1000 IU should be taken daily by infants and patients 1 to 10 years of age, respectively. Patients older than 10 years should take 800 to 2000 IU daily. Vitamin D concentrations should be measured annually in the winter for evaluation of dosing.[31] Total weekly or biweekly doses of 12,000 IU for children younger than 5 years of age and 50,000 IU for patients 5 years of age and older may be required to achieve target vitamin D concentrations. Supplemental calcium should be provided if 1300 to 1500 mg of elemental calcium intake cannot be achieved through diet.[9]

Patient Encounter Part 2

The parents received education about CF and met with the multidisciplinary CF team. The team would like to initiate first-line CF therapies because the baby displays symptoms of pancreatic insufficiency (see Part 1). The neonate weighs 2.95 kg and is 51 cm long.

Given this information, what is your assessment of the infant's nutritional status?

What are the treatment goals for this patient?

What nonpharmacologic therapy should be initiated?

What pharmacologic therapy should be initiated?

Antiresorptive agents (oral or IV bisphosphonates) may be used to treat adult CF patients with osteoporosis. Remaining upright daily for 30 minutes after dosing may be difficult for patients needing to perform airway clearance therapy, so products offering less frequent dosing should be considered.[9] Pamidronate 30 mg IV every 3 months or zoledronic acid 5 mg IV once yearly may be considered in adult CF patients. Androgen replacement may benefit bone health in some adult male CF patients with documented hypogonadism.[9]

▶ Precision Therapy

Since the discovery of the CF gene and the CFTR protein defect, research has focused on gene mutation-specific pharmacologic therapy to correct or modulate dysfunctional CFTR protein. Ivacaftor (Kalydeco, VX-770) is a CFTR potentiator that activates defective CFTR at the cell surface and improves CFTR function in patients with gating mutations. Ivacaftor is indicated for CF patients 6 months and older who have at least one mutation in the *CFTR* gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data. Ivacaftor treatment (added to standard CF care) is associated with improved lung function (approximately 10% increase in FEV_1), decreased pulmonary exacerbations, weight gain, and increased quality of life.[18,32] Ivacaftor given alone is not effective for patients homozygous for *Phe508del*. Ivacaftor should not be recommended, prescribed, or dispensed without first verifying that the patient has an appropriate *CFTR* gene mutation that has been identified to be responsive to ivacaftor.

The ivacaftor dose is 150 mg orally every 12 hours for patients aged 6 years and older. Patients 4 months to 5 years of age should receive 25 mg (if 5–6.9 kg), 50 mg (if 7–13.9 kg), or 75 mg (if > 14 kg) orally every 12 hours. Ivacaftor should be given with a fat-containing meal or snack and with PERT if pancreatic insufficient. Dosage must be reduced in moderate-to-severe hepatic impairment (Child-Pugh Class B or C) and when coadministered with moderate or strong CYP3A inhibitors (eg, azole antifungals, clarithromycin, erythromycin). Use with strong CYP3A inducers (eg, rifampin, rifabutin, phenytoin, phenobarbital, carbamazepine) is contraindicated. Ivacaftor therapy is generally well tolerated, although elevated liver enzymes have been reported. Hepatic enzymes should be monitored at least quarterly in the first year of therapy, and slit lamp eye exams should be performed at baseline and annually in pediatric patients to evaluate for potential cataract formation.

Another precision therapy contains a combination of lumacaftor (a CFTR corrector) and ivacaftor (Orkambi, VX-809/VX-770) to treat CF in patients 2 years and older who are homozygous for *Phe508del*. It is associated with a modest increase in FEV$_1$ (3.5%) and has been shown to reduce pulmonary exacerbations by 35%.[32] Lumacaftor stabilizes the CFTR protein so more reaches the cell surface, whereas ivacaftor potentiates ion transport. Lumacaftor/ivacaftor should not be prescribed without first verifying that the patient has two copies of the *Phe508del* gene mutation. Dosing is lumacaftor 400 mg/ivacaftor 250 mg orally every 12 hours for patients aged 12 years and older, lumacaftor 200 mg/ivacaftor 250 mg orally every 12 hours for patients 6 to 11 years of age, and lumacaftor 150 mg/ivacaftor 188 mg orally every 12 hours (≥14 kg) or lumacaftor 100 mg/ivacaftor 125 mg (< 14 kg) orally every 12 hours for patients 2 to 5 years of age. Lumacaftor/ivacaftor should be given with a fat-containing meal or snack and with PERT if pancreatic insufficient. Dosage must be reduced in moderate-to-severe hepatic impairment (Child-Pugh Class B or C). Dose titration may be needed when imitated in patients already on strong CYP3A inhibitors, and use with strong CYP3A inducers is contraindicated. Lumacaftor is also a strong inducer of several CYP enzymes, and interactions with many medications may require dose adjustment or alternative therapy. Hepatic enzymes should be monitored at least quarterly in the first year of therapy, and slit lamp eye exams should be performed at baseline and annually in pediatric patients to evaluate for potential cataract formation. Chest tightness, sometimes severe, has been observed in patients with lower lung function (FEV$_1$ < 40%).[32]

A third precision therapy consisting of tezacaftor and ivacaftor (Symdeko, VX-661/VX-770) is approved for CF patients 6 years and older who are homozygous for *Phe508del* or who have at least one gene responsive to therapy. Clinical outcomes are similar to those seen with lumacaftor/ivacaftor.[32] Oral dosing for patients 12 years and older and patients 6 to 11 years of age (≥ 30 kg) is tezacaftor 100 mg/ivacaftor 150 mg in the morning and ivacaftor 150 mg in the evening. Patients 6 to 11 years of age (< 30 kg) receive oral tezacaftor 50 mg/ivacaftor 75 mg in the morning and ivacaftor 75 mg in the evening. Tezacaftor/ivacaftor should be given with a fat-containing meal or snack and with PERT if pancreatic insufficient. Dosage must be reduced in moderate-to-severe hepatic impairment (Child-Pugh Class B or C) and when coadministered with moderate or strong CYP3A inhibitors. Use with strong CYP3A inducers is contraindicated. Hepatic enzymes should be monitored at least quarterly in the first year of therapy, and slit lamp eye exams should be performed at baseline and annually in pediatric patients to evaluate for potential cataract formation.

The groundbreaking triple modulator therapy consisting of elexacaftor/tezacaftor/ivacaftor (Trikafta), two correctors and a potentiator, is approved for patients with at least one copy of *Phe508del* or at least one gene responsive to therapy. Once approved in all age groups, CFTR modifier therapy will be available for up to 90% of CF patients. This highly effective modulator therapy is associated with an increased FEV$_1$ of 14.3%.[32] Dosing for patients 12 years of age and older and patients 6 to 11 years of age (≥ 30 kg) is elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg in the morning and ivacaftor 150 mg in the evening given orally with a fat-containing meal or snack and with PERT if pancreatic insufficient. Patients 6 to 11 years of age (< 30 kg) receive oral elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg in the morning and ivacaftor 75 mg in the evening. Dosage must be reduced in moderate-to-severe hepatic impairment (Child-Pugh Class B or C) and when coadministered with moderate or strong CYP3A inhibitors. Use with strong CYP3A inducers is contraindicated. As with other modulators, hepatic enzymes should be monitored at least quarterly in the first year of therapy, and slit lamp eye exams should be performed at baseline and annually in pediatric patients to evaluate for potential cataract formation. Clinical studies in younger patients are underway in 2021.

Patient Encounter Part 3

The infant is now 6 months old (weight: 7 kg) and is brought to a routine CF clinic appointment. His parents report that he has had a runny nose with green discharge, cough productive of yellow sputum for the past week, and an intermittent fever of up to 101.3°F (38.5°C) at home. Also, the baby has had some posttussive emesis, reduced oral intake, and has been sleeping more. Vital signs are as follows: BP 82/44 mm Hg, HR 130 beats/min, RR 44/min, 100.8°F (38.2°C), oxygen saturation 94% (0.94). Review of throat cultures since diagnosis reveals the following organisms:

- *Staphylococcus aureus*: sensitive to trimethoprim–sulfamethoxazole, minocycline, linezolid, and vancomycin; resistant to clindamycin, erythromycin, and nafcillin
- *Pseudomonas aeruginosa*: sensitive to ceftazidime, cefepime, piperacillin/tazobactam, aztreonam, meropenem, ciprofloxacin, and tobramycin; resistant to levofloxacin, amikacin, and gentamicin
- *Achromobacter xylosoxidans*: sensitive to trimethoprim–sulfamethoxazole, minocycline, ceftazidime, and piperacillin/tazobactam; resistant to meropenem and ciprofloxacin

The infant has no known drug allergies.

Based on the information available, design an antibiotic regimen for outpatient therapy of this first pulmonary exacerbation.

What antibiotic(s) and dose(s) would you recommend for inpatient therapy?

Develop a monitoring plan to assess antibiotic response.

What other therapy would you recommend?

Multiple agents, including gene and gene-editing therapies, are under investigation for the 10% of patients who do not have a qualifying genetic profile for current CFTR modulator therapies.

OUTCOME EVALUATION

Pulmonary Function

- Monitor for changes in pulmonary symptoms (cough, sputum production, respiratory rate, and oxygen saturation). Symptoms should improve with antibiotics and aggressive airway clearance therapy. PFTs should be markedly increased after 1 week and trend back to preexacerbation levels after 2 weeks of therapy. If improvement lags, 3 weeks of therapy may be needed.
- For IV antimicrobial therapy, obtain serum drug levels for aminoglycosides and/or vancomycin and perform pharmacokinetic analysis. Adjust the dose, if needed, according to the targets in Table 17–3. Obtain follow-up trough levels and serum creatinine at least weekly or more frequently if renal function is unstable.

Gastrointestinal Function

- Monitor short- and long-term nutritional status through evaluation of height, weight, and BMI. Ideally, parameters should be near the normals (50th percentile) for non-CF patients.
- Evaluate the patient's stool patterns. Steatorrhea indicates suboptimal enzyme replacement or noncompliance. Infants

Patient Care Process

Collect Information:

- Conduct a history of prescription, nonprescription, and alternative medications. Review drug allergies and intolerances, especially antibiotics.
- Review the medical history and physical assessment findings with a focus on frequency and quality of cough, sputum production, dyspnea, respiratory rate, oxygen saturations, temperature, and PFT trends. Review the patient's airway clearance methods and order of inhaled therapies. Review the patient's CFTR gene profile.
- Speak with the patient and/or caregivers and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Evaluate for signs and symptoms of pulmonary exacerbation. If present, determine if antibiotics are indicated.
- Review culture and sensitivity tests over the last 1 to 2 years. Review pharmacokinetic history. What antibiotics were used previously? Was response better to a particular regimen?
- Review other available laboratory tests (renal and hepatic function, complete blood count, vitamin levels, IgE level, blood glucose, A1C, bone density). Identify presence of CF comorbidities (eg, diabetes, liver disease, bone disease).
- Determine nutritional status, weight, height, and BMI trends. Assess GI symptoms: quantity and quality of bowel movements, gastroesophageal reflux, bloating, flatulence, or abdominal pain. Are oral supplements or tube feedings being used?
- Evaluate medications for effectiveness, drug interactions, and adverse reactions. Are all appropriate maintenance medications prescribed and dosed appropriately for weight and age?
- Assess adherence, including timing of inhaled medications with respect to airway clearance therapies and timing of enzymes, CFTR modulator therapy, and insulin with regard to meals.

Develop a Care Plan:

- Devise an appropriate IV or oral/inhaled antibiotic regimen for a pulmonary exacerbation. Optimize doses based on pharmacokinetic and pharmacodynamic parameters.
- Optimize maintenance therapies, doses, and schedules that promote efficacy and ease care burden.

Implement the Care Plan:

- Educate the patient and family about any changes in drug therapy, medication administration requirements, and potential side effects. Emphasize importance of therapy adherence.
- Review the patient's practices and technique for self-administration or caregiver-administration of therapies.
- Determine if the patient has insurance coverage, if there are any specialty pharmacy medication access restrictions, and if recommended agents are included on the institution's formulary. Determine if the patient qualifies for any patient assistance programs.

Follow-up: Monitor and Evaluate:

- For antibiotic regimens, evaluate pulmonary symptoms daily if inpatient or every 1 to 2 weeks if outpatient.
- For IV antibiotic regimens, obtain drug levels and perform pharmacokinetic dose adjustments as necessary. Monitor renal function labs at least weekly. Evaluate fluid intake and urine output daily.
- Review physical examination, lab tests, and results of other diagnostic tests to assess changes in clinical status. Assess effectiveness and safety of maintenance therapies at least quarterly.
- Assess medication adherence and access at least quarterly.

should have two to three well-formed stools daily, whereas older children and adults may have one or two stools daily.

- Monitor efficacy of vitamin supplementation through yearly serum vitamin levels. Obtain levels more frequently if treating a deficiency.

CF-Related Diabetes

- Monitor morning fasting and 2-hour postprandial blood glucose in patients with CFRD or those taking systemic corticosteroids. Follow A1C levels on an outpatient basis to assess long-term glucose control. Levels may be falsely low in CF due to a shorter red blood cell half-life.

Abbreviations Introduced in This Chapter

ABPA	Allergic bronchopulmonary aspergillosis
CF	Cystic fibrosis
CFRD	Cystic fibrosis-related diabetes
CFTR	Cystic fibrosis transmembrane regulator
CPT	Chest physiotherapy
DIOS	Distal intestinal obstruction syndrome
FEV$_1$	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HFCC	High-frequency chest compression
IPV	Intrapulmonary percussive ventilation
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
OPEP	Oscillating positive expiratory pressure
PEG	Polyethylene glycol
PERT	Pancreatic enzyme replacement therapy
PFT	Pulmonary function test
PMN	Polymorphonuclear
PT	Prothrombin time
RDA	Recommended daily allowance

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18 Gastroesophageal Reflux Disease

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the underlying causes of gastroesophageal reflux disease (GERD).
2. Understand the difference between typical, atypical, and alarm symptoms.
3. Determine when diagnostic tests should be recommended based on the clinical presentation.
4. Identify the desired therapeutic outcomes for patients with GERD.
5. Recommend appropriate nonpharmacologic and pharmacologic interventions for patients with GERD.
6. Educate patients on appropriate lifestyle modifications and drug therapy issues including adherence, adverse effects, and drug interactions.
7. Formulate a monitoring plan to assess the effectiveness and safety of pharmacotherapy for GERD.

INTRODUCTION

Gastroesophageal reflux is the retrograde, effortless movement of stomach contents into the esophagus. When troublesome symptoms or mucosal damage occurs as a result of this process, this is defined as gastroesophageal reflux disease (GERD).[1,2] Treatment is usually initiated based on symptom presentation rather than laboratory tests or invasive monitoring and consists of various lifestyle interventions and pharmacotherapy. Lack of response to empiric therapies may require further evaluation to identify potential underlying complicating conditions.[1,3]

EPIDEMIOLOGY AND ETIOLOGY

GERD is one of the most common gastrointestinal diagnoses associated with outpatient clinic visits in the United States. Up to 40% of Americans report intermittent GERD symptoms, with around 20% of the US population reporting at least weekly symptoms.[1] GERD symptoms can result in decreased work productivity and morbidity, accounting for approximately 110,000 hospital admissions annually.[4] In 2015, the US annual health-care expenditures for gastrointestinal diseases was $135.9 billion, with $18.1 billion from esophageal disorders.[5] The incidence of GERD complications such as erosive esophagitis and Barrett esophagus increases with age, especially in Caucasian men over 50 years of age with symptoms for more than 10 years.[3,4,6]

The precise etiology of GERD is difficult to determine in most patients. Increased intra-abdominal pressure or decreased lower esophageal sphincter (LES) tone may allow gastric refluxate to enter the esophagus causing GERD symptoms in some patients. These processes can be transient and are often due to physical activity, food, or medications.

PATHOPHYSIOLOGY

Retrograde movement of gastric contents into the esophagus, oral cavity, or lungs is the origin of symptoms or complications that define GERD. Reflux is normally prevented through muscle tone of the LES. Reduction in LES function or tone may allow reflux of gastric contents into the esophagus. Other physiologic and mucosal defense mechanisms may also become compromised and affect the refluxate composition and development of GERD. Such mechanisms include slowed esophageal clearance, decreased salivary buffering, impaired mucosal resistance, delayed gastric emptying, and increased intra-abdominal pressure.

Lower Esophageal Sphincter Pressure

In the normal state, the LES maintains a tonic pressure that separates gastric contents from the esophagus, relaxing during swallowing to allow esophageal contents to pass into the stomach. Decreased LES pressure can occur via spontaneous relaxation, increased intra-abdominal pressure, and an atonic LES. Spontaneous relaxation of the LES occurs during vomiting, belching, retching, and esophageal distention. Transient increases in intra-abdominal pressure may occur during straining, exercise, bending over, or Valsalva maneuver. An atonic LES allows unopposed passage of refluxate from the stomach into the esophagus. A hiatal hernia may cause or worsen GERD symptoms by increasing intragastric pressure and decreasing LES tone. Some foods and medications may worsen LES dysfunction, whereas others can directly irritate the esophageal mucosa (Table 18–1).

Esophageal and Mucosal Protection

Several normal processes protect the esophageal tissue and mucosal barrier from irritants such as refluxed gastric fluid. Swallowing enhances esophageal clearance by increasing salivary flow, which contains bicarbonate that buffers the acidic gastric contents. This usually maintains a neutral esophageal pH; however, salivary production decreases during sleep and in older persons, which may contribute to GERD symptoms. Mucus-secreting glands in the esophageal mucosa and submucosa also help neutralize acidic refluxate by releasing bicarbonate. Most patients with GERD do not produce abnormally large amounts of acid but slowed esophageal clearance of gastric contents increases contact time of

Table 18–1

Foods and Medications That May Worsen GERD Symptoms

Decreased LES Pressure

Foods

Fatty meals
Carminatives (eg, peppermint)
Chocolate
Coffee, cola, tea
Garlic
Onions
Chili peppers
Alcohol

Medications

Anticholinergics
Barbiturates
Caffeine
Dihydropyridine calcium channel blockers
Dopamine
Estrogen
Nicotine
Nitrates
Progesterone
Tetracycline
Theophylline

Direct Irritants to the Esophageal Mucosa

Spicy foods
Orange juice
Tomato juice
Coffee
Tobacco
Aspirin
Bisphosphonates
NSAIDs
Iron
Quinidine
Potassium chloride

GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter; NSAIDs, nonsteroidal anti-inflammatory drugs.

Adapted from May D, Thiman ML, Rao SSC. Gastroesophageal reflux disease. In: DiPiro JT, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill, 2020; with permission.

refluxate with esophageal mucosa, possibly leading to symptoms or erosion. Refluxate contains gastric acid, pepsin, bile acids, and pancreatic enzymes that promote mucosal erosion and GERD symptoms. The frequency and severity of symptoms do not correlate with the degree of esophageal damage.[4]

Gastric Emptying and Increased Abdominal Pressure

Gastric fluid volume depends on the rate of gastric acid secretion, stomach emptying time, and the amount of gastric fluid that refluxes from the duodenum into the stomach. Prolonged stomach emptying time increases the volume of fluid in the stomach, thereby increasing intragastric pressure. Increased gastric volume can increase the amount and frequency of fluid being refluxed, which may cause or worsen GERD symptoms. Factors that increase gastric volume and/or decrease gastric emptying, such as smoking and high-fat meals, are often associated with reflux.

Obesity is a major risk factor for developing GERD symptoms and complications. Patients with GERD and abdominal obesity have an increased risk of Barrett esophagus, esophageal adenocarcinoma, and erosive esophagitis.[4] Morbidly obese patients may also have more transient LES relaxations, incompetent LES function, and impaired esophageal motility.[7] Reduction in body mass index by at least 3.5 kg/m^2 or decreased waist circumference may decrease or eliminate GERD symptoms.[3,4,8]

Patient Encounter 1, Part 1

A 23-year-old African American man reports of heartburn and regurgitation 3 days/week. He reports no recent weight loss. He is attending college in an engineering program, and his diet consists of mostly fast food, pizza, and energy drinks. He has been self-medicating with OTC calcium carbonate tablets and famotidine for the last month with no improvement. His weight is 100 kg, and his height is 5 ft 11 in (180 cm). He has no known drug allergies.

Are this patient's symptoms consistent with GERD?

Would the patient's symptoms be described as typical, atypical, or alarm?

What risk factors does he have that may worsen GERD symptoms?

CLINICAL PRESENTATION AND DIAGNOSIS

KEY CONCEPT Patients with GERD may have symptoms classified as (a) typical, (b) atypical, or (c) alarm (see accompanying box Clinical Presentation of GERD).[3]

Diagnosis of GERD

Diagnosis of GERD is suggested when heartburn or regurgitation symptoms occur two or more times per week.[8] Initial diagnostic testing should be reserved for patients with atypical or alarm symptoms. **Endoscopy** is preferred for assessing mucosal injury and to identify complications such as **esophageal strictures** (which can cause difficulty swallowing) and erosive esophagitis due to repeated and prolonged exposure to gastric refluxate. A mucosal biopsy should be taken to identify Barrett esophagus, which is associated with an increased risk of developing esophageal cancer. Endoscopy may also be performed in patients not responding to an adequate trial of a twice-daily proton pump inhibitor (PPI).[1,3] **Ambulatory esophageal reflux monitoring** identifies excessive esophageal acid exposure and the frequency of reflux episodes. **Esophageal manometry** may be beneficial for patients who have failed twice-daily PPIs and have normal endoscopic findings or those contemplating antireflux surgery. These tests help to determine whether symptoms are acid related and

Clinical Presentation of GERD

Symptoms

- *Typical symptoms* (may be aggravated by activities that worsen reflux such as recumbent position, bending over, or eating a high-fat meal): Heartburn, often described as a substernal sensation of warmth or burning rising up from the abdomen that may radiate to the neck and may be waxing and waning in character; hypersalivation; **regurgitation**; belching.
- *Atypical symptoms* (associated with GERD, but causality should only be considered if typical symptoms are also present): chronic cough, laryngitis, hoarseness, wheezing, noncardiac chest pain, asthma (~50% with asthma have GERD).
- *Alarm symptoms* (may indicate GERD complications such as Barrett esophagus, esophageal strictures, or esophageal adenocarcinoma and require further diagnostic evaluation): **Dysphagia**, **odynophagia**, weight loss, bleeding.

may also be useful in patients not responding to acid suppression therapy or prior to antireflux surgery.

GERD and dyspepsia (often occurring with peptic ulcer disease) commonly overlap in presentation. Dyspepsia is characterized predominantly by epigastric pain but may also be associated with other upper gastrointestinal (GI) symptoms including heartburn.[9] Care should be taken when evaluating patient symptom history to differentiate GERD from dyspepsia due to differing treatment strategies. Patients reporting epigastric pain for at least 1 month should be evaluated for dyspepsia. Although *Helicobacter pylori*-positive patients may present with gastritis, symptomatic reflux does not correlate well with active *H. pylori* infection. Routine screening for *H. pylori* in patients with GERD is controversial and not currently recommended.[3,10,11]

TREATMENT

Desired Outcomes

KEY CONCEPT The goals of GERD treatment are to alleviate symptoms, decrease the frequency of recurrent disease, promote healing of mucosal injury, and prevent complications.

General Approach to Treatment

KEY CONCEPT Treatment for GERD involves one or more of the following modalities: (a) patient-specific lifestyle changes, (b) pharmacologic intervention primarily with acid-suppressing therapy, or (c) antireflux surgery (Table 18–2).[3,12] The best initial therapeutic option depends on the frequency, severity, and type of symptoms and need for further diagnostic evaluation (Figure 18–1).[1,3,13,14]

Nonpharmacologic Therapy

▶ *Lifestyle Modifications*

Although most patients do not respond adequately to lifestyle changes alone, it is helpful to maintain these changes throughout therapy to reduce the need for long-term pharmacologic therapies. The most beneficial lifestyle changes include (a) losing weight if overweight or obese, particularly a reduction in waist circumference, and (b) elevating the head of the bed with a foam wedge if symptoms are worse when recumbent. Elevating the head of the bed decreases the contact time of gastric acid with the esophageal mucosa at night.[15]

Other lifestyle modifications should be considered based on patient circumstances. These might include (a) eating smaller meals and avoiding meals 3 hours before sleeping, (b) avoiding foods or medications that exacerbate GERD, (c) smoking cessation, and (d) avoiding alcohol. The patient's medication and food histories should be evaluated to identify potential factors that may exacerbate GERD symptoms (Table 18–1).

▶ *Surgical Treatment*

While pharmacologic therapies are typically the treatment of choice following lifestyle modifications, antireflux surgical options may be considered when there is a large hiatal hernia, evidence of aspiration or cardia dysfunction, or when pharmacologic management is undesirable due to side effects or adherence challenges in patients with well-documented GERD.[8,10] The goal of surgery is to reestablish the antireflux barrier, position the LES within the abdomen where it is under positive (intra-abdominal)

Table 18–2

Therapeutic Approach to GERD in Adults

Recommended Regimen	Brand Name	Oral Dose	Comments
Intermittent, Mild Heartburn (individualized lifestyle modifications + patient-directed therapy with antacids and/or nonprescription H$_2$RA *or* PPI)			
Individualized lifestyle modifications			Lifestyle modifications should be individualized for each patient
Patient-directed therapy with antacids (≥ 12 years old)			
Magnesium hydroxide/aluminum hydroxide with simethicone	Maalox	10–20 mL as needed or after meals and at bedtime	If symptoms are unrelieved with lifestyle modifications and nonprescription medications after 2 weeks, patient should seek medical attention; do not exceed 16 teaspoonfuls per 24 hours
Antacid/alginic acid	Gaviscon	2–4 tablets or 10–20 mL after meals and at bedtime	Note: Content of alginic acid varies greatly among products; the higher the alginic acid, the better
Calcium carbonate	Tums	500 mg, 2–4 tablets as needed	
Patient-directed therapy with nonprescription H$_2$RA (up to twice daily) (≥ 12 years old)			
Cimetidine Famotidine Nizatidine	Tagamet HB Pepcid AC Axid AR	200 mg 10–20 mg 75 mg	If symptoms are unrelieved with lifestyle modifications and nonprescription H$_2$RA after 2 weeks, patient should seek medical attention
Patient-directed therapy (> 18 years old) with nonprescription PPI (taken once daily)			
Esomeprazole Lansoprazole Omeprazole Omeprazole/sodium bicarbonate	Nexium 24HR Prevacid 24HR Prilosec OTC Zegerid OTC	20 mg 15 mg 20 mg 20 mg/1100 mg	If symptoms are unrelieved with lifestyle modifications and nonprescription PPI after 2 weeks, patient should seek medical attention

(*Continued*)

Table 18–2

Therapeutic Approach to GERD in Adults (*Continued*)

Recommended Regimen	Brand Name	Oral Dose	Comments
Symptomatic Relief of GERD (individualized lifestyle modifications + prescription-strength H$_2$RA or PPI)			
Individualized lifestyle modifications			Lifestyle modifications should be individualized for each patient
Prescription-strength H$_2$RA			
Cimetidine (off-label use)	Tagamet	400 mg four times daily or 800 mg twice daily	• For typical symptoms, treat empirically with prescription-strength acid suppression therapy • If symptoms recur, consider maintenance therapy. Note: Most patients require standard doses for maintenance therapy
Famotidine	Pepcid	20 mg twice daily	
Nizatidine	Axid	150 mg twice daily	
Prescription-strength PPI			
Dexlansoprazole	Dexilant	30 mg once daily for 4 weeks	• For typical symptoms, treat empirically with prescription-strength acid suppression therapy • Patients with moderate-to-severe symptoms should receive a PPI as initial therapy • If symptoms recur, consider maintenance therapy
Esomeprazole	Nexium	20–40 mg once daily	
Lansoprazole	Prevacid	15 mg once daily	
Omeprazole	Prilosec	20 mg once daily	
Omeprazole/sodium bicarbonate	Zegerid	20 mg once daily	
Pantoprazole (Off-label use)	Protonix	40 mg once daily	
Rabeprazole	Aciphex	20 mg once daily	
Healing of Erosive Esophagitis or Treatment of Moderate-to-Severe Symptoms or Complications (individualized lifestyle modifications + high-dose H$_2$RA *or* PPI *or* antireflux surgery)			
Individualized lifestyle modifications			Lifestyle modifications should be individualized for each patient
PPI (up to twice daily for up to 12 weeks)			
Dexlansoprazole	Dexilant	60 mg daily	• For atypical or alarm symptoms, obtain endoscopy with biopsy to evaluate mucosa • If symptoms are relieved, consider maintenance therapy. PPIs are the most effective maintenance therapy for patients with atypical symptoms, complications, and erosive disease. Start with twice-daily PPI therapy if reflux chest syndrome present • Patients not responding to pharmacologic therapy should be evaluated via manometry and/or ambulatory reflux monitoring • Twice daily dosing of PPIs is considered off-label use
Esomeprazole	Nexium	20–40 mg daily	
Lansoprazole	Prevacid	30 mg once or twice daily	
Omeprazole	Prilosec	20 mg once or twice daily	
Rabeprazole	Aciphex	20 mg once or twice daily	
Pantoprazole	Protonix	40 mg once or twice daily	
High-dose H$_2$RA (for 8–12 weeks)			
Cimetidine	Tagamet	400 mg four times daily or 800 mg twice daily	Note: If high-dose H$_2$RA needed, may consider using PPI to lower cost, increase convenience, and increase tolerability Note: Four times daily use is considered off-label for nizatidine
Famotidine	Pepcid	20–40 mg twice daily	
Nizatidine	Aciphex	150 mg two–four times daily	
Interventional therapy			
Antireflux surgery			

GERD, gastroesophageal reflux disease; H$_2$RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

Note: Ranitidine was withdrawn from the market by the FDA in April 2020.

Adapted from: May D, Thiman M:L, Rao SSC. Gastroesophageal reflux disease. In: DiPiro JT, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill, 2020; with permission.

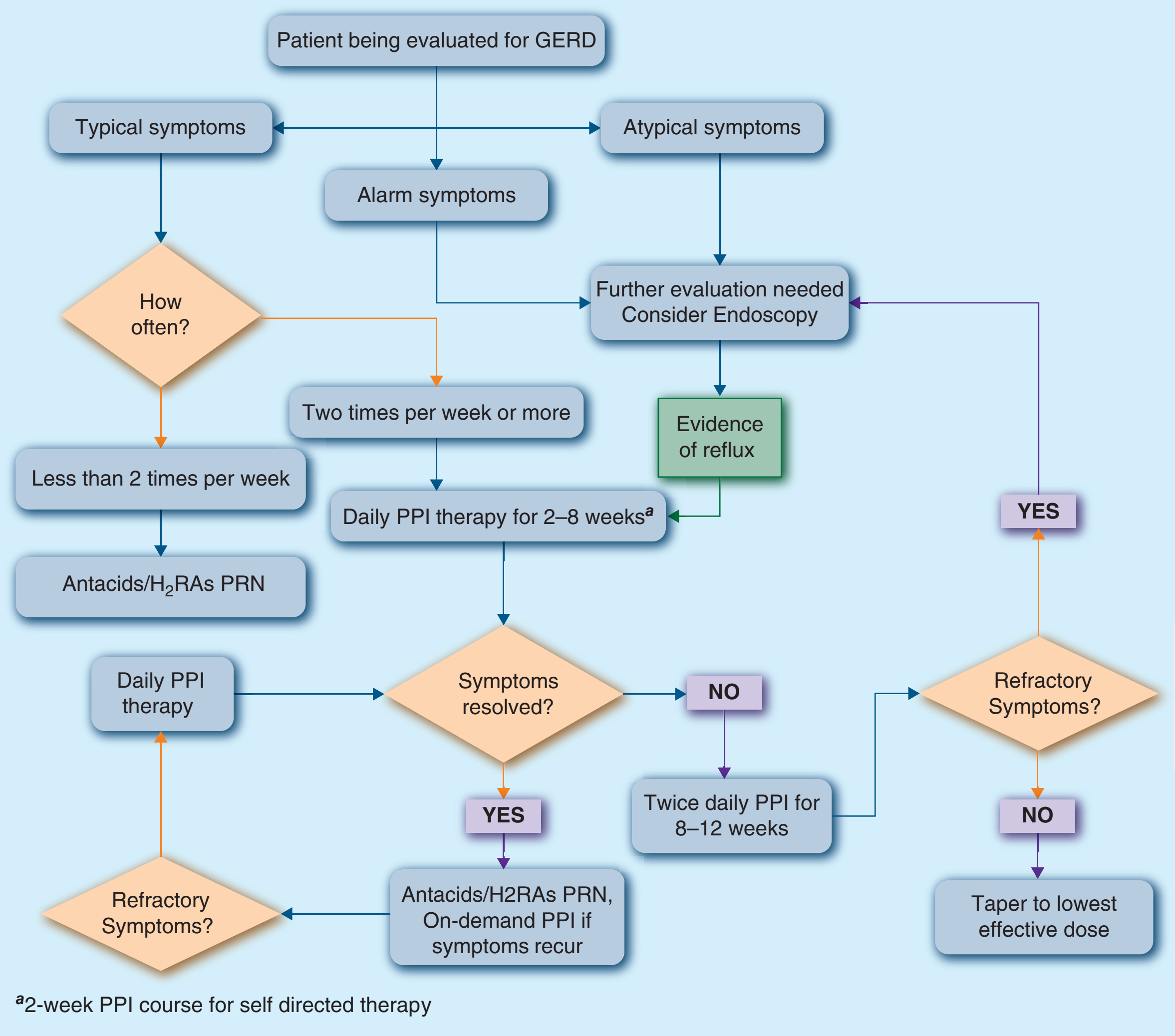
Patient being evaluated for GERD
Typical symptoms
Atypical symptoms
Alarm symptoms
How often?
Further evaluation needed Consider Endoscopy
Two times per week or more
Evidence of reflux
Less than 2 times per week
Daily PPI therapy for 2–8 weeks[a]
YES
Antacids/H2RAs PRN
Daily PPI therapy
Symptoms resolved?
NO
Refractory Symptoms?
YES
Twice daily PPI for 8–12 weeks
NO
Antacids/H2RAs PRN, On-demand PPI if symptoms recur
Taper to lowest effective dose
Refractory Symptoms?
[a]2-week PPI course for self directed therapy

FIGURE 18–1. GERD treatment algorithm for adults. (GERD, gastroesophageal reflux disease; H_2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; PRN, as needed.)

pressure, and close any associated hiatal defect. Surgical options are effective in reducing GERD symptoms, with as many as 90% of patients symptom free after 10 years, and up to 60% remaining off PPIs at 17 years. Other studies have shown antireflux surgery provided more symptom control than omeprazole in patients with esophagitis in a 7-year follow-up study.[16] However, the evidence for surgery is not as strong in patients who do not respond to PPI therapy.[3,10] Roux-en-Y gastric bypass has been shown to reduce symptoms of GERD in obese patients; however, not all forms of bariatric surgery, such as vertical banded gastroplasty, have been shown to improve GERD symptoms.[3,17]

Fundoplication is frequently employed for surgical intervention; it increases LES pressure by wrapping the fundus of the stomach around the distal esophagus; the wrap may include the total esophageal circumference (Nissen fundoplication), only the posterior circumference (Toupet), or only the anterior circumference (Dor). Other forms of surgical intervention include magnetic sphincter augmentation, such as the LINX procedure, which involves implanting a band of interlinked titanium beads with magnetic cords around the LES to maintain LES pressure.[18] Alternatives include LES stimulators that are surgically inserted to modulate LES pressures and reduce refluxate from the stomach.[19] Endoscopic options include radiofrequency application at the esophagogastric junction and transoral incisionless fundoplication, both of which have shown limited success in reducing PPI use and GERD symptoms.[18]

Surgical options may be considered at any time during therapy; however, surgery is not recommended for patients who respond to adequate PPI therapy. Surgical therapies have significant inherent risks including mortality; therefore, it is critical to inform patients of the benefits and risks of procedures and select the most appropriate modality carefully.[3]

Pharmacologic Therapy

Pharmacologic therapies for GERD typically involve increasing the pH of gastric contents through either direct gastric acid neutralization or reducing acid production through inhibition of stimulation pathways, thereby reducing GERD symptoms and tissue damage. Pharmacologic options can be stratified by effectiveness: antacids are inferior to histamine-2 receptor antagonists (H_2RAs), and H_2RAs decrease acid secretion less than PPIs.[3]

▶ *Antacids and Alginic Acid*

Antacids are useful for intermittent treatment of GERD symptoms and can be used for patients with infrequent typical reflux symptoms. They are effective for immediate, symptomatic relief but require frequent dosing (Table 18–2). Aluminum or magnesium-containing antacids may result in electrolyte abnormalities, particularly in patients with renal impairment. Antacids are usually well tolerated, and potential side effects include constipation or diarrhea depending on the formulation being used. Antacids may also chelate with medications such as fluoroquinolones, tetracyclines, iron products, and thyroid hormones; therefore, doses should be separated by several hours to avoid decreased efficacy.

Alginic acid creates a viscous barrier that can aid in acid neutralization and is often used in combination with antacids.[18]

▶ *Histamine-2 Receptor Antagonists*

The H_2RAs (cimetidine, famotidine, nizatidine) decrease acid secretion by blocking histamine$_2$-receptors in gastric parietal cells. H_2RAs provide relief from typical acute GERD symptoms and can also be administered prophylactically. H_2RAs are more effective than antacids at controlling chronic GERD symptoms but less effective than PPIs. H_2RAs may be dosed intermittently or on a scheduled basis depending on the degree of symptom control (Table 18–2).

H_2RAs are generally well tolerated; side effects are mild and include headache and nausea. Cimetidine is a weak inhibitor of the cytochrome P-450 system with many common drug interactions; other H_2RAs have limited drug interactions. Cimetidine also has unique adverse effects such as gynecomastia and vitamin B_{12} deficiency, which limit patient tolerance during chronic therapy.[20] Most H_2RAs are renally eliminated and may require dose adjustment in renal dysfunction.

▶ *Proton Pump Inhibitors*

KEY CONCEPT PPIs (eg, omeprazole, lansoprazole) block gastric acid secretion by inhibiting gastric H^+/K^+-adenosine triphosphatase in gastric parietal cells, producing a profound, long-lasting antisecretory effect capable of maintaining the gastric pH above 4, even during postprandial acid surges. Primary uses of PPIs are treating frequent reflux symptoms and healing of gastric or esophageal ulcerations. **KEY CONCEPT** PPIs provide significant reduction in gastric acid and the greatest relief of symptoms, especially in patients with moderate-to-severe GERD, with high rates of healing erosive disease. PPIs are available as both prescription and nonprescription products with various formulations available (Table 18–2).

Because PPIs degrade in acidic environments, they are typically formulated in delayed-release capsules or tablets. For patients unable to swallow intact capsules (including children) or those with nasogastric tubes, the capsule contents can be mixed in applesauce or orange juice. Esomeprazole pellets can be mixed with water prior to administration.[21]

Most patients should be instructed to take their PPI in the morning, 30 to 60 minutes before breakfast to maximize efficacy. Due to their slow onset of action, PPIs are most effective when taken on a scheduled basis. Patients requiring a second dose if nighttime symptoms are predominant should take the dose before the evening meal. Dexlansoprazole and the combination product omeprazole–sodium bicarbonate may be taken without regard to food.[12] All PPIs can decrease the absorption of medications that require an acidic environment to be absorbed (eg, dabigatran, encapsulated itraconazole, dipyridamole) and are metabolized by the cytochrome P-450 system to some extent.[22,23]

PPIs are generally well tolerated; the most common side effects are headache and GI effects such as diarrhea and nausea. Several concerns have been raised about consequences of long-term PPI use. Renal complications (acute kidney injury and chronic kidney disease), bone fractures, and dementia have been reported from retrospective observational studies and case reports; however, prospective data are limited and additional study is needed to determine causality.[24] Reduced absorption of micronutrients such as calcium, magnesium, and vitamin B_{12} with long-term use has also been reported in observational studies; however, routine screening and supplementation of these vitamins and minerals based solely on chronic PPI use is not warranted.[3,10,13] In patients with documented hypocalcemia, it is reasonable to replete calcium with the citrate rather than the carbonate salt due to improved absorption in a less acidic environment.[25]

Concerns for drug interactions with clopidogrel and PPIs that inhibit CYP 2C19 were initially raised by pharmacodynamic studies showing possible attenuation of clopidogel's antiplatelet function. Clopidogrel is a prodrug requiring a two-step activation via CYP 2C19, which may be competitively depleted due to metabolism of PPIs.[26,27] However, the 2010 COGENT study found no meaningful interaction or increase in the incidence of myocardial infarction in patients who used omeprazole with aspirin and clopidogrel.[28] Although the COGENT study had several limitations, the interaction between clopidogrel and PPIs is not considered to be clinically significant, and use of PPIs may decrease GI-related events such as upper GI hemorrhage when used with dual antiplatelet agents. Use of a PPI with clopidogrel should be considered based on the individual patient's cardiovascular and bleeding risk. If patients or providers wish to avoid the combination, alternatives include switching to a P2Y12 inhibitor not activated by CYP2C19, switching to a PPI with less CYP2C19 metabolism, or changing to an H_2RA.[29]

Infectious complications attributed to chronic PPI use include spontaneous bacterial peritonitis, small intestinal bacterial overgrowth, *Clostridium difficile* infection, and pneumonia.[30] Studies have been mostly small observational trials attributing a low-to-moderate overall increased infection risk with PPI treatment. The potential risks of chronic PPI use must be evaluated on an individual basis to guide clinical decisions.

▶ *Prokinetic Agents and Sucralfate*

Metoclopramide, a central dopamine antagonist, accelerates gastric emptying and can increase LES pressure. Metoclopramide has been studied for GERD symptom relief in conjunction with a PPI; however, potential side effects can be significant and include extrapyramidal effects and tardive dyskinesia.[3] Domperidone is a peripherally acting dopamine antagonist that does not have central nervous system toxicities; however, it is not approved for use in the United States and requires monitoring for QT prolongation. In patients without gastroparesis, there is no clear role for the use of prokinetic agents for treatment of GERD.[3]

Sucralfate, a nonabsorbed aluminum salt of sucrose octasulfate, has limited value for treating GERD. Sucralfate is suboptimal compared with PPI therapy and has no role in nonpregnant patients with GERD.[3]

Initial Therapy of GERD

▶ *Self-directed Therapy*

Many patients who have heartburn symptoms two or more times per week may successfully self-treat with a short-term (maximum 2-week) course of nonprescription PPI therapy. Although this strategy is neither sensitive nor specific for diagnostic purposes, it is a reasonable initial option to achieve symptom control. Patients experiencing symptoms beyond the 2-week course should be evaluated by a provider.[8]

Patient Encounter 1, Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: ADHD

FH: Mother has GERD, Father has hypertension

SH: Currently in his final year in college. Lives in an apartment with two other roommates. Does not smoke. Reports drinking about six alcoholic beverages per week

Meds: Dexmethylphenidate 20 mg daily

ROS: (+) Heartburn, regurgitation; (–) chest pain, nausea, vomiting, diarrhea, weight loss, change in appetite, shortness of breath or cough

PE: WNL

VS: BP 126/78 mm Hg, P 82 beats/min, RR 16 breaths/min, T 37°C (98.6°F)

CV: RRR, normal S_1, S_2; no murmurs, rubs, or gallops

Abd: Soft, nontender, nondistended; (+) bowel sounds, (–) hepatosplenomegaly, heme (–) stool

Does this patient require further diagnostic evaluation based on his clinical presentation? If so, which procedure would you recommend?

What nonpharmacologic and pharmacologic changes would you recommend for his GERD therapy?

▶ *Provider-directed Therapy*

On presentation to a health-care provider, patients may have already attempted a nonprescription trial of self-directed therapy with all three of the major pharmacologic classes. After confirmation of a GERD diagnosis, a trial of a scheduled PPI for 8 weeks is typically recommended, monitoring for symptomatic improvement. Most patients with nonerosive GERD respond positively to a PPI trial and therefore should be evaluated for an appropriate long-term maintenance therapy. Adherence and appropriate administration should be monitored throughout therapy. For patients with refractory nocturnal symptoms or symptoms not controlled with daily therapy, a trial of twice-daily PPIs may provide benefit.[13]

Patients with erosive esophagitis on endoscopy should be treated with at least 8 weeks of twice-daily PPI therapy.[3] Maintenance therapy in these patients should be individualized after the initial treatment period; if PPIs are continued, they should be used at the lowest effective dose and schedule.[3]

Maintenance GERD Therapy

KEY CONCEPT Maintenance therapy may be necessary in patients with refractory symptoms while on maximal acid suppression (Table 18–2).[3,10,13] **KEY CONCEPT** Adding an H_2RA to a PPI regimen may provide initial benefit for refractory symptoms but may result in tachyphylaxis with continued use. While maintenance daily PPI therapy may be necessary in some patients, on-demand PPI dosing may also be effective.[31] On-demand therapy consists of stopping PPI therapy upon resolution of GERD symptoms, with reinitiation of therapy for 2 to 4 weeks if symptoms occur two or more times within 7 days while off therapy.[13] In a large prospective study of GERD patients (most of whom had erosive esophagitis) who used on-demand therapy, 70% had 0 or 1 relapse and only 30% changed to chronic daily PPI therapy after almost 1 year of follow-up.[32] Other studies found that on-demand therapy can decrease PPI exposure by 60% to 80%, with more than 80% of patients being willing to continue the dosing strategy when given the option.[33]

KEY CONCEPT Patients who wish to stop long-term PPI therapy should be slowly titrated off using a stepwise or prolonged taper due to the potential for rebound gastric acid hypersecretion with sudden withdrawal. Rebound hypersecretion can occur with continual PPI use for at least 2 months. For these reasons, the PPI dose and frequency should be tapered slowly, using H_2RAs for breakthrough symptoms. The duration of the taper must be individualized; rebound hypersecretion symptoms can last 3 months or longer after PPI discontinuation.[34]

Special Populations

▶ *Infants and Children with GERD*

Reflux is a common physiologic process in infants that may occur several times a day with no clinical consequence; however, as with adults, GERD is present when symptoms become troublesome or if complications are present.[35,36] Regurgitation is common in infants and may occur daily in as many as 50% of infants younger than 3 months.[35] Most babies who "spit up" are "happy spitters"; they are comfortable, gaining weight, and have no breathing problems caused by vomiting. More troublesome symptoms that require further investigation include vomiting, apnea, poor weight gain, sleep disturbances, and refusing to eat.[35,36]

Reflux episodes are common during transient LES relaxations not related to swallowing because of developmental immaturity of the LES.[35] Other causes include impaired luminal clearance of gastric acid and infant diet. Formula-fed infants are more likely than breastfed infants to exhibit GERD symptoms.[37] Children with neurologic impairment and impaired swallowing, obesity, repaired congenital abnormalities of the esophagus, cystic fibrosis, or hiatal hernia are at a higher risk for developing GERD.[35]

Patient Encounter 2

A 65-year-old, 5 ft 2 in (157 cm), 141-kg woman with a history of hypertension, diabetes, asthma, and GERD presents for her primary care appointment after 2 years of taking esomeprazole 20 mg daily. Her other medications include amlodipine 5 mg daily, albuterol inhaler as needed, and metformin 500 mg twice daily. The patient does not smoke or consume alcohol. Despite good adherence to her PPI regimen, the patient reports having heartburn three times a week. Her primary care physician wants to address the GERD and asks for your recommendations for better symptom control.

VS: BP 140/72 mm Hg, P 80 beats/min, RR 18 breaths/min, T 37°C (98.6°F)
Laboratory values are within normal limits; A1C 5.9% (0.059; 41 mmol/mol Hb).

What nonpharmacologic treatment options are available for treating this patient's symptoms?

Create a pharmacotherapy plan for this patient.

What counseling points should be discussed with the patient regarding any regimen change?

How would you monitor for effectiveness of the treatment plan?

Patient Encounter 3

A 23-year-old woman presents to the pharmacy counter with a bottle of over-the-counter omeprazole to purchase. The patient reports that she is pregnant (approximately 12-week gestation) and has been having occasional heartburn (about one time per week).

What is the most appropriate treatment recommendation for this patient?

What counseling points should be discussed with the patient regarding safety of medication use in pregnancy?

Lifestyle modifications should be emphasized in pediatric patients with uncomplicated GERD. Symptoms usually resolve by 12 to 18 months of life and often respond to supportive therapy, including dietary adjustments such as smaller meals and more frequent feedings. Milk protein allergy in infants can mimic the presentation of GERD, so changes in maternal diet such as restricting milk may be useful in breastfed infants, switching to an extensively hydrolyzed protein or amino acid-based formula, or thickening infant formula with rice cereal. However, excessive thickening of infant formula is discouraged, particularly in preterm infants due to concerns of increased risk for necrotizing enterocolitis.[36] Postural management (ie, positioning the infant in an upright position, especially after meals) may be helpful but should not be used to treat GERD symptoms in sleeping infants. In older children, as with adults, maintaining a healthy body weight is recommended.[35]

If a 2- to 4-week trial of lifestyle modifications is not effective, medical therapy may be indicated. Acid suppression with a PPI is the mainstay of pharmacologic therapy for pediatric GERD.[35] Monotherapy with an H_2RA can be used if PPIs are unavailable or contraindicated in specific patients. A 4- to 8-week course can be attempted, followed by a taper. If symptoms return or if the patient is unable to discontinue the PPI (or H_2RA), evaluation by a pediatric gastroenterologist is recommended, and an endoscopy may be required.[35] Chronic use of antacids or routine use of prokinetics or sucralfate is not recommended.

Increased use of PPIs in children has led to concerns because long-term safety is unknown. Therefore, clinicians must carefully weigh potential risks versus benefits along with appropriate indications for therapy and duration of treatment.[38]

▸ *GERD During Pregnancy*

GERD is common during pregnancy, and 30% to 50% of pregnant women report heartburn symptoms. Lifestyle modifications such as eating smaller meals can reduce heartburn and regurgitation. Mild-to-moderate GERD symptoms can be treated with antacids that have limited systemic absorption, such as calcium, magnesium, and aluminum. Antacids containing magnesium trisilicate specifically should be avoided due to risk of respiratory distress, cardiovascular impairment, hypotonia, and nephrolithiasis if used for long periods of time at high doses. Also, compounds containing sodium bicarbonate should be avoided due to risk of metabolic alkalosis in both the mother and the fetus, as well as precipitating fluid overload.[39] Pregnant patients with severe, frequent heartburn can be started on a PPI. A large retrospective

Patient Care Process

Collect Information:

- Perform a medication history to determine use of prescription, nonprescription, and dietary supplements.
- Identify patient allergies and intolerances that may affect current or planned pharmacotherapy.
- Review the patient's medical and surgical history for issues that may be related to GERD.

Assess the Information:

- Determine whether the patient is taking medications or eating foods that may worsen GERD symptoms (Table 18–1).
- Document severity, characteristics, and frequency of GERD symptoms (eg, typical or alarm symptoms).
- Assess the efficacy, safety, and patient adherence of current therapies and identify any significant adverse effects or interactions.

Develop a Care Plan:

- Implement lifestyle modifications that the patient is willing to do to reduce GERD symptoms.
- Decide if self-treatment is an option or if the patient should be referred to a physician.
- Choose medications and doses that are appropriate considering symptoms, drug or food interactions, and the patient's ability to obtain the chosen therapies that will likely improve quality of life.

Implement the Care Plan:

- Educate the patient about the chosen drug therapy including medication administration, potential adverse effects, and follow-up parameters.
- Educate the patient about symptoms that suggest the presence of complications requiring immediate medical attention, such as dysphagia or odynophagia.
- Discuss the importance of weight loss and dietary changes (if appropriate) for reducing GERD symptoms.
- Address any patient concerns about the GERD management plan.

Follow-up: Monitor and Evaluate:

- Instruct the patient on the proper time for reassessment if symptoms have not resolved.
- Review medication adherence and timing of doses.
- Monitor for adverse drug effects and determine a plan if symptoms recur.
- Refer patients with atypical or alarm symptoms to their physician for further diagnostic evaluation.
- Determine if long-term maintenance therapy is necessary after completion of the initial course of therapy.

cohort of over 5000 patients found no increase in the number of birth defects in infants exposed to PPIs in utero.[39,40]

OUTCOME EVALUATION

- Monitor for symptom relief and the presence of symptoms.
- Record the frequency and severity of symptoms by interviewing the patient after 4 to 8 weeks of acid-suppressing therapy. Continued symptoms may indicate the need for long-term maintenance therapy.
- **KEY CONCEPT** Review the patient profile for drugs that may aggravate GERD.
- Monitor for adverse drug reactions, drug–drug interactions, and adherence.
- Reassess the need for continued PPI therapy at the completion of the recommended treatment regimen (Table 18–2).

Abbreviations Introduced in This Chapter

GABA	Gamma-aminobutyric acid
GERD	Gastroesophageal reflux disease
H_2RA	Histamine-2 receptor antagonist
LES	Lower esophageal sphincter
PPI	Proton pump inhibitor

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19

Peptic Ulcer Disease

Ashley H. Meredith

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Recognize differences between ulcers induced by *Helicobacter pylori* (H. pylori), nonsteroidal anti-inflammatory drugs (NSAIDs), and stress-related mucosal damage (SRMD) in terms of risk factors, pathogenesis, signs and symptoms, clinical course, and prognosis.
2. Identify desired therapeutic outcomes for patients with *H. pylori*–associated and NSAID-induced ulcers.
3. Select an appropriate *H. pylori* eradication regimen that considers patient-specific factors and approaches to improve regimen adherence.
4. Determine the appropriate management for a patient taking a nonselective NSAID who is at high risk for ulcer-related gastrointestinal (GI) complications (eg, GI bleed) or who develops an ulcer.
5. Utilize an algorithm for the evaluation and treatment of a patient with signs and symptoms suggestive of an *H. pylori*–associated or NSAID-induced ulcer.
6. Given patient-specific information and a prescribed treatment regimen, develop a monitoring plan for drug therapy to eradicate *H. pylori* or treat an active NSAID-induced ulcer or GI complication.

INTRODUCTION

Peptic ulcer disease (PUD) refers to a defect in the gastric or duodenal mucosal wall that extends through the **muscularis mucosa** into the deeper layers of the submucosa.[1] PUD is a significant cause of morbidity and associated with substantial health care costs.[2,3] Although there are many etiologies of PUD, the three most common are (a) *Helicobacter pylori* (H. pylori) infection, (b) use of nonsteroidal anti-inflammatory drugs (NSAIDs), and (c) stress-related mucosal damage (SRMD).

Complications of PUD include gastrointestinal (GI) bleeding, perforation, and obstruction. Complications of untreated or undiagnosed *H. pylori* infection include gastric cancer and PUD. This chapter focuses mainly on pharmacotherapy of PUD related to *H. pylori* infection or NSAID use. Prophylaxis of SRMD in hospitalized patients is discussed briefly.

EPIDEMIOLOGY AND ETIOLOGY

PUD affects approximately 10% of women and 12% of men in the United States, resulting in 4 million cases annually.[4] The mean direct medical cost (including pharmacy, inpatient, and outpatient costs) was $23,819 per patient per year in one study evaluating workplace absences, short-term medical disability, worker's compensation, and medical and pharmacy claims for six large US employers.[5]

The prevalence of *H. pylori* infection in the United States and Canada is about 30%, whereas the global prevalence is greater than 50%. Factors that influence the incidence and prevalence of *H. pylori* infection include age, ethnicity, sex, geography, and socioeconomic status.

Helicobacter Pylori

H. pylori is usually contracted in the first few years of life and tends to persist indefinitely unless treated. The infection normally resides in the stomach and is transmitted through ingestion of fecal-contaminated water or food. The organism causes **gastritis** in all infected individuals, but fewer than 10% will develop symptomatic PUD.

Nonsteroidal Anti-Inflammatory Drugs

Nearly half of people with chronic NSAID ingestion experience nausea and dyspepsia. Peptic ulceration occurs in up to 30% of chronic NSAID (including aspirin) users, with GI bleeding or perforation occurring in 1.5% of patients who develop an ulcer.[2] Ulcer-related complications result in 100,000 hospitalizations and more than 20,000 deaths in the United States each year.[2]

Risk factors for NSAID-induced PUD and complications are presented in Table 19–1. Risk factors are generally additive. Corticosteroid therapy is not an independent risk factor for ulceration but increases PUD risk substantially when combined with NSAID therapy.[6] Whether *H. pylori* infection is a risk factor for NSAID-induced ulcers remains controversial; however, *H. pylori* and NSAIDs act independently to increase ulcer risk and ulcer-related bleeding and also appear to have synergistic effects.[7,8]

Stress-Related Mucosal Damage

SRMD occurs most frequently in critically ill patients due to mucosal defects caused by gastric mucosal ischemia and intraluminal acid.[9] The ulcers are usually superficial, but SRMD may

Table 19–1

Risk Factors for Ulcers and GI Complications Related to NSAID Use

- Age older than 65 years
- Concomitant anticoagulant use
- Preexisting coagulopathy (elevated INR or thrombocytopenia)
- Concomitant corticosteroid therapy
- Previous PUD or PUD complications (bleeding/perforation)
- Cardiovascular disease and other comorbid conditions
- Multiple NSAID use (eg, low-dose aspirin plus another NSAID)
- Longer duration of NSAID use
- High-dose NSAID use

GI, gastrointestinal; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; PUD, peptic ulcer disease.

Adapted from Lanza FL, Chan FKL, Quigley EMM, et al. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009;104:728–738.

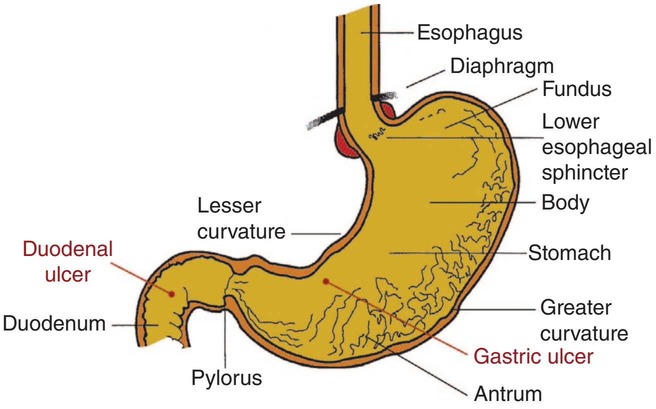


FIGURE 19–1. Anatomic structure of the stomach and duodenum and most common locations of gastric and duodenal ulcers. (From Love BL, Mohorn PL. Peptic ulcer disease and related disorders. In: DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V, eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020: Chapter 50)

also penetrate into the submucosa and cause significant GI bleeding. Physiologically stressful situations that lead to SRMD include sepsis, organ failure, prolonged mechanical ventilation, thermal injury, and surgery. Critical care patients with these specific characteristics are at highest risk.[10]

Zollinger–Ellison Syndrome

Zollinger–Ellison syndrome (ZES) is caused by a gastrin-producing tumor called a gastrinoma. The resulting gastric acid hypersecretion causes diarrhea and malabsorption. Ulcers tend to be numerous and have a high risk of perforation and bleeding.[11] Treatments include surgical resection when feasible and high-dose oral proton pump inhibitor (PPI) therapy.

Other Causative Factors

Cigarette smoking is associated with a higher prevalence of ulcers in *H. pylori*-infected patients.[2] The detrimental effects of smoking on the gastric mucosa may involve increased pepsin secretion, duodenogastric reflux of bile salts, elevated levels of free radicals, and reduced prostaglandin-2 (PG_2) production, resulting in decreased mucus and bicarbonate secretion.[12]

Although psychosocial factors such as life stress, personality patterns, and depression may influence PUD prevalence, a clear causal relationship has not been demonstrated.[2] Dietary factors such as coffee, tea, cola, alcohol, and spicy foods may cause dyspepsia but have not been shown to independently increase PUD risk.

PATHOPHYSIOLOGY

Ulcers related to *H. pylori* infection more commonly affect the duodenum (duodenal ulcers [DUs]), whereas NSAID-related ulcers more frequently affect the stomach (gastric ulcers [GUs]) (Figure 19–1). However, ulcers may be found in either location from either cause.[11]

Ulcer formation in the GI tract results from disrupted homeostasis between factors that break down food (eg, gastric acid and pepsin) and those that promote mucosal defense and repair (eg, bicarbonate, mucus secretion, and PGs).

Gastric Acid and Pepsin

Hydrochloric acid and pepsin are the primary substances that cause gastric mucosal damage in PUD. Three different stimuli (histamine, acetylcholine, and gastrin) cause acid secretion through interactions with the histaminic, cholinergic, and gastrin receptors on the surface of parietal cells. Gastric acid output occurs in two stages: (a) basal acid output in the fasting state and (b) maximal acid output in response to meals. Basal acid secretion follows a circadian cycle and is modulated by the effects of acetylcholine and histamine on parietal cells.[13]

Food increases gastric acid secretion in two ways: (a) vagus nerve stimulation in response to sight, smell, or taste; and (b) stomach distention during the gastric and intestinal phases of acid secretion.

After stimulation by histamine, acetylcholine, or gastrin, acid is secreted by the H^+-K^+-$ATPase^+$ (proton) pump, located on the luminal side of parietal cells. Acid secretion in PUD is usually normal or only slightly elevated. NSAID ingestion does not usually affect acid secretion, whereas *H. pylori* infection often slightly increases acid output.[13]

Pepsinogen released from chief cells in the body of the stomach is converted to pepsin in an acidic environment; pepsin initiates protein digestion and collagen proteolysis and serves as a signal for the release of other digestive enzymes such as gastrin and cholecystokinin.[14] The proteolytic activity of pepsin appears to influence ulcer formation.

Mucosal Defense and Repair

Several normal processes prevent mucosal damage and subsequent ulcer formation. The buffering action of the mucus/phospholipid and bicarbonate barrier shields the gastric epithelial surface from gastric acid.[2] This allows an acidic environment in the gastric lumen but a near neutral pH on the epithelial lining.

PGs inhibit gastric acid secretion and protect gastric mucosa by stimulating mucus, bicarbonate, and phospholipid production. PGs also increase mucosal blood flow and stimulate epithelial cell regeneration.[2] Damage to the mucosal defense system is the primary method by which *H. pylori* and NSAIDs cause peptic ulcers.

▸ *Helicobacter pylori*

H. pylori, a Gram-negative rod, is found on the surface of the gastric epithelium. Flagella provide motility that allows the organism to penetrate the mucous gel barrier and infect epithelial cells.[6] Cellular invasion by *H. pylori* is necessary for an active infection. The organism survives in the acidic milieu of the stomach by producing urease, an enzyme that hydrolyzes the urea in gastric juice into carbon dioxide and ammonia.[6]

H. pylori may cause gastroduodenal mucosal injury through (a) direct mucosal damage, (b) alterations in host inflammatory responses, and (c) hypergastrinemia and elevated acid secretion.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs can cause gastric mucosal damage by two mechanisms: (a) direct irritation of the gastric epithelium and (b) systemic inhibition of endogenous mucosal PG synthesis. Direct irritation occurs because NSAIDs are weak acids. Less acidic agents, such as nonacetylated salicylates, may lead to decreased GI toxicity.[6] Direct irritant effects contribute to NSAID-induced gastritis but play only a minor role in the development of NSAID-induced PUD.

Systemic inhibition of PG synthesis is the primary means by which NSAIDs cause PUD. NSAID inhibition of PG production by blocking the cyclooxygenase-2 (COX-2) enzyme produces beneficial analgesic and anti-inflammatory effects. However, NSAIDs may also block the COX-1 enzyme, which produces PGs that provide gastroprotection. NSAIDs given parenterally (eg, ketorolac) and rectally (eg, indomethacin) have an incidence of PUD similar to oral NSAIDs. Topical NSAIDs (eg, diclofenac) are unlikely to cause PUD because very low serum concentrations are achieved. The antiplatelet effects of NSAIDs may worsen bleeding complications associated with PUD.

CLINICAL PRESENTATION AND DIAGNOSIS

Clinical Presentation

See text box for the clinical presentation of PUD. Dyspepsia (upper abdominal discomfort) is found in 10% to 40% of the general population. PUD is found in 5% to 15% of patients with dyspepsia.

PUD can be classified as uncomplicated or complicated. Uncomplicated disease is typically characterized by mild epigastric pain, whereas complicated disease involves acute upper GI complications such as GI bleeding, obstruction, or perforation. Bleeding may be occult or may present as melena or hematemesis. Up to 20% of patients who develop a PUD-related hemorrhage do not have prior symptoms. Gastric outlet obstruction is usually caused by ulcer-related inflammation or scar formation. Patients typically present with early satiety after meals, nausea, vomiting, abdominal pain, and weight loss. Perforation requires emergent surgical intervention, and these patients should not undergo endoscopy.

Clinical Presentation of PUD

Symptoms

- Dyspepsia and mild epigastric pain that may be described as burning, gnawing, or aching in character.
- Epigastric pain with DUs typically occurs 1 to 3 hours after meals or at night and is often relieved by food.
- Pain with GUs is often aggravated by food.
- Abdominal pain may be described as burning or a feeling of discomfort.
- Pain severity often fluctuates and the character can vary from dull to sharp.
- Patients may also complain of heartburn, belching, bloating, nausea, or vomiting.

Signs

- Weight loss may be associated with nausea and vomiting.
- Complications such as bleeding, perforation, or obstruction may occur.
- Alarm findings include family history of upper GI malignancy, unintentional weight loss, overt GI bleeding, iron deficiency anemia, progressive dysphagia or odynophagia, early satiety, persistent vomiting, palpable mass, or lymphadenopathy.

Diagnosis

Radiologic and/or endoscopic procedures are usually required to document the presence of ulcers. Because endoscopic testing is invasive and expensive, it is only indicated in patients 60 years of age or older with new-onset dyspepsia.[15] Patients with dyspepsia who are younger than 60 years may forego endoscopy but should be tested for *H. pylori* using noninvasive methods and treated if positive.[15] Those who test negative for *H. pylori* should be offered a trial (4–8 weeks) of acid suppression therapy or proceed to endoscopy. Persistent dyspepsia despite a trial of acid suppressive therapy warrants upper endoscopy evaluation.[1]

Testing for *H. pylori* infection is indicated in patients with active PUD, history of documented PUD, low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma, or history of endoscopic resection of early gastric cancer.[16] Diagnostic tests to detect *H. pylori* presence can be either endoscopic or nonendoscopic.[16,17] Endoscopic diagnosis involves extraction of gastric tissue samples that are subsequently tested for *H. pylori*.[16] Histology is the standard identification method, but culture, polymerase chain reaction (PCR), and the rapid urease test can also identify *H. pylori* in tissue samples.[18]

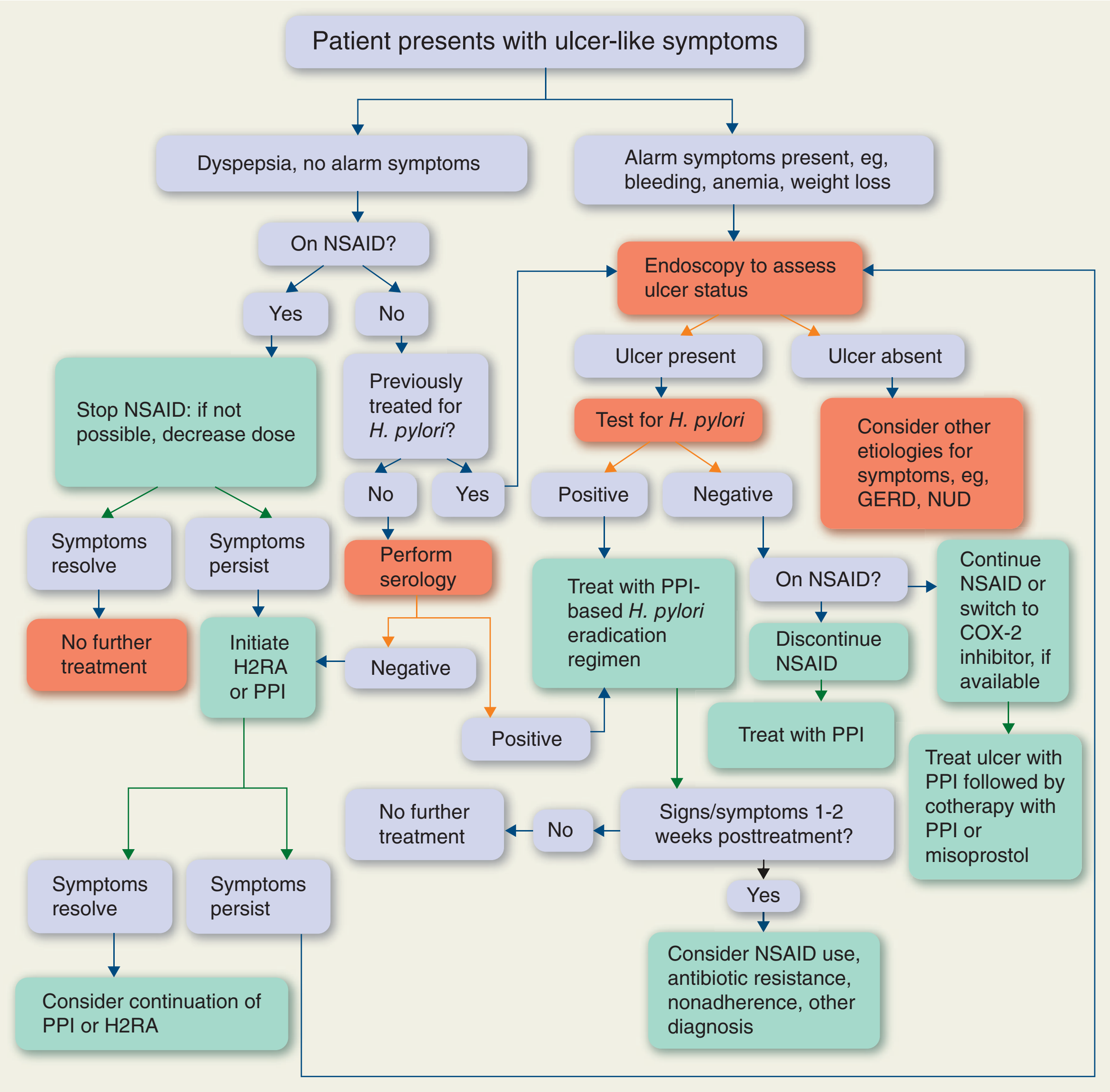
Nonendoscopic testing methods for *H. pylori* include the urea breath test, serologic testing, and stool antigen assay.[16,17] These tests are less invasive and less expensive than endoscopy. The urea breath test is usually first line because of its high sensitivity and specificity and short turnaround time.[18] Concomitant acid-suppressive or antibiotic therapy may give false-negative results.[18] The urea breath test can also be used to confirm eradication of *H. pylori* infection.[18]

Serologic testing provides a quick (within 15 minutes) office-based assessment of exposure to *H. pylori*, but it cannot differentiate active infection from previously treated infection; patients can remain seropositive for years after eradication. Serologic testing is also less sensitive and specific than the urea breath test.[17] Serologic testing is recommended in patients with recent or current antibiotic or acid-suppressive therapy.[18]

Stool antigen assays can be useful for initial diagnosis or to confirm *H. pylori* eradication. They have high sensitivity and specificity and are affected less by concomitant medication use.[17] Use of antimicrobial agents within 4 weeks, PPIs within 2 weeks, and histamine-2 receptor antagonists (H_2RAs) within 24 hours of testing can suppress the infection and reduce the sensitivity of testing.[17]

TREATMENT

The treatment selected for PUD depends on the etiology of the ulcer, whether the ulcer is new or recurrent, and whether complications have occurred. Figure 19–2 shows an algorithm for evaluation and treatment of a patient with signs and symptoms suggestive of an *H. pylori*–associated or NSAID-induced ulcer.



Patient presents with ulcer-like symptoms
Dyspepsia, no alarm symptoms
Alarm symptoms present, eg, bleeding, anemia, weight loss
On NSAID?
Yes
No
Endoscopy to assess ulcer status
Stop NSAID: if not possible, decrease dose
Previously treated for *H. pylori*?
Ulcer present
Ulcer absent
Test for *H. pylori*
Consider other etiologies for symptoms, eg, GERD, NUD
No
Yes
Positive
Negative
Symptoms resolve
Symptoms persist
Perform serology
Treat with PPI-based *H. pylori* eradication regimen
On NSAID?
Continue NSAID or switch to COX-2 inhibitor, if available
No further treatment
Initiate H2RA or PPI
Negative
Discontinue NSAID
Treat with PPI
Positive
Treat ulcer with PPI followed by cotherapy with PPI or misoprostol
No further treatment
No
Signs/symptoms 1-2 weeks posttreatment?
Symptoms resolve
Symptoms persist
Yes
Consider continuation of PPI or H2RA
Consider NSAID use, antibiotic resistance, nonadherence, other diagnosis

FIGURE 19–2. Guidelines for the evaluation and management of a patient who presents with dyspeptic or ulcer-like symptoms. (COX-2, cyclooxygenase-2; GERD, gastroesophageal reflux disease; H_2RA, H_2-receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; NUD, nonulcer dyspepsia; PPI, proton pump inhibitor.) (From Love BL, Mohorn PL. Peptic ulcer disease and related disorder. In: DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V, eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020: Chapter 50.)

Desired Outcomes

The goals of PUD therapy are to resolve symptoms, reduce acid secretion, promote epithelial healing, prevent ulcer-related complications, and prevent ulcer recurrence. For *H. pylori*–related PUD, eradication of *H. pylori* is an additional outcome.

Nonpharmacologic Therapy

▶ *Risk Factor Avoidance*

KEY CONCEPT Patients with PUD should avoid exposure to factors known to worsen the disease, exacerbate symptoms, or lead to ulcer recurrence. Patients should be advised to reduce psychological stress and avoid cigarette smoking, alcohol consumption, and NSAID or aspirin use, if possible. Patients who require chronic NSAID therapy (eg, for rheumatoid arthritis) may be given prophylaxis with misoprostol or a PPI (see Prevention of NSAID-Induced Ulcers section).

▶ *Surgery*

The high success rates of medical therapies have reduced the need for surgical procedures. Elective surgeries performed for PUD have decreased dramatically since the 1980s, mainly due to *H. pylori* eradication.[19] Surgical interventions are generally reserved for complicated or refractory PUD.

For patients with acute GI bleeding, endoscopic hemostasis can be achieved using contact thermal therapy, mechanical therapy using clips, or epinephrine injection followed by either thermal or mechanical therapy.[19] Angiography with embolization of bleeding lesions can be used if the bleeding cannot be stopped endoscopically and the patient is either high risk for surgery or not a surgical candidate.[19]

Pharmacologic Therapy

▶ *Treatment of* Helicobacter pylori*–Associated Ulcers*

The goal of *H. pylori* therapy is to eradicate the organism using an effective antibiotic-containing regimen. KEY CONCEPT Reliance on

Table 19–2

Drug Regimens to Eradicate *Helicobacter pylori*

Treatment Regimen	Medications	Duration
Clarithromycin triple therapy	Clarithromycin 500 mg BID + amoxicillin 1 g BID OR metronidazole 500 mg TID + PPI BID	14 days
Bismuth quadruple therapy[a]	Bismuth subsalicylate 300 mg QID + metronidazole 250–500 mg QID + tetracycline 500 mg QID + PPI BID	10–14 days
Concomitant therapy[a]	Clarithromycin 500 mg BID + amoxicillin 1 g BID + nitroimidazole[c] 500 mg BID + PPI BID	10–14 days
Sequential therapy	Amoxicillin 1 g BID + PPI BID followed by: clarithromycin 500 mg BID + nitroimidazole[c] 500 mg BID + PPI BID	5–7 days 5–7 days
Hybrid therapy	Amoxicillin 1 g BID + PPI BID followed by amoxicillin 1 g BID + clarithromycin 500 mg BID + nitroimidazole[c] 500 mg BID + PPI BID	7 days 7 days
Levofloxacin triple therapy	Levofloxacin 500 mg daily + amoxicillin 1 g BID + PPI BID	10–14 days
Levofloxacin sequential therapy	Amoxicillin 1 g BID + PPI BID followed by amoxicillin 1 g BID + levofloxacin 500 mg daily + nitroimidazole[c] 500 mg BID + PPI BID	5–7 days 5–7 days
Rifabutin triple therapy[b]	Rifabutin 300 mg daily + amoxicillin 1 g (BID or TID)[d] + PPI BID	10 days
High-dose dual therapy	Amoxicillin (1 g TID or 750 mg QID) + PPI (TID or QID)	14 days
Combination Therapies		
PREVPAC	Clarithromycin 500 mg BID + amoxicillin 1 g BID + lansoprazole 30 mg BID (contained in blister pack cards)	10–14 days
Pylera + omeprazole	(Bismuth subcitrate potassium 140 mg + metronidazole 125 mg + tetracycline 125 mg) three capsules QID + omeprazole 20 mg BID	10 days

[a] Regimens with strong recommendation based on current guidelines.

[b] Salvage regimen only.

[c] Metronidazole or tinidazole.

[d] Dosing varied in clinical trials.

BID, twice daily; H_2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; QID, four times daily; TID, three times daily.

From Chey WD, Leontiadis GI, Howden CW, et al. ACG Clinical Guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol. 2017;112:212–238.

conventional acid-suppressive drug therapy alone as an alternative to *H. pylori* eradication is inappropriate because it is associated with a higher incidence of ulcer recurrence and ulcer-related complications. Reinfection rates are generally low after the initial course of therapy as long as the patient is adherent. In addition to proven efficacy, the optimal treatment regimen should cause minimal adverse events, have low risk for development of bacterial resistance, and be cost-effective.[16,17]

H. pylori treatment regimens are presented in Table 19–2. **KEY CONCEPT** Eradication therapy should be pursued in all patients who test positive for *H. pylori* infection. Several regimens are recommended as first-line eradication therapy. Different antibiotics should be used if a second course of *H. pylori* eradication therapy is required. The cure rates of *H. pylori* with H_2RAs in combination with antibiotics are lower than when PPIs are included in the regimen.[16]

Important considerations in selecting first-line treatment regimens include presence of a penicillin allergy and previous exposure to macrolide antibiotics. Acceptable first-line regimens that carry strong recommendations include bismuth quadruple therapy as well as concomitant therapy. Other acceptable regimens for first-line treatment with weak recommendations include (a) clarithromycin triple therapy in regions with clarithromycin resistance less than 15% when a patient has no previous macrolide exposure, (b) sequential therapy, (c) hybrid therapy, (d) levofloxacin triple therapy, and (e) fluoroquinolone sequential therapy. Substitution of one PPI for another is acceptable and does not affect eradication rates. Alcohol consumption must be considered prior to selecting a metronidazole containing treatment regimen.[16]

The duration of therapy for *H. pylori* eradication is controversial; US guidelines recommend either 10 or 14 days.[16] A treatment duration of 14 days should be considered because of higher eradication rates than with a 10-day course; however, the data supporting this recommendation are based on a relatively small number of participants in clinical trials.[16,20] Treatment courses longer than 14 days may decrease adherence and increase drug costs; ultimately, the most effective eradication regimens still fail in 10% to 20% of patients.[16]

Bismuth-based four-drug regimens have clinical cure rates similar to three-drug PPI-based regimens.[21] Bismuth salts promote ulcer healing through antibacterial and mucosal protective effects. Disadvantages of bismuth-based regimens include frequency of administration (four times a day), risk for salicylate toxicity in renal impairment, and bothersome side effects (eg, stool and tongue discoloration, constipation, nausea, vomiting).[16]

Pylera and PREVPAC are proprietary products designed to improve regimen adherence (Table 19–2). Pylera is a combination product, whereas PREVPAC is a conveniently packaged eradication regimen. Both products are substantially more expensive than their individual generic and nonprescription components.

Recent literature has indicated a potential role for probiotics in first-line treatment of *H. pylori*. Probiotic therapy has been associated with increased cure rates and reduced side effects

Patient Encounter 1

A 55-year-old man presents with abdominal pain and indigestion that occur two to three times per week. He also reports that his abdominal pain worsens a couple of hours after eating. He does not report any recent antibiotic use.

PMH: Hypertension × 5 years, hyperlipidemia × 7 years

FH: Mother alive at 81 with hypertension, type 2 diabetes; father alive at 83 with hypertension

SH: Smokes half pack per day; occasional alcohol use; no illicit drug use

Allergies: Sulfa

Meds: Lisinopril 40 mg daily, amlodipine 10 mg daily, atorvastatin 40 mg daily, ibuprofen 200 mg as needed for headache

Based on this patient's clinical presentation, what is the most appropriate course of action to establish a diagnosis?

The patient receives a diagnosis of Helicobacter pylori infection based on the diagnostic method recommended. What eradication therapy would you recommend?

The patient completed the course of eradication therapy recommended; however, he returns with similar symptoms 3 months later. What regimen would you recommend for eradication therapy?

compared to conventional eradication regimens. However, further study is needed due to limitations of the available evidence. Current guidelines reinforce several areas for additional research regarding optimal dosing of probiotic therapy.[16]

Patients may remain infected with *H. pylori* after the initial treatment course because of reinfection, nonadherence, or antimicrobial resistance. Factors associated with decreased adherence include polypharmacy, need for frequent drug administration or long treatment duration, and use of drugs that may cause intolerable side effects. Potential adverse drug effects include taste disturbances (clarithromycin and metronidazole), nausea, vomiting, abdominal pain, and diarrhea. Superinfections with oral thrush or vaginal candidiasis can occur. Alcohol should be avoided during treatment with metronidazole or tinidazole due to the potential for a disulfiram-like reaction.

Resistance data for *H. pylori* in the United States are limited. Data from a Veterans Affairs Medical Center demonstrated clarithromycin resistance rates exceeding the threshold for use in current guidelines. A threshold of 15% to 20% is recommended to differentiate between regions of high and low clarithromycin resistance. In the setting of resistance, efficacy of a three-drug regimen containing clarithromycin can decrease to 10% to 30%. Culture and sensitivity tests are not routinely performed with *H. pylori* infection unless a patient has already failed two different treatment regimens; these tests are not widely available in the United States.[16,20]

Initiation of a second *H. pylori* treatment regimen after failure of the initial treatment is usually associated with a lower success rate. Reasons for failure are often the same as for failure of the initial regimen. Selection of a salvage treatment regimen should be based on the initial treatment the patient received, history of quinolone exposure, and penicillin allergy status.

- If clarithromycin triple therapy was used as the initial treatment regimen and the patient is not penicillin allergic, recommended salvage therapies include (a) bismuth quadruple therapy, (b) levofloxacin triple therapy, (c) rifabutin triple therapy, or (d) high-dose dual therapy. For patients who received initial clarithromycin triple therapy and are penicillin allergic, bismuth quadruple therapy is recommended.
- When bismuth quadruple therapy was the initial treatment regimen and the patient is not penicillin allergic, recommended salvage regimens include (a) levofloxacin triple therapy, (b) concomitant therapy, (c) rifabutin triple therapy, or (d) high-dose dual therapy. Levofloxacin triple therapy should be avoided in patients with previous quinolone exposure. Salvage regimens are less well defined for patients who received bismuth quadruple therapy as initial treatment and are penicillin allergic.
- There is no standard third-line therapy for *H. pylori* treatment.[16]

Confirmation of *H. pylori* infection eradication is recommended in all treated patients.[16] Testing should occur at least 4 weeks after completion of the eradication regimen and 1 to 2 weeks after discontinuation of PPI.[16] Eradication may be confirmed by either the urea breath test or stool antigen testing. Eradication may also be confirmed by endoscopy, but this should only be done when endoscopy is required because it is more expensive and invasive.[17]

▶ *Treatment of NSAID-Induced Ulcers*

Treatment recommendations to heal NSAID-induced ulcers or provide maintenance therapy in patients receiving NSAIDs are shown in Table 19–3. Choice of regimen depends on whether NSAID use is to be continued. NSAIDs should be discontinued and replaced with alternatives (eg, acetaminophen), when possible. For patients who cannot discontinue NSAID therapy, PPIs, H_2RAs, or sucralfate are effective for ulcer healing and to prevent further recurrences.[11] PPIs are usually preferred because

Patient Encounter 2

A 61-year-old man presents with persistent epigastric pain and bloating. His chief complaint today is, "It feels like my ulcer is back!"

PMH: Hypertension × 15 years

FH: Mother deceased at age 66, cancer; father alive at 85 with hypertension, dyslipidemia

SH: Nonsmoker, 1 to 2 alcoholic beverages three times weekly, no illicit drug use

Allergies: NSAIDs

Meds: Lisinopril 40 mg daily, hydrochlorothiazide 25 mg daily, amlodipine 10 mg daily

The patient previously completed the following course for *Helicobacter pylori* eradication but admits to maybe missing a day or two:

- PREVPAC for 14 days

H. pylori recurrence is confirmed with a urea breath test.

What are possible reasons for treatment failure in this patient?

What regimen would you recommend for salvage eradication therapy?

Table 19–3

Oral Drug Regimens to Heal Peptic Ulcers or Maintain Ulcer Healing in the Absence of Antibiotic Therapy

Drug	DU or GU Healing	Maintenance of DU or GU Healing
Mucosal Protectant		
Sucralfate	1 g four times a day 2 g two times a day	1 g four times a day 1–2 g two times a day
H_2-Receptor Antagonists		
Cimetidine	300 mg four times a day 400 mg two times a day 800 mg at bedtime	400–800 mg daily
Famotidine	20 mg two times a day 40 mg at bedtime	20–40 mg daily
Nizatidine	150 mg two times a day 300 mg at bedtime	150–300 mg daily
Proton Pump Inhibitors		
Dexlansoprazole	30–60 mg daily	30–60 mg daily
Esomeprazole	20–40 mg daily	20–40 mg daily
Lansoprazole	15–30 mg daily	15–30 mg daily
Omeprazole	20–40 mg daily	20–40 mg daily
Pantoprazole	40 mg daily	40 mg daily
Rabeprazole	20 mg daily	20 mg daily

DU, duodenal ulcer; GU, gastric ulcer.

they provide more rapid relief of symptoms, have the strongest acid suppression, and heal ulcers more quickly than H_2RAs or sucralfate.[11] Standard doses of H_2RAs effectively heal DUs but are minimally effective in GUs. A PPI provides equivalent efficacy with treatment duration of only 4 weeks. PPI therapy should only be continued for longer than 4 weeks if an ulcer is confirmed to still be present or if the patient develops severe complications from PUD.

▸ *Prevention of NSAID-Induced Ulcers*

Prophylactic regimens against PUD are often required in patients receiving long-term NSAID or aspirin therapy for osteoarthritis, rheumatoid arthritis, or cardioprotection.[22] Misoprostol, H_2RAs, PPIs, and COX-2 selective inhibitors have been evaluated in controlled trials to reduce the risk of NSAID-induced PUD. KEY CONCEPT In patients at risk for NSAID-induced ulcers, PPIs at standard doses reduce the risk of both GUs and DUs as effectively as misoprostol and more effectively than H_2RAs. In addition, PPIs are generally better tolerated than misoprostol.

Misoprostol A synthetic prostaglandin E_1 (PGE_1) analog that exogenously replaces PG stores, misoprostol is indicated for reducing the risk of NSAID-induced GUs in patients at high risk of complications from ulcers (eg, the elderly and patients with concomitant debilitating disease), as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcers. Misoprostol 200 mcg four times a day reduces ulcer complications by inhibiting acid secretion and promoting mucosal defense. It is superior to H_2RAs for prevention of NSAID-induced ulcers.[23] Misoprostol use is limited by a high frequency of bothersome GI effects such as abdominal pain, flatulence, and diarrhea, and it is contraindicated in pregnancy due to potential abortifacient effects. Arthrotec is a combination product that contains diclofenac (either 50 or 75 mg) and misoprostol 200 mcg in a single tablet.

H_2-Receptor Antagonists The efficacy of H_2RAs (eg, famotidine 40 mg daily) in preventing NSAID-related ulcers varies. DUs appear to respond better than GUs (the most frequent type of ulcer associated with NSAIDs). Higher doses of H_2RAs (eg, famotidine 40 mg twice daily) may reduce the risk of NSAID-induced GUs and DUs but results from clinical trials are variable.

Duexis, a prescription combination product containing ibuprofen 800 mg and famotidine 26.6 mg, is indicated for relief of signs and symptoms of rheumatoid arthritis and osteoarthritis and to decrease the risk of developing upper GI ulcers. The recommended dosage is one tablet orally three times daily. Clinical trials evaluating this agent are 6 months or less in duration and primarily evaluated patients younger than 65 years with no ulcer history.

Proton Pump Inhibitors PPI therapy is more effective than H_2RAs in reducing the risk of nonselective NSAID-related GUs and DUs.[23] PPIs are as effective as misoprostol but better tolerated. All PPIs are effective when used in standard doses. In patients who experience a PUD-related bleeding event while taking aspirin but who require continued aspirin therapy, the addition of a PPI reduces the incidence of recurrent GI bleeding.[24] Prevacid NapraPAC provides naproxen (either 250, 375, or 500 mg) and lansoprazole 15 mg in individual blister packages. Vimovo provides naproxen (either 375 or 500 mg) and esomeprazole 20 mg in each tablet.

COX-2 Selective Inhibitors NSAIDs with COX-2 selectivity were developed in an attempt to reduce the incidence of PUD and its complications. KEY CONCEPT Selective COX-2 inhibitors are no more effective than the combination of a PPI and a nonselective NSAID in reducing the incidence of ulcers. Celecoxib is the only agent in this class available in the United States. There was no difference in cardiovascular outcomes when celecoxib was compared to ibuprofen and naproxen.[25,26]

Sucralfate This drug is a negatively charged, nonabsorbable agent that forms a complex by binding with positively charged proteins in exudates, forming a viscous, paste-like adhesive substance that protects the ulcerated area of the gastric mucosa against gastric acid, pepsin, and bile salts.[6] Limitations of sucralfate include the need for multiple doses per day, large tablet size, and interaction with a number of other medications (eg, digoxin, fluoroquinolones).

Adverse effects of sucralfate include constipation, nausea, metallic taste, and the possibility for aluminum toxicity in patients with renal failure. Sucralfate is effective for treatment of NSAID-related ulcers when the NSAID will be stopped, but it is not recommended for NSAID-related ulcer prophylaxis.

▸ *Prevention of Stress-Related Mucosal Damage*

Prevention of stress ulcers involves maintaining hemodynamic stability to maximize mesenteric perfusion and pharmacologic suppression of gastric acid production. Stress ulcer prophylaxis (SUP) is only indicated in intensive care unit (ICU) patients with certain risk factors (see Table 19–4).[9,27] The clinician must weigh the risks and benefits of using acid suppression, especially PPIs, in low-risk patients. PPIs and H_2RAs are the drugs of choice for SUP; however, antacids and sucralfate may be acceptable options in some patients.

Table 19–4

Appropriate Indications for Stress Ulcer Prophylaxis in Intensive Care Unit Patients

- Mechanical ventilation for longer than 48 hours
- Coagulopathy or hepatic failure (platelet count < 50 × $10^3/\text{mm}^3$ [50 × 10^9/L], INR > 1.5, or aPTT > two times control)
- History of GI ulceration or bleeding within 1 year of admission
- Head trauma or Glasgow Coma Score of 10 or less (or inability to obey simple commands)
- Thermal injuries to more than 35% of body surface area
- Multiple traumas (injury severity score of 16 or greater)
- Partial hepatectomy
- Transplant patients in the ICU perioperatively
- Spinal cord injuries
- Two of the following risk factors: sepsis, ICU stay for more than 1 week, occult bleeding lasting 6 or more days, and use of high-dose corticosteroids (> 250 mg/day of hydrocortisone or equivalent)

aPTT, activated partial thromboplastin time; GI, gastrointestinal; ICU, intensive care unit; INR, international normalized ratio.

Data from Plummer MP, Reintam Blaser A, Deane AM. Stress ulceration: prevalence, pathology and association with adverse outcomes. Crit Care. 2014;18(2):213 and Nissen SE, Yeomans ND, Solomon DH. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med. 2016;375:2519–2529.

▶ *Long-Term Maintenance of Ulcer Healing*

KEY CONCEPT Low-dose maintenance therapy with a PPI or H_2RA is only indicated in patients with severe complications secondary to PUD, such as gastric outlet obstruction or patients who need to be on long-term NSAIDs or high-dose corticosteroids and are at high risk for bleeding. Drug regimens and doses for PUD treatment and maintenance are presented in Table 19–3.

▶ *Treatment of GI Bleeding*

The immediate priorities in treating patients with a bleeding peptic ulcer are to achieve IV access, correct fluid losses, and restore hemodynamic stability. Insertion of a nasogastric tube is helpful in initial patient assessment, but the absence of bloody or coffee-ground material in any gastric content drainage does not definitively rule out ongoing or recurrent bleeding.

Patients should be started on IV PPI therapy because optimal platelet aggregation, partially inhibited fibrinolysis, and better clot stabilization on the ulcer are achieved when the gastric pH is greater than 6.[28] Intravenous PPI therapy should be continued for 72 hours (because most rebleeding occurs during this time) followed by oral PPI therapy. Three-day PPI infusion therapy has been shown to be as effective as twice-daily IV PPI therapy.[28]

▶ *Treatment of Refractory Ulcers*

Refractory ulcers are defined as ulcers that fail to heal despite 8 to 12 weeks of acid suppressive therapy.[1] The presence of refractory ulcers requires a thorough assessment, including evaluation of medication adherence, extensive counseling and questioning regarding recent over-the-counter and prescription medication use, and testing for *H. pylori* using a different method than previously done, if testing was negative. Changing from H_2RA therapy to a PPI should be considered.[6] Other considerations include esophagogastroduodenoscopy (EGD) with biopsy of the

Patient Encounter 3

A 63-year-old woman presents with reports of dark, tarry stools for 3 days. She denies coffee-ground emesis or recent weight loss but reports occasional heartburn and belching.

PMH: Hypertension × 20 years, type 2 diabetes × 15 years, dyslipidemia × 15 years, osteoarthritis × 10 years, asthma × 25 years, myocardial infarction 5 years ago

FH: Mother deceased at age 82, stroke; father deceased at age 74, MI; one sister alive at 66 with hypertension, type 2 diabetes, and dyslipidemia

SH: Denies smoking, alcohol, or illicit drug use

Allergies: NKDA

Meds: Lisinopril 40 mg daily, amlodipine 10 mg daily, metformin 1000 mg twice daily, glipizide 10 mg twice daily, rosuvastatin 20 mg daily, naproxen 500 mg two times daily, aspirin 81 mg daily, prednisone 5 mg daily, albuterol 2 puffs every 4 to 6 hours as needed for shortness of breath, fluticasone/salmeterol 250/50 mcg 1 inhalation twice daily, Tums Extra Strength as needed for heartburn

Other: An endoscopy reveals a duodenal ulcer that is negative for *Helicobacter pylori*

What risk factors does this patient have for GI complications related to NSAID use?

Make a recommendation for treatment of this patient's ulcer.

Discuss the use of prophylactic therapy in this patient after the treatment course is completed.

Patient Encounter 4

A 53-year-old man is brought to the surgical ICU after emergency surgery following a motor vehicle accident with significant head trauma. The patient is intubated and placed on mechanical ventilation. The physician would like him to remain mechanically ventilated and NPO (nothing by mouth) for several days until he improves clinically.

PMH: Hypertension × 20 years

FH: Father with hypertension

SH: Nonsmoker; 1 drink 1–2 times weekly; no illicit drug use

Allergies: Penicillin

Meds: Lisinopril/hydrochlorothiazide 20/25 mg daily, aspirin 81 mg daily, oxycodone 5 mg/acetaminophen 325 mg two tablets every 8 hours for surgical site pain

Based on this patient's clinical presentation, is he a candidate for stress ulcer prophylaxis?

What pharmacologic therapy would you recommend for this patient?

Four days later, the patient's condition has improved significantly and he is extubated. He is transferred to a general medicine floor and begins a regular diet that is well tolerated. He is alternating between oxycodone/acetaminophen and acetaminophen alone to relieve incision site pain. He is now sitting up in bed and feeling much better. Is this patient currently a candidate for stress ulcer prophylaxis?

Patient Care Process: Peptic Ulcer Disease

Collect Information:

- Obtain a history of prescription and over-the-counter medications and dietary supplements.
- Verify patient allergies and intolerances.
- Review the medical history and physical assessment findings.
- Speak with the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Based on review of signs and symptoms and assessment of risk factors (Table 19–1), determine whether the patient is experiencing signs or symptoms of PUD.
- Review available diagnostic tests (eg, serologic testing, urea breath test, stool antigen assay, endoscopy) to determine etiology of peptic ulcer.
- If patient is already receiving pharmacotherapy, assess its efficacy, safety, and patient adherence.
- Assess the potential for drug interactions, particularly in patients taking regimens containing metronidazole, clarithromycin, or cimetidine.

Develop a Care Plan:

- If patient has been diagnosed with a peptic ulcer, determine which course of therapy is indicated.
- Recommend an appropriate regimen (Tables 19–2 and 19–3) that will eradicate *Helicobacter pylori* and/or heal the peptic ulcer.
- Avoid drug classes to which the patient is allergic.
- If the patient has been treated for *H. pylori* previously, recommend different antibiotics if this episode is a result of treatment failure.
- Evaluate patient accessibility to medication (eg, formulary status, insurance coverage).

Implement the Care Plan:

- Inform patient about potential adverse drug effects and drug interactions.
- Educate the patient on the importance of adherence to eradication and ulcer-healing therapy.
- Identify appropriate lifestyle modifications.

Follow-up: Monitor and Evaluate:

- Assess patient adherence and progress toward efficacy and safety goals.
- Monitor annually for signs and symptoms of complications such as unintentional weight loss or bleeding.
- Evaluate the need for a prophylactic acid suppressive regimen in patients requiring chronic NSAID therapy.

ulcer to exclude malignancy, *H. pylori* testing (if not done initially), serum gastrin measurement to exclude ZES, and gastric acid studies.

OUTCOME EVALUATION

- Obtain a baseline complete blood count (CBC). Recheck the CBC if the patient exhibits alarm signs or symptoms.
- Obtain a baseline serum creatinine. Calculate the estimated creatinine clearance and adjust the dose of H_2RAs and sucralfate if needed.
- Obtain a history of symptoms from the patient. Monitor for improvement in pain symptoms (eg, epigastric or abdominal pain) daily.
- Monitor the patient for development of any alarm signs and symptoms.
- Recommend a follow-up visit if signs and symptoms worsen at any time or do not improve within the defined treatment period.
- Assess for potential drug interactions whenever there is a change in the patient's medications.
- Educate the patient on the importance of adhering to the *H. pylori* eradication regimen.
- Monitor the patient for complications related to antibiotic therapy (eg, diarrhea or oral thrush) during and after completion of *H. pylori* eradication therapy.
- Recommend follow-up care if the patient's signs and symptoms do not improve after completion of *H. pylori* eradication therapy.

Abbreviations Introduced in This Chapter

COX	Cyclooxygenase
DU	Duodenal ulcer
EGD	Esophagogastroduodenoscopy
GI	Gastrointestinal
GU	Gastric ulcer
H_2RA	Histamine-2 receptor antagonist
INR	International normalized ratio
MALT	Mucosa-associated lymphoid tissue
NSAID	Nonsteroidal anti-inflammatory drug
NUD	Nonulcer dyspepsia
PG	Prostaglandin
PGE_1	Prostaglandin E1
PPI	Proton pump inhibitor
PUD	Peptic ulcer disease
SRMD	Stress-related mucosal damage
SUP	Stress ulcer prophylaxis
ZES	Zollinger–Ellison syndrome

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20

Inflammatory Bowel Disease

Brian A. Hemstreet

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Characterize the pathophysiologic mechanisms underlying inflammatory bowel disease (IBD).
2. Recognize the signs and symptoms of IBD, including major differences between ulcerative colitis (UC) and Crohn disease (CD).
3. Identify appropriate therapeutic outcomes for patients with IBD.
4. Describe pharmacologic treatment options for patients with acute or chronic symptoms of UC and CD.
5. Create a patient-specific drug treatment plan based on symptoms, severity, and location of UC or CD.
6. Recommend appropriate monitoring parameters and patient education for drug treatments for IBD.

INTRODUCTION

KEY CONCEPT The term inflammatory bowel disease (IBD) encompasses ulcerative colitis (UC) and Crohn disease (CD). Both disorders are associated with acute and chronic inflammation of the gastrointestinal (GI) tract. Differences exist between UC and CD with regard to regions of the GI tract that may be affected and the distribution and depth of intestinal inflammation. Patients with IBD may also develop inflammation involving organs other than the GI tract, known as *extraintestinal manifestations*. Symptoms of IBD are associated with significant morbidity, reduction in quality of life, and costs to the health-care system.[1–6]

EPIDEMIOLOGY AND ETIOLOGY

IBD is most common in Western countries such as the United States and Northern Europe. The age of initial presentation is bimodal, with patients typically diagnosed between the ages of 20 to 40 or 60 to 80 years. Approximately 1.5 million Americans have UC or CD.[2] Up to 70,000 new cases of IBD are diagnosed in the United States each year.[3]

Men and women are approximately equally affected by IBD in Western countries.[6] In general, White patients are affected more often than African American and Asian patients, and persons of Jewish descent are also at higher risk.[1,5,6] A positive family history of IBD is found in 8% to 14% of patients, and genetic risk may be more of a contributing factor in some ethic groups.[1,2,6]

The cause of IBD is not fully understood. Dysregulation of the inflammatory response within the GI tract in response to environmental or microbiologic factors is thought to be the prevailing mechanism.[3–5] The fact that a positive family history is a strong predictor of IBD supports the theory that genetic predisposition is involved in many cases. Many potential candidate genes have been identified.[1,2,4–6]

An alteration in the inflammatory response regulated by intestinal epithelial cells may also contribute to development of IBD. This may involve inappropriate processing of antigens presented to the GI epithelial cells.[3–5,7,8] The inflammatory response in IBD may be directed at bacteria that normally colonize the GI tract. Products derived from these bacteria may translocate across the mucosal layer of the GI tract and interact with various cells involved in immunologic recognition. The result is T-cell stimulation, excess production of proinflammatory cytokines, and persistent inflammation within the GI tract. Drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) that disrupt the integrity of the GI mucosa may facilitate mucosal entry of intestinal antigens and lead to IBD flares.[9]

Use of oral contraceptives has been associated with increased development of CD in White patients in some cohort studies, but a strong causal relationship has not been proven.[5] Use of antibiotics in childhood and low levels of vitamin D have also been reported to increase risk of UC and CD.[5]

Smoking has protective effects in UC, leading to reductions in disease severity.[1,5] The opposite is true in CD because smoking may lead to increases in symptoms or worsening of the disease in Caucasian and Middle Eastern migrants.[5] Tea or coffee consumption is protective in Asian patients.[5]

PATHOPHYSIOLOGY

Ulcerative Colitis

The inflammatory response in UC is propagated by atypical type 2 helper T cells that produce proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α).[1,3,4,10,11] Alterations in colonocyte function, epithelial cell function, and in trefoil factors are implicated, as are alterations in intestinal bacterial composition, known as *dysbiosis*.[1] The potential role of environmental factors in development of UC implies that the immune response is directed against an unknown antigen. The findings that development and severity of UC are reduced in patients who smoke, those who have had appendectomies, and patients who were breastfed may support the theory that these factors may somehow modify either the genetic component or phenotypic response to immunologic stimuli.[3–5]

The inflammatory process within the GI tract is limited to the colon and rectum in patients with UC (Figure 20–1). Most

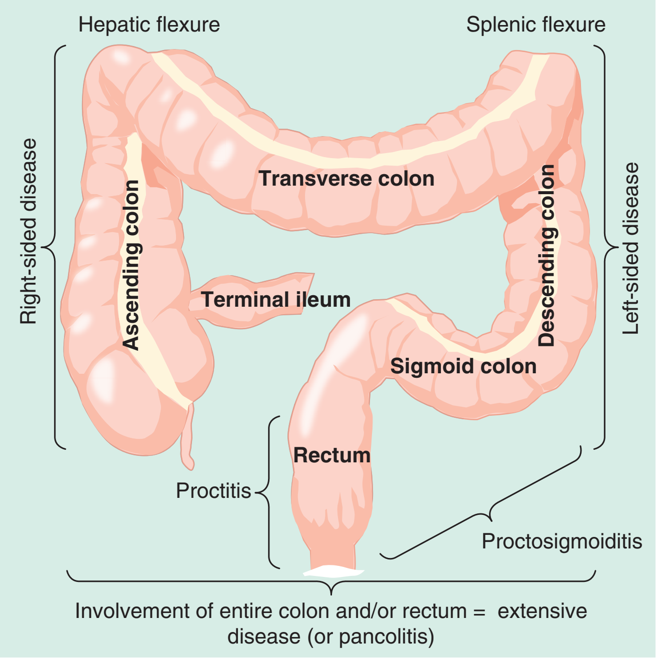

FIGURE 20–1. Major GI landmarks and disease distribution in inflammatory bowel disease.

patients with UC have involvement of the rectum (**proctitis**) or both the rectum and the sigmoid colon (**proctosigmoiditis**). Inflammation involving the entire colon is referred to as **extensive colitis**. Left-sided (distal) disease, defined as inflammation extending from the rectum to the splenic flexure, occurs in 16% to 45% of patients.[1,3,8,10] Up to 20% of cases of UC involve mild inflammation of the terminal ileum, referred to as *backwash ileitis*.[1]

The pattern of inflammation in UC is continuous and confluent throughout the affected areas of the GI tract. The inflammation is superficial and does not typically extend below the submucosal layer of the GI tract (**Figure 20–2**). Ulceration or erosion of the GI mucosa may be present, with loss of the normal vascular patter and friability.[1] Formation of **crypt abscesses** within the mucosal layers of the GI tract is characteristic of UC and may help to distinguish it from CD. Severe inflammation may also result in areas of hypertrophied GI mucosa, which may manifest as **pseudopolyps** within the colon.[1,10,11] The inflammatory response may progress in severity, leading to significant GI bleeding.

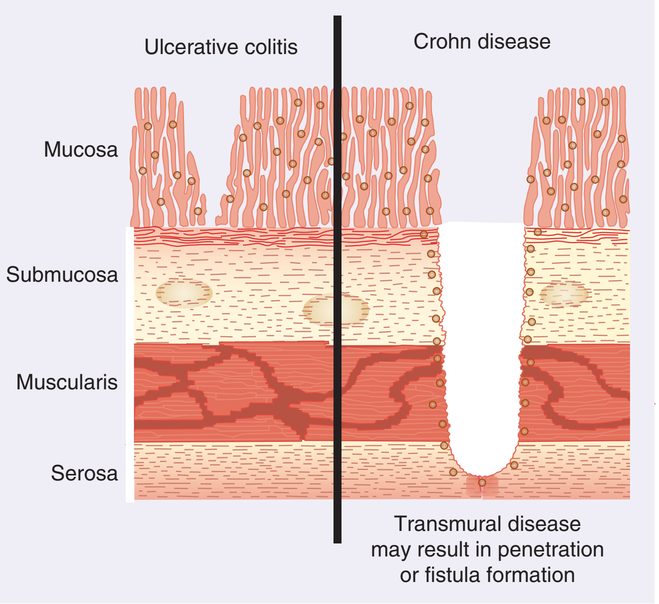
Ulcerative colitis
Crohn disease
Mucosa
Submucosa
Muscularis
Serosa
Transmural disease may result in penetration or fistula formation

FIGURE 20–2. Depth of disease penetration in ulcerative colitis and Crohn disease.

Crohn Disease

As with UC, the immune activation seen in CD involves the release of many proinflammatory cytokines. Cytokines thought to play major roles in CD are derived from T-helper type 1 cells and include interferon-γ, transforming growth factor-β, TNF-α, and IL-1, IL-6, IL-8, IL-12, and IL-23. TNF-α, IL-12, and IL-23 are major contributors to the inflammatory process and development of fibrosis in CD.[2–6,11,12] TNF-α effects include activation of macrophages, procoagulant effects in the vascular endothelium, and increased production of matrix metalloproteinases in mucosal cells.[10–15] TNF-α is also thought to induce production of nuclear factor κβ, which stimulates further production of TNF-α and other proinflammatory cytokines.[3,11] Alterations in Paneth cell function may also dictate the phenotypes of CD that are observed.[12] IL-12 and IL-23 are involved in T-cell and lymphocyte differentiation and expansion as part of the inflammatory process.[13]

In contrast to UC, the inflammation in CD may affect any part of the entire GI tract from the mouth to the anus. The small intestine is most commonly involved, and the terminal ileum and cecum are usually affected. Approximately 20% of patients have isolated colonic involvement, whereas inflammation proximal to the small intestine is almost never seen without the presence of small or large intestinal disease.[2,6]

The pattern of inflammation in CD is discontinuous; areas of inflammation are intermixed with areas of normal GI mucosa, resulting in characteristic “skip lesions.” Superficial **aphthous ulcers** may also develop in the GI mucosa. These ulcers may coalesce into larger linear ulcers, resulting in fissure formation as they increase in depth, giving rise to the characteristic “cobblestone” pattern observed upon examination of the mucosa.

The inflammation may be **transmural**, penetrating to the muscularis or serosal layers of the GI tract (Figure 20–2). This propensity for transmural involvement may lead to serious complications such as **strictures**, **fistulae**, abscesses, and perforation.[2,11] Although rectal inflammation is typically less common in CD than UC, several types of perianal lesions may be observed including skin tags, hemorrhoids, fissures, anal ulcers, abscesses, and fistulae.[14]

CLINICAL PRESENTATION AND DIAGNOSIS

KEY CONCEPT Differentiation between UC and CD is based on signs and symptoms as well as characteristic endoscopic findings, including the extent, pattern, and depth of inflammation. See accompanying box for the clinical presentation of IBD.

Extraintestinal Manifestations and Complications of IBD

KEY CONCEPT Patients may manifest signs and symptoms of disease in areas outside the GI tract (extraintestinal manifestations).[1,6,15] Painful joint complications associated with IBD include sacroiliitis

Clinical Presentation of IBD

General

- Patients with UC or CD may present with similar symptoms.
- The onset may be insidious and subacute.
- Some patients present with extraintestinal manifestations before GI symptoms occur.
- It may be impossible to distinguish between UC and CD in approximately 10% of cases. These patients are described as having "indeterminate colitis."

Symptoms

- *Ulcerative colitis*: Diarrhea (bloody, watery, or mucopurulent), rectal bleeding, abdominal pain/cramping, weight loss and malnutrition, **tenesmus**, constipation (with proctitis)
- *Crohn disease*: Diarrhea (less bloody than UC), rectal bleeding (less than UC), abdominal pain/cramping, weight loss and malnutrition (more common than UC), fatigue/malaise

Signs

- *Ulcerative colitis*: Fever, tachycardia (with severe disease), dehydration, arthritis, hemorrhoids, anal fissures, perirectal abscesses
- *Crohn disease*: Fever, tachycardia (with severe disease), dehydration, arthritis, abdominal mass and tenderness, perianal fissure or fistula

Laboratory Tests

- *Ulcerative colitis*: Leukocytosis, decreased hematocrit/hemoglobin, elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), positive test for fecal occult blood, (+) perinuclear antineutrophil cytoplasmic antibodies (pANCA; up to 70% of patients), and elevated fecal calprotectin
- *Crohn disease*: Leukocytosis, decreased hematocrit/hemoglobin, elevated ESR or CRP, positive test for fecal occult blood, (+) anti–*Saccharomyces cerevisiae* antibodies (up to 50% of patients), hypoalbuminemia with severe disease, and elevated fecal calprotectin

and ankylosing spondylitis. Ocular involvement with episcleritis, uveitis, or iritis may manifest as blurred vision, eye pain, and photophobia. Associated skin findings include pyoderma gangrenosum (papules and vesicles that develop into painful ulcerations) and erythema nodosum (red nodules of varying size typically found on the lower extremities). Nephrolithiasis may also develop at a higher rate in patients with IBD. Oxalate stones are more common in CD, and uric acid-containing stones are more common in UC.[15]

Liver and biliary manifestations of IBD include increased incidence of gallstone formation in patients with CD and development of sclerosing cholangitis or cholangiocarcinoma in patients with UC. Patients with UC are at increased risk for developing colorectal cancer and should undergo periodic cancer screening. Ongoing inflammation due to active IBD may induce a hypercoagulable state, resulting in higher rates of both arterial and venous thromboembolism, including deep vein thrombosis and pulmonary embolism. Likewise, inflammation and recurrent blood loss may result in chronic anemia. Patients with IBD also have higher rates of osteopenia, osteoporosis, and fractures, which are most strongly associated with use of corticosteroids.[16]

A serious complication of UC is toxic megacolon, defined as dilation of the transverse colon greater than 5.5 cm (2.2 in.).[1] Patients with toxic megacolon typically manifest systemic signs of severe inflammation such as fever, tachycardia, and abdominal distention.[1] Surgical intervention, including colonic resection, may be necessary to acutely manage toxic megacolon.

Patients with CD may develop significant weight loss or nutritional deficiencies secondary to malabsorption of nutrients in the small intestine, or as a consequence of multiple small- or large-bowel resections. Common nutritional deficiencies in IBD include vitamin B_{12}, fat-soluble vitamins, zinc, folate, and iron. Malabsorption in children with CD may contribute to significant reductions in growth and development.[2,6,15]

Diagnosis

Because patients often present with nonspecific GI symptoms, initial diagnostic evaluation includes methods to characterize the disease and rule out other potential etiologies. This may include stool cultures to examine for infectious causes of diarrhea.[8] Use of fecal calprotectin, a protein found in neutrophil granulocytes and released during leukocyte trafficking, is measured in the stool and may help to differentiate IBD from nonorganic disease (intestinal damage due to external causes such as drugs or mechanical intervention).[6,8] Levels greater than 120 mcg/g are considered abnormal.

Endoscopic approaches are typically used and may include colonoscopy, proctosigmoidoscopy, or possibly upper GI endoscopy in patients with suspected CD. Endoscopy is useful for determining the disease distribution, pattern and depth of inflammation, and to obtain mucosal biopsy specimens. Supplemental information from imaging procedures, such as computed tomography, abdominal X-ray, abdominal ultrasound, or intestinal barium studies may provide evidence of complications such as obstruction, abscess, perforation, or colonic dilation.[8]

The information derived from diagnostic testing and the patient's medical history and symptoms are used to gauge disease severity. Traditionally, the severity of active IBD is classified as mild, moderate, severe, or fulminant.[1,2] These categories are determined using a mix of signs, symptoms, and laboratory markers such as daily stool count, hydration status, presence of tachycardia, and elevated ESR or CRP.

A clinical care pathway developed by the American Gastroenterological Association (AGA) provides guidance on assessing severity of UC based on risk for colectomy.[17] After a diagnosis is made, inflammatory status (based on signs/symptoms, lab markers, and endoscopic findings), comorbidities, and therapy-related complications (if the patient is already receiving treatment) are assessed. Patients are then stratified according to low risk for colectomy (limited anatomic extent and mild endoscopic disease) or high risk for colectomy (extensive colitis, age less than 40 years, deep ulcers, high ESR/CRP, steroid dependence, history of hospitalization, and *Clostridioides difficile* or cytomegalovirus infection).

The AGA also developed a similar clinical decision support tool for managing CD.[18] Initially, the patient's inflammatory status, comorbidities, and disease and therapy-related complications are assessed. Categorization is slightly different from UC, and patients are considered low risk (age at initial diagnosis

Patient Encounter 1

A 28-year-old woman presents to the clinic for initial treatment of UC. A colonoscopy revealed disease confined to the rectum. She reports 2 to 3 loose stools per day on 2 to 3 days per week with intermittent tenesmus. This has caused a significant impact on her daily activities and quality of life. Her medical history is significant for seasonal allergies and she takes nonprescription cetirizine as needed. She reports no tobacco use and social intake of alcohol. She has an allergy to penicillin (hives). Her medical provider has determined this episode to be of mild to moderate severity and would like to initiate a mesalamine suppository.

How does the effectiveness of the mesalamine suppository compare to the oral formulations?

How would you educate this patient on the appropriate use of the mesalamine suppository?

over 30 years, limited anatomic involvement, no perianal and/or severe rectal disease, superficial ulcers, no prior surgical resection, and no stricturing and/or penetrating disease) or moderate-to-high risk (age at initial diagnosis less than 30 years, extensive anatomic involvement, perianal and/or severe rectal disease, deep ulcers, prior surgical resection, and stricturing and/or penetrating disease).

TREATMENT

Desired Outcomes

Treatment goals for IBD involve both management of active disease and prevention of disease relapse. **KEY CONCEPT** Major treatment goals include alleviation of signs and symptoms and suppression of inflammation during acute episodes and maintenance of remission thereafter. Addressing active IBD in a timely and appropriate manner may prevent major complications and reduce the need for hospitalization or surgical intervention.

Once control of active disease is obtained, treatment regimens are designed to achieve these long-term goals: (a) maintain remission and prevent disease relapse, (b) improve the patient's quality of life, (c) prevent the need for surgical intervention or hospitalization, (d) manage extraintestinal manifestations, (e) prevent malnutrition, and (f) prevent treatment-associated adverse effects.

General Approach to Treatment

Pharmacologic interventions for IBD are designed to target the underlying inflammatory response. **KEY CONCEPT** When designing a drug regimen for treatment of IBD, several factors should be considered, including the patient's symptoms; medical history; current medication use; drug allergies; and extent, location, and severity of disease. The history may also help identify a family history of IBD or potential exacerbating factors, such as tobacco or NSAID use.

Nonpharmacologic Therapy

No specific dietary restrictions are recommended for patients with IBD, but avoidance of high-residue foods in patients with strictures may help prevent obstruction.[1,6,7] Avoidance of excess dietary fat and foods containing emulsifying agents (eg, mayonnaise, salad dressing, ice cream) may also be preferred.[7] Nutritional strategies in patients with longstanding IBD may include vitamin and mineral supplementation and intake of soluble fiber.[7] Administration of vitamin B_{12}, folic acid, fat-soluble vitamins, and iron may be needed to prevent or treat deficiencies. In severe cases, enteral or parenteral nutrition may be needed to achieve adequate caloric intake.[7]

Patients with IBD, particularly those with CD, are also at risk for bone loss. This may be a function of malabsorption of vitamin D or repeated courses of corticosteroids.[15,16] Risk factors for osteoporosis should be determined, and baseline bone density measurement may be considered.[16] Vitamin D and calcium supplementation should be used in all patients receiving long-term corticosteroids. Oral bisphosphonate therapy may also be considered in patients receiving prolonged courses of corticosteroids or in those with osteopenia or osteoporosis.

Surgical intervention is an option in patients with complications such as fistulae or abscesses, or in patients with medically refractory disease. UC is curable with performance of a total colectomy; patients with UC may opt to have a colectomy to reduce the chance of developing colorectal cancer. Patients with CD may have affected areas of intestine resected. Unfortunately, CD may recur following surgical resection. Repeated surgeries in CD may lead to significant malabsorption of nutrients and drugs consistent with development of short-bowel syndrome.

Pharmacologic Therapy

Several pharmacologic classes are available for acute treatment and maintenance therapy of IBD. Selection of an initial agent for patients with active IBD should be designed to deliver maximum efficacy while minimizing toxicity. Response rates to individual classes of medications for both UC and CD are discussed within the specific treatment section for each disease.

▶ *Symptomatic Interventions*

Patients with active IBD often have severe abdominal pain and diarrhea. Medications used to manage these symptoms may have adverse consequences. **KEY CONCEPT** Antidiarrheal medications that reduce GI motility such as loperamide, diphenoxylate/atropine, and codeine should be avoided in patients with active IBD due to the risk of precipitating acute colonic dilation (toxic megacolon).[1,2,6] Drugs with anticholinergic properties, such as hyoscyamine and dicyclomine, are often used to treat intestinal spasm and pain, but these drugs may also reduce GI motility and should generally be avoided in active IBD.

Patients who have had multiple intestinal resections due to CD may have diarrhea related to the inability to reabsorb bile salts. Cholestyramine may improve diarrheal symptoms in this population.[14] NSAIDs should be avoided for pain management because they can worsen IBD symptoms. Opioid analgesics should be used with caution because they may significantly reduce GI motility.

▶ *Aminosalicylates*

The aminosalicylates are among the most commonly used drugs for inducing and maintaining remission in patients with mild to moderate IBD (Table 20–1). These drugs are designed to deliver 5-aminosalicylate (5-ASA, mesalamine) to areas of inflammation within the GI tract. The mechanism of mesalamine is not fully understood, but it appears to have favorable anti-inflammatory effects. The delivery of mesalamine to the affected sites is accomplished by either linking mesalamine to a carrier molecule or altering the formulation to release drug in response to changes in intestinal pH. Topical suppositories and enemas are designed to deliver mesalamine directly to the distal colon and rectum.[10,19–21]

Table 20–1

Aminosalicylates for Treatment of IBD

Drug	Trade Names	Formulation	Strengths	Daily Dosage Range (g)	Site of Action
Sulfasalazine	Azulfidine Azulfidine EN-tabs	Immediate-release or enteric-coated tablets Suspension	500 mg 250 mg/5 mL	1.6–4.8	Distal ileum and colon
Mesalamine	Rowasa	Enema	4 g/60 mL	4	Distal left colon and rectum
Mesalamine	Asacol Asacol-HD	Delayed-release resin tablet	400, 800 mg	1.6–4.8	Distal ileum and colon
	Delzicol	Delayed-release capsule	400 mg	1.6–4.8	Distal ileum and colon
	Canasa	Rectal suppository	1000 mg	1	Rectum
	Pentasa	Delayed-release capsule	250, 500 mg	2–4	Small bowel and colon
	Lialda	MMX-formulated pH-dependent polymer film–coated tablet	1.2 g	1.2–4.8	Terminal ileum and colon
	Apriso	Enteric-coated granules in polymer matrix	375 mg	1.5	Colon
Olsalazine	Dipentum	Delayed-release capsule	250 mg	1–3	Colon
Balsalazide	Colazal	Delayed-release capsule	750 mg	2–6.75	Colon
	Giazo	Tablet	1.1 g	2.2–6.6	Colon

The prototypical aminosalicylate is sulfasalazine, which chemically is mesalamine linked by a diazo bond to the carrier molecule sulfapyridine. This linkage prevents premature absorption of mesalamine in the small intestine. Once sulfasalazine is delivered to the colon, bacterial degradation of the diazo bond frees mesalamine from sulfapyridine. Sulfapyridine is then absorbed and excreted renally while mesalamine acts locally within the GI tract.

Newer mesalamine products utilize nonsulfapyridine methods for drug delivery. Olsalazine consists of two mesalamine molecules linked together, whereas balsalazide uses the inert carrier molecule 4-aminobenzoyl-β-alanine. Both drugs use a diazo bond similar to sulfasalazine. Lialda is a proprietary multimatrix (MMX) mesalamine formulation with a pH-sensitive coat that releases in the terminal ileum, allowing for once-daily dosing.[19–21] Apriso contains enteric-coated mesalamine granules also with a polymer matrix for extended release that can be given once daily.

Sulfasalazine is associated with various adverse effects, most of which are thought to be due to the sulfapyridine component. Common dose-related adverse effects include headache, dyspepsia, nausea, vomiting, and fatigue.[20–22] Idiosyncratic effects include bone marrow suppression, reduction in sperm counts in males, hepatitis, and pulmonitis. Hypersensitivity reactions may occur in patients allergic to sulfonamide-containing medications.

Nonsulfapyridine-based aminosalicylates are better tolerated than sulfasalazine. Although the types of adverse effects are similar, they occur much less frequently. However, olsalazine is associated with a higher incidence of secretory diarrhea than other aminosalicylates. These agents can be used safely in patients with a reported sulfonamide allergy, but they are more expensive than generic sulfasalazine.

▶ *Corticosteroids*

Corticosteroids have potent anti-inflammatory properties and are used in active IBD to suppress inflammation rapidly. They may be administered systemically or delivered locally to the site of action (Table 20–2). Corticosteroids usually improve symptoms and disease severity rapidly, but use should be restricted to short-term management of active disease. Long-term systemic corticosteroid use is associated with significant adverse effects, including cataracts, skin atrophy, hypertension, hyperglycemia, adrenal suppression, osteoporosis, increased risk of infection, and delayed growth in children, among others.[22–24]

Budesonide is a high-potency glucocorticoid used in IBD that has low systemic bioavailability when administered orally or rectally.[23,24] Oral formulations may release in either the terminal ileum or colon. Rectal foam formulations reach up to 40 cm from the anal verge. Compared to traditional corticosteroids, budesonide may reduce long-term adverse effects and can be used for induction therapy.[22–24]

▶ *Immunomodulators and Immunosuppressants*

Agents targeting the immune response or cytokines involved in IBD are potential treatment options (Table 20–3). Azathioprine

Table 20–2

Corticosteroids for Treatment of IBD

Drug	Trade Names	Daily Dose
Prednisone	Generic	20–60 mg orally
Prednisolone	Generic	20–60 mg orally
Methylprednisolone	Medrol (orally) Solu-Medrol (IV)	15–60 mg orally or IV
Hydrocortisone	Solu-Cortef	300 mg IV in three divided doses
	Cortenema	100 mg rectally at bedtime
	Cortifoam	90 mg rectally once or twice daily
	Anusol-HC	25–50 mg rectally twice daily
	Proctocort	30 mg rectally twice daily
Budesonide	Uceris 9-mg tablet	9 mg orally once daily
	Entocort 3-mg capsule	9 mg orally once daily
	Ortikos 6, 9 mg capsule	6 or 9 mg orally once daily
	Uceris rectal foam	2 mg twice daily, then once daily

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Table 20–3

Immunomodulators and Biologic Agents for Treatment of IBD

Drug	Trade Name(s)	Dose
Azathioprine	Imuran, Azasan	1.5–2.5 mg/kg/day orally
Mercaptopurine	Purinethol, Purixan	1.5–2.5 mg/kg/day orally
Methotrexate	Trexall	15–25 mg weekly (IM/SC/orally)
Cyclosporine	Sandimmune	4 mg/kg/day IV continuous infusion
Infliximab	Remicade	Induction: 5 mg/kg IV at 0, 2, and 6 weeks; 10 mg/kg per dose IV for nonresponders Maintenance: 5 mg/kg IV every 8 weeks
Infliximab-dyyb	Inflectra	
Infliximab-abda	Renflexis	
Adalimumab	Humira	Induction: 160 mg SC day 1 (given as four 40-mg injections in 1 day or as two 40-mg injections per day for 2 consecutive days), then 80 mg SC 2 weeks later (day 15) Maintenance: 40 mg SC every other week, starting on day 29 of therapy
Adalimumab-bwwd	Hadlima	
Adalimumab-adbm	Cyltezo	
Adalimumab-adaz	Hyrimoz	
Adalimumab-afzb	Abrilada	
Adalimumab-atto	Amjevita	
Certolizumab	Cimzia	Induction: 400 mg SC initially, then 400 mg SC at 2 and 4 weeks Maintenance: 400 mg SC every 4 weeks if initial response
Golimumab	Simponi	200 mg SC at week 0 and 2; then every 4 weeks
Natalizumab	Tysabri	Induction/maintenance: 300 mg IV every 4 weeks; discontinue by 12 weeks if no response or if unable to withdraw steroids within 6 months
Vedolizumab	Entyvio	300 mg IV at weeks 0, 2, and 6; then every 8 weeks; discontinue if no response at 14 weeks
Ustekinumab	Stelara	Weight-based initial IV dose < 55 kg (260 mg), 55–85 kg (390 mg), > 85 kg (520 mg); then 90 mg SC every 8 weeks
Tofacitinib	Xeljanz, Xeljanz XR	10 mg orally twice daily or 22 mg XR once daily for 8 weeks; may continue for up to 16 weeks Maintenance: 5 mg twice daily or 11 mg XR once daily

IM, intramuscular; IV, intravenously; SC, subcutaneously, XR, extended release.

and 6-mercaptopurine (6-MP) are immunomodulators that inhibit purine biosynthesis and reduce IBD-associated GI inflammation. They are most useful for maintaining remission of IBD or reducing the need for long-term use of corticosteroids.[1,6,25–27] Use in active disease is limited by their slow onset of action, which may be as long as 3 to 12 months. Azathioprine is metabolized to 6-MP, which is further metabolized to the active 6-thioguanine (6-TGN) nucleotide, which functions as a purine antagonist. Evaluation of 6-TGN concentrations can be performed in patients who may not be responding to therapy or may be experiencing toxicity. Adverse effects associated with azathioprine and 6-MP include hypersensitivity reactions resulting in pancreatitis, fever, rash, hepatitis, and leukopenia.[22,25–27] Patients should be tested for activity of thiopurine methyltransferase (TPMT), the major enzyme responsible for metabolism of azathioprine prior to use. Deficiency or reduced activity of TPMT may result in toxicity from azathioprine and 6-MP and may require dose reductions.

Methotrexate, also an immunomodulator, is a folate antagonist used primarily for maintaining remission of CD. It may be administered orally, subcutaneously, or IV and may have a steroid-sparing effect in patients with steroid-dependent disease.[1,6,27] Long-term methotrexate use may result in serious adverse effects, including hepatotoxicity, pulmonary fibrosis, and bone marrow suppression.

Cyclosporine is a cyclic polypeptide immunosuppressant typically used to prevent organ rejection in transplant patients. Its use in IBD is restricted to patients with fulminant or refractory symptoms in patients with active disease. Significant toxicities associated with cyclosporine are nephrotoxicity, risk of infection, seizures, hypertension, and liver function test abnormalities.[1,6,22]

▶ *Biologic Agents*

Several biologic agents targeting TNF-α are used for treatment of IBD (Table 20–3). Reduction in TNF-α activity is associated with improvement in the underlying inflammatory process. Infliximab is a chimeric anti–TNF-α agent (ie, 75% human, 25% mouse), certolizumab is a pegylated antibody fragment, and both adalimumab and golimumab are humanized anti–TNF-α antibodies.[28]

"Biosimilars" are highly similar to an Food and Drug Administration (FDA)-approved biologic agent (called the reference product) and have been shown to have no clinically meaningful differences in efficacy or adverse effects from the reference product.[28] They are not identical in structure or considered generically equivalent to the originator compound because of molecular complexity and production using recombinant DNA techniques in living organ systems. However, some biosimilars may be considered to be interchangeable with the reference product. The FDA will approve a biosimilar product only if it has the same mechanism of action, route of administration, dosage form, and strength as the reference product. Also, a biosimilar can only be approved for the indications that were previously approved for the reference product. Biosimilars have a nonproprietary name plus an FDA-designated suffix consisting of four lowercase letters that have no intended meaning. Several biosimilars are approved for use in UC and CD: Infliximab-dyyb, infliximab-abda, infliximab-qbtx, infliximab-axxq, adalimumab-adbm, adalimumab-atto, adalimumab-adaz, adalimumab-afzb, and adalimumab-bwwd. Despite being FDA approved, the adalimumab biosimilar agents were not commercially available at the time of this writing due to ongoing legal disputes with the manufacturers of the reference products.

Disadvantages of anti-TNF biologic therapy include the need for parenteral administration, significant drug cost, and the potential for serious adverse effects. Adalimumab, golimumab, and certolizumab are administered subcutaneously, whereas infliximab requires intravenous (IV) infusion. Adverse effects of IV infliximab may include infusion-related reactions such as fever, chest pain, hypotension, and dyspnea. Antibodies may develop to infliximab over time that may reduce its efficacy and predispose patients to development of infusion-related adverse effects.

All TNF-α inhibitors have been associated with reactivation of serious infections, particularly intracellular pathogens such as tuberculosis, as well as hepatitis B.[22,27] Biologic agents should not be used in patients with existing infections, and patients should be screened for latent tuberculosis and viral hepatitis prior to initiating therapy. Exacerbation of heart failure is also a potential adverse effect, so these agents should be avoided in patients with advanced or decompensated heart failure.[22] Anti–TNF-α agents also carry a risk of developing lymphoma, including a rare form known as hepatosplenic T-cell lymphoma. The risk appears to be highest in younger male patients and those using concomitant azathioprine or 6-MP.[22,27,28]

Natalizumab and vedolizumab are humanized monoclonal antibodies that antagonize integrin heterodimers, prevent α_4-mediated leukocyte adhesion to adhesion molecules, and prevent migration across the endothelium.[28,29] Natalizumab is associated with development of progressive multifocal leukoencephalopathy (PML). Vedolizumab carries a theoretical risk of PML, but this has not been reported to date. Use of natalizumab is restricted to patients who have failed all other therapies, including anti–TNF-α agents, whereas vedolizumab is a first-line alternative to anti-TNF therapy.[29]

Ustekinumab is a biologic therapy that blocks IL-21 and IL-23 action by binding to the p40 protein subunit used by these cytokines.[30] It is approved for use in moderate-to-severe UC and CD and is generally reserved for patients failing other therapies. Tofacitinib is an inhibitor of Janus kinase (JAK) and is approved for moderate to severe UC.[31] While tofacitinib is an attractive option due to its oral route of administration, it is associated with severe toxicities, such as risk of thrombosis and bone marrow suppression, and also has several drug interactions that require dose adjustment. For these reasons, it is recommended for use only after failure or intolerance of any TNF agents.[36,37]

▶ *Other Agents*

Antibiotics have been used in IBD based on the rationale that they may interrupt the inflammatory response directed against endogenous bacterial flora. Metronidazole and ciprofloxacin have been the two most widely studied agents. Metronidazole may benefit some patients with pouchitis (inflammation of surgically created intestinal pouches) and patients with CD who have had ileal resection or have perianal fistulas.[32] Ciprofloxacin has shown some efficacy in refractory active CD and may be used in combination with metronidazole. Long-term metronidazole use is associated with development of peripheral neuropathy.

Because smoking is associated with reduced UC symptoms, transdermal nicotine has been studied as a potential treatment option. Improvement in mild to moderate UC symptoms may be seen and may be more evident in patients who are ex-smokers.[1,33] Daily doses between 15 and 25 mg appear to be most effective.

Probiotics such as *Lactobacillus acidophilus* or *Bifidobacterium* have been used with the rationale that modification of host flora may alter the inflammatory response. There are minimal data to support use of probiotics in CD.[32,34] There is limited evidence for use in UC; however, the probiotic preparation VSL#3 demonstrated efficacy in reducing recurrence of pouchitis in patients with ileal pouch anal anastomosis and may prevent relapse in mild to moderate disease.[34–36]

Treatment of UC

In general, the approach to treatment of UC is based on the severity, location, and extent of disease. Both the AGA and the American College of Gastroenterology (ACG) have recently published evidence-based guidelines to assist clinicians with therapy recommendations.[35–37] The ACG guidelines also provide poor prognostic factors that are associated with a more aggressive disease course and possible need for colectomy.[36] These include age less than 40 years, extensive colitis, severe endoscopic disease, hospitalization, elevated CRP, and low serum albumin. If multiple factors are present, more aggressive treatment may need to be initiated to prevent poor outcomes.

▶ *Induction Therapy for Mild to Moderate UC*

KEY CONCEPT Treatment of acute episodes of UC is dictated by the severity and extent of disease. First-line therapy of mild to moderate disease involves oral or topical aminosalicylate derivatives, oral or topical budesonide, or oral prednisone and/or rectal steroids. The recommended treatment approach for UC is outlined in Figure 20–3. Topical mesalamine is superior to both topical corticosteroids and oral aminosalicylates for inducing remission in active mild-to-moderate UC in patients with distal disease.[21,24,35,36] Enemas are appropriate for patients with left-sided disease because the medication will reach the splenic flexure. Suppositories deliver mesalamine up to approximately 20 cm and are most appropriate for treating proctitis.[20] The combination of oral and topical mesalamine preparations is more effective and recommended in patients with extensive or left-sided disease.[20,35,36] The oral mesalamine dose target dose should be 2 to 3 g/day, with doses of greater than 3 g/day reserved for lack of response to standard doses.[35,36] Use of once-daily formulations may improve patient adherence. Induction of remission may require 4 to 8 weeks of therapy at appropriate treatment doses. Switching to an alternate formulation of mesalamine may be considered in nonresponsive patients.[36]

Topical corticosteroids have a limited role and are reserved for patients who are intolerant or unresponsive to topical mesalamine. Patients should be properly educated about appropriate use of topical products, including proper administration and adequate retention to maximize efficacy. The oral budesonide MMX formulation is recommended for patients unresponsive to optimized topical or oral mesalamine.[35,36] Oral prednisone is also an option; however, its effects are systemic, and oral formations targeting specific areas of the colon are not available. Patients requiring systemic corticosteroids should have them tapered over 4 to 12 weeks.[23]

▶ *Induction Therapy for Moderate to Severe UC*

Oral budesonide MMX may be used for short-term treatment of patients with moderately active extensive UC, whereas short-term

Patient Encounter 2, Part 1

A 27-year-old Hispanic man with mild UC presents to the gastroenterology clinic because of a 2-week history of crampy abdominal pain and 2 to 3 loose stools 2 to 3 days/week. He denies vomiting, fever, or chills.

What other pertinent information from the history would be beneficial to help determine the cause of his symptoms?

What additional information would you obtain prior to recommending drug therapy?

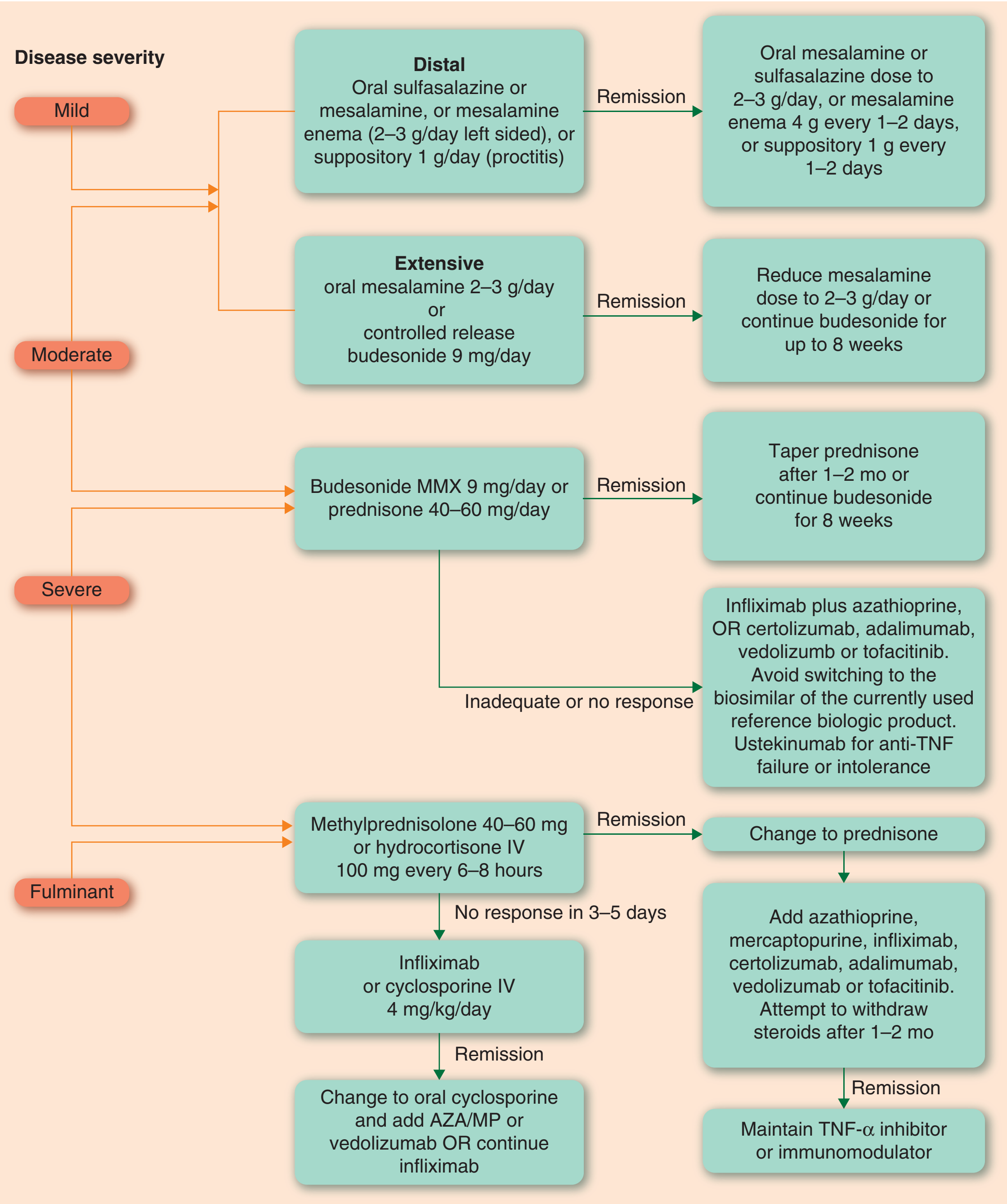
Disease severity
Mild
Moderate
Severe
Fulminant
Distal
Oral sulfasalazine or mesalamine, or mesalamine enema (2–3 g/day left sided), or suppository 1 g/day (proctitis)
Remission
Oral mesalamine or sulfasalazine dose to 2–3 g/day, or mesalamine enema 4 g every 1–2 days, or suppository 1 g every 1–2 days
Extensive
oral mesalamine 2–3 g/day or controlled release budesonide 9 mg/day
Remission
Reduce mesalamine dose to 2–3 g/day or continue budesonide for up to 8 weeks
Budesonide MMX 9 mg/day or prednisone 40–60 mg/day
Remission
Taper prednisone after 1–2 mo or continue budesonide for 8 weeks
Inadequate or no response
Infliximab plus azathioprine, OR certolizumab, adalimumab, vedolizumb or tofacitinib. Avoid switching to the biosimilar of the currently used reference biologic product. Ustekinumab for anti-TNF failure or intolerance
Methylprednisolone 40–60 mg or hydrocortisone IV 100 mg every 6–8 hours
Remission
Change to prednisone
No response in 3–5 days
Infliximab or cyclosporine IV 4 mg/kg/day
Add azathioprine, mercaptopurine, infliximab, certolizumab, adalimumab, vedolizumab or tofacitinib. Attempt to withdraw steroids after 1–2 mo
Remission
Change to oral cyclosporine and add AZA/MP or vedolizumab OR continue infliximab
Remission
Maintain TNF-α inhibitor or immunomodulator

FIGURE 20–3. Treatment approaches for ulcerative colitis. (AZA, azathioprine, IV, intravenous; MMX, multimatrix system; MP, mercaptopurine, TNF, tumor necrosis factor.) (Reproduced with permission from Hemstreet B. Inflammatory bowel disease. In: DiPiro JT, Yee GC, Posey LM, et al/, eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. McGraw-Hill: New York. www.accesspharmacy.com).

(less than 4 weeks) prednisone 40 to 60 mg/day (or equivalent) is recommended for any disease extent in patients with moderate to severe disease.[23,36,37] Biologic agents are generally considered the mainstay of therapy for moderate to severe UC. The choice of agent depends on previous exposure to biologic agents. For treatment-naive patients, infliximab or vedolizumab in combination with an immunomodulator (eg, azathioprine) is recommended. Recent data demonstrated that the efficacy of vedolizumab is superior to adalimumab in moderate to severe UC.[38] For patients previously exposed to infliximab, ustekinumab or tofacitinib are recommended.[37]

▶ *Treatment of Acute Severe UC*

Patients with acute severe UC (ASUC) generally require hospitalization. A course of methylprednisolone 40 to 60 mg IV per day should be initiated.[36,37] Infliximab as a single dose or cyclosporine (given as a continuous IV infusion of 2–4 mg/kg/day) can be used for patients not responding to IV methylprednisolone after 3 to 4 days.[36,37]

▶ *Maintenance of Remission in UC*

Unfortunately, up to 50% of patients receiving oral therapies and up to 70% of untreated patients relapse within 1 year after achieving remission.[1,36] For this reason, patients may require maintenance drug therapy indefinitely to preserve remission.

KEY CONCEPT Maintenance of remission of UC may be achieved with oral or topical aminosalicylates. In patients with mildly active proctitis, mesalamine suppositories 1 g daily are recommended, whereas mesalamine enemas are appropriate for left-sided disease and may often be dosed 2 to 3 times weekly. Oral mesalamine at doses of at least 2 g/day is recommended and may be combined with topical therapies to maintain remission.[36]

Oral or topical corticosteroids are not effective for maintaining remission and should be avoided due to the high incidence of adverse effects. Budesonide oral MMX may be continued for up to 8 weeks; however, systemic corticosteroids should be tapered over 4 to 12 weeks in moderately active UC patients achieving remission.[22,23,37]

KEY CONCEPT Immunomodulators (eg, azathioprine, 6-MP), anti-TNF agents (eg, infliximab, adalimumab, golimumab), vedolizumab, ustekinumab, or tofacitnib can be used to maintain UC remission in moderately to severely active patients who achieve remission or in those who develop corticosteroid dependency. In general, mesalamine products should be discontinued in patients who progress to moderately to severely active disease, because its effectiveness is diminished. Intermittent anti-TNF agent dosing may be used to maintain remission and reduce the need for corticosteroids in patients with moderate to severe UC. Combining a thiopurine and anti-TNF agent is more effective, and patients may be able to be transitioned to azathioprine monotherapy. Vedolizumab may be used as an alternate maintenance option if patients had a favorable response to induction therapy and is also recommended in combination with azathioprine.[36,37] Ustekinumab or tofacitinib can be continued if the patient responds, and thiopurine monotherapy can be considered in patients who achieve corticosteroid-induced remission.[36] For patients with ASUC, if remission with infliximab is achieved, this agent can be continued as maintenance therapy, while azathioprine or vedolizumab are recommended as maintenance therapies in patients achieving remission with cyclosporine.[36] Colectomy is an option for patients with progressive disease who cannot be maintained on drug therapy alone.

▶ *Treatment of CD*

See Table 20–4 for a summary of the AGA treatment recommendations for CD based on risk level.

▶ *Low-Risk Active CD*

KEY CONCEPT Induction of remission in low-risk patients with mild to moderate active CD may be accomplished with oral budesonide, with or without azathioprine, in patients with ileal and/or proximal colonic involvement and no to minimal systemic symptoms, or a tapering course of prednisone with or without azathioprine in patients with diffuse or left colonic involvement. Budesonide MMX 9 mg orally once daily for up to 8 weeks is effective for low-risk, active CD in patients with involvement of the terminal ileum or ascending colon, with success expected in 50% to 69% of patients.[2,6,18,32,39] Because the formulation releases budesonide in the terminal ileum, it is not effective in reaching sites distal to the ascending colon.[39] Conventional oral corticosteroids (eg, prednisone, methylprednisolone) may also be used with or without an immunomodulator and are preferred if there is diffuse or left-sided disease.[39] However, other oral corticosteroids carry a higher risk of adverse effects than budesonide.[6,22,32]

Sulfasalazine or mesalamine products have demonstrated minimal efficacy in patients with ileal, ileocolonic, or colonic CD but are often used due to their more favorable adverse effect profile when compared to corticosteroids.[2,6,32] Metronidazole or ciprofloxacin have not demonstrated efficacy as primary induction therapies and should be avoided.[32]

Table 20–4

Crohn Disease Initial Inductive and Maintenance Therapy Based on Risk

Risk Level	Inductive Therapy	Maintenance Therapy (Remission)
Low risk	1. Ileum and/or proximal colon with no to minimal systemic symptoms. Options: • Oral budesonide 9 mg/day without or without azathioprine • Tapering course of prednisone with or without azathioprine 2. Diffuse or left colon with no to minimal systemic symptoms. Options: • Tapering course of prednisone with or without azathioprine	Options: • Stop therapy and observe (high chance of relapse over 1 year) • Oral budesonide 6 mg/day (prolongs median time to relapse by about 114 days, but no difference in remission rates vs placebo at 1 year) • Immunosuppressive therapy (azathioprine, mercaptopurine, and methotrexate are effective in maintaining prednisone- or prednisolone-induced remissions but are associated with rare risk of infection and lymphoma)
Moderate to high risk	Moderately severe Crohn disease. Options: • Systemic corticosteroids • Use anti-TNF monotherapy over no therapy or thiopurine monotherapy • Use anti-TNF agent plus thiopurine over monotherapy with either thiopurine or anti-TNF agent • Use methotrexate for patients who do not tolerate thiopurine plus anti-TNF agent	Options: • Steroid-induced remission: Use thiopurine or methotrexate over no immunomodulator; or use anti-TNF agent with or without thiopurine over no anti-TNF agent • Anti-TNF alone or anti-TNF plus thiopurine-induced remission: Use anti-TNF agent with or without thiopurine over no anti-TNF agent

Thiopurine = azathioprine or mercaptopurine.

Anti-TNF agent = adalimumab, certolizumab, golimumab, infliximab.

Adapted from: Sandborn WJ. Crohn's disease evaluation and treatment: clinical decision tool. Gastroenterology. 2014;147:702–705.

▶ *Moderate- to High-Risk Active CD*

Patients with moderate- to high-risk CD may be treated with oral corticosteroids (eg, prednisone 40–60 mg daily). Per the AGA recommendations (Table 20–4), moderately severe patients can be treated with anti-TNF monotherapy or anti-TNF therapy combined with a thiopurine.[32,40,41] Methotrexate can be used in patients who do not tolerate purine therapy.

For patients with perianal fistulae, antibiotics (metronidazole or ciprofloxacin), infliximab, adalimumab, and certolizumab are appropriate treatment options. Complex perianal fistulae may require surgical intervention but may also be amenable to treatment with antibiotics, azathioprine, 6-MP, or anti–TNF-α agents.[14,32,41,42]

Many patients with severe CD require hospitalization for appropriate treatment. Patients should be assessed for possible surgical intervention if abdominal distention, masses, abscess, or obstruction are present. Daily IV corticosteroid doses equivalent to prednisone 40 to 60 mg may be tried as initial therapy to rapidly suppress severe inflammation.

Anti-TNF agents or vedolizumab may be used in severe active CD. Anti-TNF therapy can be combined with a thiopurine for increased effectiveness.[18,27,28,32,41] Patients failing to respond should have drug trough concentrations and antidrug antibodies assessed if anti-TNF agents are being used. Depending on the outcome, this may necessitate a dose increase or a switch to another drug within the class.[43,44] Ustekinumab is generally reserved for outpatients with severe disease who have failed other traditional therapies.

Adjunctive therapy with fluid and electrolyte replacement should be initiated. Nutritional support with enteral or parenteral nutrition may be indicated for patients unable to eat for more than 5 to 7 days. Limited evidence indicates that cyclosporine or tacrolimus are effective as salvage therapy for patients who fail IV corticosteroid therapy.[32] Surgical intervention may ultimately be necessary for medically refractory disease.

▶ *Maintenance of Remission in CD*

Patients with CD are at high risk for disease relapse after induction of remission. Within 2 years, up to 80% of patients experience a relapse; therefore, many patients require indefinite maintenance therapy. **KEY CONCEPT** Maintenance of remission of CD may be achieved with immunosuppressants (azathioprine, 6-MP, or methotrexate), biologic agents (infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab), and less frequently with oral or topical aminosalicylate derivatives.

In contrast to their use in UC, sulfasalazine and the newer aminosalicylates are marginally effective in preventing CD relapse in patients with medically induced remission, with success rates of only 10% to 20% at 1 year.[2,32,41] Despite not being recommended as first-line therapy, aminosalicylates are routinely used to attempt maintenance of remission of CD.[41]

The anti-TNF agents are effective in maintaining remission in CD.[26,27,32,41] Azathioprine and 6-MP in oral doses up to 2.5 mg/kg/day have also been shown to maintain remission in 45% of patients for up to 5 years and may be preferred for maintenance following a steroid-induced remission.[25,27,28,32] There is evidence to support use of combination therapy with an anti-TNF agent or vedolizumab plus azathioprine or methotrexate to maintain remission in CD in patients achieving steroid-induced remission.[27,28,32] Anti-TNF agents are preferred for patients with surgically induced remission and may also be combined with azathioprine in this situation.[42] Vedolizumab or ustekinumab may be used for maintenance in patients unresponsive to anti–TNF-α agents.[32,41]

Patient Encounter 2, Part 2: Medical History and Physical Examination

PMH: Mild extensive UC diagnosed 4 months ago

FH: Both parents alive; father has a history of myocardial infarction; mother has a history of hypothyroidism

SH: Works as IT support professional for a cable company, social alcohol use; no tobacco use

Allergies: Penicillin (rash)

Meds: Apriso 1.5 g/day in the morning and mesalamine enema 1 g nightly

ROS: (+) Diarrhea, abdominal pain

PE:

VS: BP 121/68 mm Hg, P 99 beats/min, RR 18/min, T 37.7°C (99.8°F)

CV: Tachycardia with normal rhythm. No murmurs, rubs, or gallops

HEENT: Slightly dry mucous membranes

Skin: No evidence of tenting

Abd: Soft, nondistended, mild diffuse tenderness, (+) bowel sounds, (–) hepatosplenomegaly, (–) masses, heme (+) stool

MS: 5/5 strength in upper and lower extremities; normal ROM

Labs:

Sodium 132 mEq/L (mmol/L)
Potassium 3.7 mEq/L (mmol/L)
Chloride 100 mEq/L (mmol/L)
Bicarbonate 25 mEq/L (mmol/L)
BUN 15 mg/dL (5.4 mmol/L)
Serum creatinine 1 mg/dL (88 μmol/L)
Glucose 100 mg/dL (5.6 mmol/L)
AST 21 IU/L (0.35 μkat/L)
ALT 20 IU/L (0.33 μkat/L)
Albumin 3.9 g/dL (39 g/L)
CRP 3.1 mg/dL (31 mg/L)
A1C 5% (0.05; 31 mmol/mol Hb)
ESR 100 mm/hr
Hemoglobin 10 g/dL (100 g/L; 6.21 mmol/L)
Hematocrit 37% (0.37)
WBC 16.0 × $10^3/mm^3$ (16.0 × $10^9/L$)
Platelets 460 × $10^3/mm^3$ (460 × $10^9/L$)

Abdominal X-ray: (–) obstruction, free-air, or colonic dilation

Colonoscopy: Superficial continuous inflammation involving the rectum and extending proximally with evidence of recent bleeding, (–) polyps or strictures, biopsy taken

Pathology: Evidence of crypt abscesses

What factors should you consider in choosing appropriate therapy for this patient?

What treatment options would you consider at this time?

What are some important educational points you would provide to this patient regarding appropriate use of his medication?

Patients not responding to anti-TNF agents should have drug trough levels obtained and be assessed for presence of antibodies.[43] Dose escalation or switching to another anti-TNF agent may be required. Similarly, evaluation of azathioprine metabolites, particularly 6-thioguanine, should be performed to evaluate the need for dose escalation if there is lack of response or in the setting of potential thiopurine toxicity.[35,44]

Systemic or topical corticosteroids should not be used for maintaining remission in patients with CD. Unfortunately, up to 50% of patients treated acutely with corticosteroids become dependent on them to prevent symptoms.[2] Budesonide 6 mg (2 × 3-mg Entocort capsules) orally once daily may be used in place of conventional corticosteroids after remission induction in mild to moderate CD or in patients dependent on corticosteroids for up to 4 months; however, it has minimal effectiveness.[2,22,41]

Treatment of IBD in Special Populations (Table 20–5)

▶ *Older Persons*

Approximately 10% to 30% of patients with IBD initially develop symptoms after age 60.[45] In general, IBD presents similarly in older patients and younger individuals. Elderly patients may have more comorbid diseases, some of which may make the diagnosis of IBD more difficult. Such conditions include ischemic colitis, diverticular disease, and microscopic colitis. Increased age is also associated with a higher incidence of adenomatous polyps, but the onset of IBD at an advanced age does not appear to increase the risk of developing colorectal cancer. Older patients may also use more medications, particularly NSAIDs, which may induce or exacerbate colitis. Adherence may be more challenging for older patients, especially for injectable products, and costs of some

Table 20–5

Dosing Considerations of IBD Therapies in Special Populations

Therapy	Pediatric Patients	Older Patients	Pregnancy
Sulfasalazine	Age > 2 years: 40–60 mg/kg/day in 3–6 divided doses; 30 mg/kg/day in 3–6 divided doses for maintenance	No specific changes	Category B[a] Administer folic acid 2 mg daily during prenatal period and pregnancy
Mesalamine	No specific changes; Balsalazide indicated for age > 5 years	No specific changes	Category B (Olsalazine Category C) Generally considered safe and effective
Corticosteroids	No specific changes	No specific changes Elderly patients at high risk for osteoporosis	Older agents not rated Budesonide category C Generally considered safe and effective
TNF-α inhibitors	Infliximab indicated for pediatric patients: 5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks Adalimumab indicated for patients age ≥ 6 or greater: 80 mg (< 40 kg), 40 mg week 2, then 20 mg every other week or 160 mg (> 40 kg) initial followed by 80 mg week 2, then 40 mg every other week	Avoid in patients with heart failure Elderly patients at higher risk for infections	Category B Pregnancy registry for adalimumab via manufacturer
Natalizumab	Dose of 3 mg/kg IV at 0, 4, and 8 weeks reported; data are lacking in children	No specific changes	Category C Report pregnancy to manufacturer's pregnancy registry
Vedolizumab	Not indicated	No specific changes	Category B Manufacturer pregnancy exposure registry
Ustekinumab	Not indicated	No specific changes	Manufacturer pregnancy exposure registry
Azathioprine, 6-Mercaptopurine	1.5–2 mg/kg/day to start	No specific changes	Category D Accepted as safe Avoid initiating during pregnancy, but continue if patient is already receiving when pregnant
Methotrexate	17 mg/m^2 orally/SC/IM	No specific changes	Category X Contraindicated
Cyclosporine	No specific changes	No specific changes	Category C Use only in refractory patients
Tofacitinib	Not indicated	Adjust for renal/hepatic function	Manufacturer pregnancy exposure registry
Metronidazole	30–50 mg/kg/day divided every 6 hours	No specific changes	Category B Use short courses if possible
Ciprofloxacin	Avoid use	Adjust dose for CrCl < 50 mL/min (0.83 mL/s)	Category C Consider other alternatives

[a] In 2015, the FDA recommended that the pregnancy categories be replaced with narrative recommendations to better inform clinical decision-making. Drugs submitted for approval after June 30, 2015 will use this new designation immediately, whereas those approved after June 30, 2001 will be gradually phased in (https://www.drugs.com/pregnancy-categories.html).

CrCl, creatinine clearance; IM, intramuscular; SC, subcutaneously.

agents may be problematic depending on the patient's financial or insurance situation.

Treatment of older patients with IBD is similar to that for younger patients, but special consideration should be given to some of the medications used. Corticosteroids may worsen diabetes, hypertension, heart failure, or osteoporosis. The TNF-α inhibitors should be used cautiously in patients with heart failure and should be avoided in New York Heart Association class III or IV disease. Older patients requiring major surgical interventions may be at higher risk for surgical complications or may not meet eligibility criteria for surgery because of comorbid conditions, age-related organ dysfunction, or reduced functional status.[45]

▶ *Children and Adolescents*

Crohn disease occurs more often than UC in pediatric patients, accounting for up to 73% of pediatric IBD cases.[46] Approximately 6% to 15% of children with IBD present at 6 years of age or younger, which is referred to as very-early-onset IBD (VEO-IBD).[47] Both forms of IBD may present similarly in children, with abdominal pain and diarrhea being common. However, risk of growth failure secondary to inadequate nutritional intake and failure to thrive or pubertal delay may be an initial presentation of IBD, especially in CD. Aggressive nutritional interventions may be required to facilitate adequate caloric intake.

The aminosalicylates, azathioprine, 6-MP, and infliximab are all viable options for treatment and maintenance of IBD in pediatric patients.[48,49] Corticosteroids should be reserved for short-term use as induction therapy. Infliximab is approved for use in the United States for patients 6 to 17 years of age with moderate-to-severe active CD. Use of immunosuppressive therapy or infliximab may help reduce overall corticosteroid exposure. Adalimumab is also approved for use in patients 6 years of age or older with CD. Certolizumab, natalizumab, vedolizumab, and ustekinumab are only FDA approved for use in adults with IBD; data in children are limited.

▶ *Pregnant Women*

Inducing and maintaining remission at least 3 to 6 months prior to conception is the optimal approach in women with IBD who plan to become pregnant. Pregnant women with IBD are at higher risk of spontaneous abortion, preterm birth, low birth weight infants, and complications of delivery such as preeclampsia and liver and platelet disorders.[50] Given these implications, preconception counseling should be provided, and good communication among medical providers is necessary. Health-care maintenance should be optimized, including ensuring vaccination schedules are up to date, and disease severity should be assessed.[50]

The aminosalicylates are considered safe in pregnancy, but sulfasalazine is associated with folate malabsorption. Because pregnancy results in a higher folate requirement, pregnant patients treated with sulfasalazine should be supplemented with folic acid 1 mg orally twice daily. Patients also may need vitamin B_{12} and iron supplementation. Methotrexate is a known abortifacient and should be discontinued at least 3 months prior to patients becoming pregnant and an alternate medication initiated.[51] Thiopurines and biologic agents are considered low risk in pregnant women, and systemic corticosteroids can be used intermittently for disease flares.[50]

As pregnancy progresses, there is a potential risk of increased placental transfer of biologic drugs. Recommendations are to modify the dosing schedule in the third trimester to allow for the last dose to be given as far in advance of delivery as possible to reduce placental transfer.[50] This may require evaluation of trough concentrations of the anti-TNF agents.[44] Metronidazole carries a theoretical risk of mutagenicity in humans, but short courses are generally safe during pregnancy. Prolonged use of metronidazole should be avoided in pregnant patients due to lack of safety data supporting its use. Ciprofloxacin should be avoided in pregnant women. Last, the safety of continuing current therapies for IBD should be evaluated if the patient is considering breastfeeding to assess potential risk if the drugs are transferred into breast milk.

OUTCOME EVALUATION

- Monitor for improvement of symptoms in patients with active IBD, such as reduction in the number of daily stools, abdominal pain, fever, and heart rate.
- For patients in remission, assure that proper maintenance doses are used and inform the patient to seek medical attention if symptoms recur or worsen.
- Evaluate patients receiving systemic corticosteroid therapy for improvement in symptoms and opportunities to taper or discontinue therapy. For patients using more than 5 mg daily of prednisone for more than 2 months or for steroid-dependent patients, consider the following:
    - Central bone mineral density testing to evaluate need for calcium, vitamin D, or bisphosphonate therapy
    - Periodic monitoring of blood glucose, lipids, and blood pressure
    - Evaluation for evidence of Cushingoid features or signs or symptoms of infection
- When considering treatment with azathioprine or 6-MP, obtain baseline complete blood count (CBC), liver function tests, and TPMT activity. These tests, except TPMT, should be monitored closely (every 2–4 weeks) at the start of therapy and then approximately every 3 months during maintenance therapy.
- With azathioprine and 6-MP, monitor for hypersensitivity reactions including severe skin rashes and pancreatitis. Educate the patient regarding signs and symptoms of pancreatitis (nausea, vomiting, and abdominal pain).
- Prior to initiating methotrexate therapy, obtain CBC, serum creatinine, liver function tests, chest X-ray, and pregnancy test (if female). Monitor blood counts weekly for 1 month, then monthly thereafter.
- Prior to initiating anti-TNF therapy, ustekinumab, vedolizumab, or tofacitinib, obtain a tuberculin skin test to rule out latent tuberculosis, monitor for signs and symptoms of tuberculosis, and measure viral hepatitis serologies. Also monitor patients with a prior history of hepatitis B virus infection for signs of liver disease, such as jaundice. Assure that patients do not have a clinically significant systemic infection or New York Heart Association class III or IV heart failure.
- In patients receiving infliximab, monitor for infusion-related reactions such as hypotension, dyspnea, fever, chills, or chest pain when administering IV doses.
- Recommended trough concentrations for anti-TNF biologic agents are infliximab ≥ 5 mcg/mL (mg/L), adalimumab ≥ 7.5 mcg/mL (mg/L), and certolizumab ≥ 20 mcg/mL (mg/L).[43,44] If trough concentrations are not

Patient Care Process

Collect Information:

- Evaluate the medical record to determine the extent and location of IBD.
- Assess for evidence of extraintestinal manifestations or GI complications related to IBD.
- Interview the patient to evaluate the impact on quality of life and to identify psychosocial problems related to the presence of IBD.

Assess the Information:

- Assess inflammatory status, severity, and classify as high versus low risk for colectomy.
- Determine if the patient is treatment-naive or if they are currently receiving pharmacotherapy.
- Evaluate the patient's current medication doses and adherence to therapy. Identify potential barriers to adherence, such as cost or inability to properly use certain drug formulations.
- Identify adverse effects related to current therapy.

Develop a Care Plan:

- Based on the current therapy and disease severity and location, choose appropriate drug(s) and formulations to target the regions of intestinal inflammation.
- Process any prior authorizations for insurance providers that require this.

Implement the Care Plan:

- Remove or switch medications that may be exacerbating IBD symptoms.
- Educate the patient on proper use of drug therapy, including when to expect symptom improvement after initiation of treatment and which signs or symptoms to report that might be adverse drug effects.
- Provide a detailed description of the tapering schedule for corticosteroids if applicable.
- Refer patients to available support groups or IBD organizational resources if they are having difficulty coping with their disease.

Follow-up: Monitor and Evaluate:

- Depending on disease severity, follow up in 2 to 4 weeks. Earlier telephone follow-up may be required to determine whether the patient is achieving some relief of symptoms.
- Assess adherence to therapy and determine if drug concentrations should be evaluated if lack of response is present.
- Assess patient quality of life and impact of treatment on ability to perform daily activities.

adequate, check for antidrug antibody levels. Based on the result, this may necessitate a dose increase or change to another agent.[43.44]

- In patients with fistulae, monitor at every anti-TNF therapy dosing interval for evidence of fistula closure and overall reduction in the number of fistulae.
- If receiving natalizumab or vedolizumab therapy, monitor for signs of PML such as mental status changes, signs of liver disease (eg, jaundice), and hypersensitivity reactions following administration.

Abbreviations Introduced in This Chapter

5-ASA	5-Aminosalicylate
6-MP	6-Mercaptopurine
ASUC	Acute severe ulcerative colitis
CD	Crohn disease
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
HLA	Human leukocyte antigen
IBD	Inflammatory bowel disease
IL	Interleukin
NSAID	Nonsteroidal anti-inflammatory drug
pANCA	Perinuclear antineutrophil cytoplasmic antibodies
PR	Per rectum
TNF-α	Tumor necrosis factor-α
TPMT	Thiopurine methyltransferase
UC	Ulcerative colitis
VEO-IBD	Very-early-onset inflammatory bowel disease

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21

Nausea and Vomiting

Sheila Wilhelm and Melissa Lipari

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Identify common causes of nausea and vomiting.
2. Describe the pathophysiologic mechanisms of nausea and vomiting.
3. Distinguish between simple and complex nausea and vomiting.
4. Create goals for treating nausea and vomiting.
5. Describe attributes of available antiemetic therapies.
6. Recommend treatment regimens for nausea and vomiting associated with cancer chemotherapy, surgery, pregnancy, or motion sickness.
7. Outline a monitoring plan to evaluate treatment outcomes for nausea and vomiting.

INTRODUCTION

Nausea and vomiting result from complex interactions of the gastrointestinal (GI) system, the vestibular system, and the brain and have a variety of causes. Preventing and treating nausea and vomiting requires pharmacologic and nonpharmacologic measures tailored to individual patients and situations.

EPIDEMIOLOGY AND ETIOLOGY

KEY CONCEPT Nausea and vomiting are symptoms that can be due to many different causes such as GI, cardiac, neurologic, and endocrine disorders and various medications (Table 21–1).[1,2] Cancer chemotherapy agents are rated according to their emetogenic potential, and antiemetic therapy is prescribed based on these ratings. Radiation therapy can induce nausea and vomiting, especially when it is used to treat abdominal malignancies.[3]

Oral contraceptives, hormone therapy, and opioids can cause nausea and vomiting.[1] Some medications, such as digoxin, cause nausea and vomiting in a dose-related fashion, which may indicate excessive drug concentrations. Ethanol and other toxins also cause nausea and vomiting.

Postoperative nausea and vomiting (PONV) occurs in 30% of surgical patients overall and in up to 70% of high-risk patients.[4] Risk factors for PONV include female sex, history of motion sickness or PONV, nonsmoking status, and use of opioids postoperatively.[5] The choice of anesthetic agents and duration of surgery may also contribute to PONV.[4,5]

Nausea and vomiting of pregnancy (NVP) affects 50% to 80% of pregnant women, especially early in pregnancy.[6] In 0.3% to 3% of pregnancies, this can lead to hyperemesis gravidarum, a potentially life-threatening condition of prolonged nausea, vomiting, and resultant malnutrition.[6]

PATHOPHYSIOLOGY

Nausea is the unpleasant subjective feeling of the need to vomit.[1,2] Autonomic symptoms of pallor, tachycardia, diaphoresis, and salivation often accompany nausea. Vomiting (or emesis) is a forceful oral expulsion of upper GI contents due to sustained contractions in the abdominal and thoracic musculature.[1] Specific areas in the central nervous system (CNS) and GI tract are stimulated when the body is exposed to noxious stimuli or GI irritants: the chemoreceptor trigger zone (CTZ) in the area postrema of the fourth ventricle of the brain, the vestibular apparatus, visceral afferents from the GI tract, and the cerebral cortex.[1] These in turn stimulate regions of the reticular areas of the medulla within the brainstem. This area is the central vomiting center, which coordinates the impulses sent to the salivation and respiratory centers, and the pharyngeal, GI, and abdominal muscles that lead to vomiting (Figure 21–1).[7]

The CTZ, located outside the blood–brain barrier, is exposed to cerebrospinal fluid and blood.[1] Therefore, it is easily stimulated by uremia, acidosis, and circulating toxins such as chemotherapeutic agents. The CTZ has many 5-hydroxytryptamine (serotonin) type 3 (5-HT_3), neurokinin-1 (NK_1), and dopamine type 2 receptors (D_2).[8] Visceral vagal nerve fibers are rich in 5-HT_3 receptors. They respond to GI distention, mucosal irritation, and infection.

Motion sickness is caused by stimulation of the vestibular system, rich in histaminic (H_1) and muscarinic cholinergic receptors.[9] The cerebral cortex is affected by sensory input such as sights, smells, or emotions that can lead to vomiting. This area is involved in anticipatory nausea and vomiting associated with chemotherapy.

Nausea and vomiting can be classified as either simple or complex.[10] Simple nausea and vomiting occurs occasionally and is either self-limiting or relieved by minimal therapy. It does not detrimentally affect hydration status, electrolyte balance, or weight. Alternatively, complex nausea and vomiting requires

Table 21–1

Causes of Nausea and Vomiting

GI or Intraperitoneal	Cardiac	Neurologic	Therapy or Toxin Induced	Endocrine/Metabolic
Mechanical obstruction	Cardiomyopathy	Vestibular disease	Antibiotics	Pregnancy (NVP or hyperemesis gravidarum)
Achalasia	Myocardial infarction	Motion sickness	Antiarrhythmics	Uremia
Enteric infections	Heart failure	Labyrinthitis	Aspirin	Diabetic ketoacidosis
Pancreatitis		Migraine headache	Cancer chemotherapy	Hyperthyroidism
Inflammatory bowel disease		Increased intracranial pressure	Digoxin	Parathyroid disease
Irritable bowel syndrome		Intracranial hemorrhage	Iron	Addison disease
Cholecystitis		Meningitis	Lead	
Hepatitis		Hydrocephalus	Marijuana	
Gastroparesis		Psychogenic causes	Oral antidiabetics	
Gastroesophageal reflux		Eating disorders	Oral contraceptives	
Peptic ulcer disease		Depression	Opioids	
Peritonitis		Anxiety disorders	Anticonvulsants	
			Radiation therapy	
			Ethanol	

more aggressive therapy because electrolyte imbalances, dehydration, and weight loss may occur.

CLINICAL PRESENTATION AND DIAGNOSIS

Refer to the accompanying box for the clinical presentation and diagnosis of nausea and vomiting.

TREATMENT

Desired Outcomes

The primary goals of treatment are to relieve the symptoms of nausea and vomiting, increase quality of life, and prevent complications such as dehydration or malnutrition. Drug therapy for nausea and vomiting should be safe, effective, and economical.

General Approach to Treatment

KEY CONCEPT To treat nausea and vomiting most effectively, it is important to first identify and treat the underlying cause. Profuse or prolonged vomiting can lead to complications of dehydration and metabolic abnormalities. Patients must have adequate hydration and electrolyte replacement orally (if tolerated) or IV to prevent and correct these problems. Some pharmacologic treatments work locally in the GI tract, whereas others work in the CNS.[1]

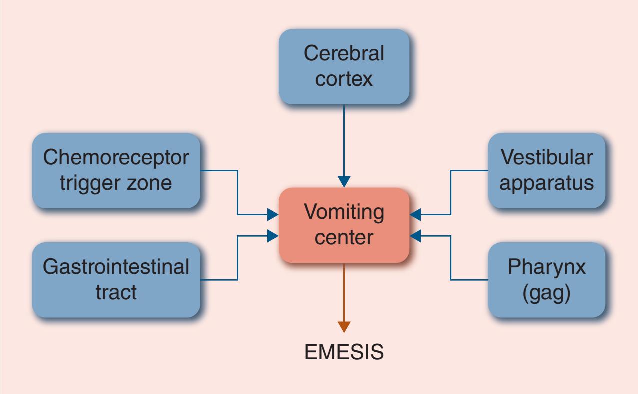

FIGURE 21–1. Primary afferent components to the vomiting center. (Reproduced, with permission, from Toy EC, Loose DS, Tischkau SA, Pillai AS, eds. Case Files: Pharmacology, 3rd ed. New York, NY: McGraw-Hill; 2014.)

Nonpharmacologic Therapy

KEY CONCEPT Nonpharmacologic approaches to nausea and vomiting include dietary, physical, and psychological measures. Dietary management is important when treating NVP due to concern for teratogenic effects with drug therapies.[11] Recommendations include eating frequent, small meals; avoiding spicy or fatty foods; eating high-protein snacks; avoiding iron-containing pills; and eating bland or dry foods the first thing in the morning.[6,11]

Clinical Presentation and Diagnosis of Nausea and Vomiting

Symptoms

- Patients with nausea often complain of autonomic symptoms such as diaphoresis, disinterest in surroundings, pallor, faintness, and salivation.

Signs

- With complex and prolonged nausea and vomiting, patients may show signs of malnourishment, weight loss, and dehydration (dry mucous membranes, skin tenting, tachycardia, and lack of axillary moisture).

Laboratory Tests

- Dehydration, electrolyte imbalances, and acid–base disturbances may be evident in complex and prolonged nausea and vomiting.
- Dehydration is suggested by elevated blood urea nitrogen (BUN), serum creatinine (SCr), and BUN-to-SCr ratio (20:1 or greater using traditional units of measurement [100:1 or greater using SI units of mmol/L]).
- Calculated fractional excretion of sodium (FeNa) less than 1% (0.01) indicates dehydration and reduced renal perfusion.
- Low serum chloride and elevated serum bicarbonate levels indicate metabolic alkalosis.
- Hypokalemia may occur from GI potassium losses and intracellular potassium shifts to compensate for alkalosis.

The dietary supplement ginger (500–1000 mg daily given in three to four divided doses) was effective in NVP in some studies and is recommended in treatment guidelines.[6,11]

Acupressure and electroacupoint stimulation of the P6 (Neiguan) point on the inside of the wrist seem safe and cost-effective; however, efficacy data for treatment of NVP, PONV, and motion sickness are conflicting.[6,12,13] Hypnosis and psychotherapy are also safe during pregnancy and in situations where adverse drug effects and interactions are a concern.

Pharmacologic Therapy

Table 21–2 contains the names, usual dosages, and common adverse effects of the pharmacologic treatments for nausea and vomiting.[1,4,10,14]

▶ *Anticholinergics (Scopolamine)*

Scopolamine blocks muscarinic receptors in the vestibular system, thereby halting signaling to the CNS. It is effective for preventing and treating motion sickness and has some efficacy in preventing PONV.[15] Scopolamine is available as an adhesive transdermal patch that is effective for up to 72 hours after application. This may be beneficial for patients unable to tolerate oral medications or those requiring continuous prevention of motion sickness (eg, passengers on cruise ships). Transdermal scopolamine should be applied 4 hours prior to motion sickness triggers and the evening before surgery if used to prevent PONV. Scopolamine is associated with adverse anticholinergic effects such as sedation, visual disturbances, dry mouth, and dizziness. These adverse effects are worsened when a patient is taking concurrent anticholinergic agents, and these agents should be used with caution in older adults.

▶ *Antihistamines*

Antihistamines are used to prevent and treat nausea and vomiting due to motion sickness, vertigo, or migraine headache.[1,9,16] Their efficacy is presumably due to the high concentration of H_1 and muscarinic cholinergic receptors within the vestibular system. First-generation antihistamines cause undesired effects including drowsiness, blurred vision, and urinary retention. Although first-generation antihistamines are effective, the second-generation antihistamines cetirizine and fexofenadine were found to be ineffective for treating motion sickness, perhaps because they lack CNS depressant properties.[17]

Some first-generation antihistamines such as diphenhydramine, dimenhydrinate, doxylamine, and meclizine are available without a prescription, making self-treatment convenient. The combination of doxylamine and vitamin B6 (pyridoxine) has efficacy in NVP. Antihistamines are available in a variety of dosage forms, including oral capsules, tablets, and liquids. Liquid formulations are convenient for children or adults who are unable to swallow solid dosage forms.

▶ *Dopamine Antagonists*

Stimulation of D_2 receptors in the CTZ leads to nausea and vomiting (Figure 21–1). There are three main groups of dopamine antagonists: phenothiazines, butyrophenones, and prokinetic agents. Phenothiazine antiemetics act primarily via a central antidopaminergic mechanism in the CTZ.[1] Phenothiazines used to treat nausea and vomiting include promethazine, prochlorperazine, and chlorpromazine. Availability in multiple dosage forms (ie, oral, parenteral, rectal) permits use in a variety of settings including severe motion sickness or vertigo, gastritis or gastroenteritis, NVP, PONV, and chemotherapy-induced nausea and vomiting (CINV).[18,19]

Phenothiazines may cause sedation, orthostatic hypotension, and **extrapyramidal symptoms (EPS)** such as dystonia (involuntary muscle contractions), tardive dyskinesia (irreversible and permanent involuntary movements), and akathisia (motor restlessness or anxiety).[1,20] Chronic phenothiazine use has been associated with EPS, but single doses have also caused these effects.[21] Promethazine intravenous injection should not be administered in an undiluted bolus because this may lead to tissue necrosis requiring limb amputation.[20] The highest risk for this adverse event is when the medication is administered intra-arterially.

Droperidol, a butyrophenone, is another centrally acting antidopaminergic agent effective for preventing PONV.[1,4] It may also be used for treating CINV for patients who are intolerant to serotonin receptor antagonists and corticosteroids.[14] Its adverse effects include sedation, agitation, and restlessness. Droperidol carries a US FDA black box warning regarding the potential for QT interval prolongation and cardiac arrhythmias that may result in torsades de pointes and sudden cardiac death.[22] Droperidol should not be used in patients with a prolonged QT interval or in those who are at risk for developing a prolonged QT interval (eg, heart failure, electrolyte abnormalities, bradycardia, or concurrent use of medications that may prolong the QT interval).[22] A 12-lead electrocardiogram (ECG) is recommended prior to treatment with droperidol.

Haloperidol is another butyrophenone with some antiemetic effects at low doses (0.5–2 mg).[23] QTc prolongation is a concern with haloperidol use. However, in a meta-analysis of PONV therapy with low-dose haloperidol versus a 5-HT_3 receptor antagonist, nausea and vomiting reduction as well as incidence of QTc prolongation did not differ significantly between treatments.[24]

Metoclopramide and domperidone (not available in the United States) act as D_2-receptor antagonists centrally in the CTZ and peripherally in the GI tract.[1] They also display cholinergic activity, which increases lower esophageal sphincter tone and promotes gastric motility. Their antiemetic and prokinetic effects are useful in PONV, CINV, gastroparesis, and gastroesophageal reflux disease (GERD).[1,4,14] Metoclopramide is available in injectable, oral solid, and oral liquid dosage forms, allowing for its use in both hospitalized and ambulatory patients.

Metoclopramide crosses the blood–brain barrier and has centrally mediated adverse effects. Young children and the elderly are especially susceptible to these effects, which include somnolence, reduced mental acuity, anxiety, depression, and EPS and occur in 10% to 20% of patients.[1,25]

Domperidone minimally crosses the blood–brain barrier and is less likely to cause centrally mediated adverse effects.[1,25] It should not be used for patients with underlying long QT interval or for those taking medications that prolong the QT interval. Both metoclopramide and domperidone can cause hyperprolactinemia, galactorrhea, and gynecomastia.

▶ *Corticosteroids*

Oral or IV corticosteroids, especially dexamethasone and methylprednisolone, are used alone or in combination with other antiemetics for preventing and treating PONV, CINV, or radiation-induced nausea and vomiting.[3,8,14,23] Efficacy is thought to be due to release of 5-HT, reduced permeability of the blood–brain barrier, and decreased inflammation.[26] Common adverse effects with short-term use include GI upset, anxiety, insomnia, and hyperglycemia.[14] Adverse effects associated with long-term use (eg, decreased bone mineral density, diabetes, cataracts) are not usually seen when corticosteroids are used for acute nausea and vomiting.

Table 21–2

Antiemetic Agents: Usual Doses for Adults and Children and Adverse Effects

Drug	Adult Dosing	Pediatric Dosing	Adverse Effects[a]
Anticholinergics			
Scopolamine	TD: 1.5 mg patch applied 1 or more hours before the procedure, 4 hours prior to motion sickness triggers, repeated every 72 hours as needed	N/A	Most common: Dry mouth, drowsiness, blurred vision Rare: Disorientation, dizziness, hallucinations
Antihistamines			
Cyclizine	Oral: 50 mg every 4–6 hours as needed	Oral: 6–11 years: 25 mg every 6–8 hours as needed (max: 3 tablets/day)	Most common: Sedation, dry mouth, constipation Less common: Confusion, blurred vision, urinary retention
Dimenhydrinate	Oral: 50–100 mg every 4–6 hours as needed	Oral: 2–6 years, 12.5–25 mg every 6–8 hours not to exceed 75 mg in 24 hours; 6–12 years, 25–50 mg every 6–8 hours, not to exceed 150 mg in 24 hours	
Diphenhydramine	Oral: 25–50 mg every 4–6 hours IV/IM: 10–50 mg every 2–4 hours as needed	Oral/IV/IM: 2–6 years, 6.25 mg every 4–6 hours	
Doxylamine	Oral: 20–40 mg daily	N/A	
Hydroxyzine	Oral/IV/IM: 25–100 mg every 4–6 hours as needed	Oral: 0.6 mg/kg IM: 0.5–1 mg/kg	
Meclizine	Oral: 12.5–25 mg every 12–24 hours as needed	Oral: ≥12 years: use adult dose	
Phenothiazines			
Chlorpromazine	Oral: 10–25 mg every 4–6 hours as needed IV/IM: 25–50 mg every 4–6 hours as needed	Oral: ≥ 6 months, 0.5 mg/kg every 4–6 hours as needed IV/IM: ≥ 6 months, 0.5–1 mg/kg every 6–8 hours	Most common: Sedation, lethargy, skin sensitization Less common: Cardiovascular effects, EPS, cholestatic jaundice, hyperprolactinemia
Prochlorperazine	Oral: 5–10 mg three to four times a day as needed Supp: 25 mg twice daily as needed IV/IM: 2.5–10 mg every 3–4 hours as needed	Oral: > 2 years and > 9 kg: 0.4 mg/kg/day or 10 mg/m^2 daily in two to three divided doses Supp: See oral dosing IM: > 2 years and > 9 kg: 0.13 mg/kg	Avoid using in pediatric patients if possible due to sensitivity to adverse effects. If use is considered necessary, employ the lowest effective dose
Promethazine	Oral/IM/IV/Supp: 12.5–25 mg every 4–6 hours as needed	Oral/IM/IV/Supp: ≥ 2 years, 0.25–0.5 mg/kg or 7.5–15 mg/m^2 four to six times daily	
Butyrophenones			
Droperidol	IM/IV: 0.625–2.5 mg every 4–6 hours as needed	IM/IV: 2–12 years: 0.05–0.1 mg/kg (max 2.5 mg) every 4–6 hours as needed	Most common: Sedation, hypotension, tachycardia Less common: EPS, dizziness, increased blood pressure, chills, hallucinations, QT prolongation
Haloperidol	Oral, IM/IV: 0.5–5 mg every 12 hours as needed	N/A	
Benzamides			
Domperidone	Oral: 10–20 mg every 4–8 hours as needed Supp: 30–60 mg every 4–8 hours as needed	Oral: 0.2–0.4 mg/kg every 4–8 hours as needed for CINV prophylaxis Supp: Max daily dose based on weight	Most common: Sedation, restlessness, diarrhea (metoclopramide), agitation, CNS depression Less common: EPS, hypotension, neuroleptic syndrome, supraventricular tachycardia (with IV), QT prolongation, serotonin syndrome (when used with serotonergic agents)
Metoclopramide	PONV: 10–20 mg oral/IV/IM 10 min prior to anesthesia CINV Prophylaxis: 1–2 mg/kg oral/IV every 2–4 hours	N/A	
Trimethobenzamide	IM: 200 mg two to four times a day as needed	Not recommended	

(*Continued*)

Table 21–2

Antiemetic Agents: Usual Doses for Adults and Children and Adverse Effects (*Continued*)

Drug	Adult Dosing	Pediatric Dosing	Adverse Effects[a]
Corticosteroids			
Dexamethasone	*CINV*: 12–20 mg oral/IV day 1, then 8–12 mg oral/IV daily *PONV*: 4–5 mg oral/IV at induction of anesthesia	*CINV*: 10 mg/m^2 prior to chemotherapy then 5 mg/m^2	Most common: GI upset, anxiety, insomnia Less common: Hyperglycemia, facial flushing, euphoria, perineal itching or burning (with dexamethasone)
Methylprednisolone	125–500 mg oral/IV every 6 hours for total of four doses	N/A	
Cannabinoids			
Dronabinol	Oral: 5–15 mg/m^2 every 2–4 hours as needed	Use adult dose with caution and adjust based on response	Most common: Drowsiness, euphoria, somnolence, vasodilation, vision changes, dysphoria
Nabilone	Oral: 1–2 mg two to three times a day as needed	N/A	Less common: Diarrhea, flushing, tremor, myalgia
Benzodiazepines			
Lorazepam	Oral/IV: 0.5–2 mg prior to chemotherapy	Oral/IV: 2–15 years old: 0.05 mg/kg (up to 2 mg) prior to chemotherapy	Most common: Sedation, amnesia Rare: Respiratory depression, ataxia, blurred vision, hallucinations
Alprazolam	Oral: 0.5–2 mg three times a day prior to chemotherapy	N/A	
Serotonin Antagonists			
Dolasetron	*CINV*: Contraindicated due to dose-dependent QTc prolongation *PONV*: 12.5 mg IV 15 min before end of anesthesia or at onset of N/V or 100 mg PO within 2 hours before surgery	*CINV*: Contraindicated due to dose-dependent QTc prolongation *PONV*: 0.35 mg/kg IV (max 12.5 mg) or 1.2 mg/kg PO (max 100 mg) within 2 hours before surgery	Most common: Headache, QT prolongation Less common: Constipation, asthenia, somnolence, diarrhea, fever, tremor or twitching, ataxia, lightheadedness, dizziness, nervousness, thirst, muscle pain, warm or flushing sensation on IV administration, serotonin syndrome (with ondansetron when used with serotonergic agents) Rare: Transient elevations in hepatic transaminases Granisetron may be degraded by light. Cover patch application site (eg, with clothing) if risk of exposure to sunlight or sunlamps during use and for 10 days after removal
Granisetron	*CINV*: 10 mcg/kg IV prior to chemotherapy; or 1 mg orally 1 hour before chemotherapy and 1 mg 12 hours after first dose, or 2 mg 1 hour before chemotherapy *PONV*: 1 mg IV before induction of anesthesia or immediately before reversal of anesthesia, or at onset of N/V	*CINV*: 2–16 years: Use adult dosing IV or PO regimen *PONV*: Not recommended for pediatric patients	
Granisetron	*CINV*: 1 patch 24–48 hours before chemotherapy; may wear for up to 7 days	N/A	
Ondansetron	*CINV*: Oral: 24 mg single dose prior to chemotherapy, or 8 mg prior to chemotherapy, repeat every 12 hours IV: 0.15 mg/kg, not to exceed 16 mg/dose, for three doses. Give the first dose 30 min prior to chemotherapy. Repeat dose 4 and 8 hours after the first dose *PONV*: 4 mg IV/IM before anesthesia induction or at onset of N/V; 16 mg orally once given 1 hour before anesthesia induction	*CINV*: Oral: 4–11 years, 4 mg 30 min prior to chemotherapy, repeat at 4 and 8 hours and every 8 hours for 1–2 days after chemotherapy completion IV: 6 months to 18 years: 0.15 mg/kg, not to exceed 16 mg/dose, for three doses. Give the first dose 30 min prior to chemotherapy. Repeat dose 4 and 8 hours after the first dose *PONV*: 1 month–12 years: 4 mg IV/IM before anesthesia induction for over 40 kg and 0.1 mg/kg IV for under 40 kg Oral recommendations not available	
Palonosetron	*CINV*: 0.25 mg IV 30 min before chemotherapy; 0.5 mg orally 1 hour before chemotherapy *PONV*: 0.075 mg IV before anesthesia induction	*CINV*: 20 mcg/kg (maximum 1.5 mg) IV 30 min before chemotherapy	

(*Continued*)

Table 21–2

Antiemetic Agents: Usual Doses for Adults and Children and Adverse Effects (*Continued*)

Drug	Adult Dosing	Pediatric Dosing	Adverse Effects[a]
Neurokinin-1 Antagonist			
Aprepitant	*CINV*: 150 mg IV (fosaprepitant) 30 min before chemotherapy on first day of chemotherapy only; or 125 mg orally on day 1, 1 hour prior to chemotherapy followed by 80 mg on days 2 and 3 *PONV*: 40 mg orally 3 hours prior to anesthesia induction	*CINV*: 12 years and older: 125 mg PO on day 1, 1 hour prior to chemotherapy followed by 80 mg on days 2 and 3 6 months to 12 years: 3 mg/kg (max 125 mg) day 1, then 2 mg/kg (max 80 mg) day 2 and 3	Most common: Fatigue, hiccups Less common: Dizziness, headache, insomnia Rare: Transient elevations in hepatic transaminases
Rolapitant	*CINV*: 180 mg PO on day 1, 1–2 hours prior to chemotherapy	N/A	
Netupitant	*CINV*: Netupitant 300 mg plus palonosetron 0.5 mg combination product on day 1, 1 hour prior to chemotherapy	N/A	
Other			
Doxylamine/ pyridoxine	Oral: 10 mg/10 mg tablets, 2 tablets PO at bedtime, titrate to a maximum of 4 tablets daily for persistent symptoms; or 20 mg/ 20 mg tablets, 1 tablet at bedtime on day 1; if symptoms persist on day 2, increase to 1 tablet in the morning and at bedtime (maximum of 2 tablets/day)	N/A	See adverse effects for antihistamines above.
Olanzapine	*CINV*: 10 mg PO daily, days 1–4 of highly emetogenic chemotherapy	N/A	Sedation

[a] Most common, greater than 10%; less common, 1% to 10%; rare, less than 1%. Based on US FDA-approved labeling and generalized to drug class.

CINV, chemotherapy-induced nausea and vomiting; EPS, extrapyramidal symptoms; IM, intramuscularly; Inj, injectable dosage form for IV or IM use; N/A, not available; PO, orally; PONV, postoperative nausea and vomiting; TD, transdermal; Supp, rectal suppository.

▶ *Cannabinoids*

Cannabinoids have antiemetic and appetite stimulant activity when used alone or in combination with other antiemetics.[27] Oral dronabinol and nabilone are used for preventing and treating refractory or delayed CINV.[14,27] Cannabinoids are thought to exert their antiemetic effect centrally, although the exact mechanism of action is unknown.[27] Sedation, euphoria, hypotension, ataxia, dizziness, and vision difficulties can occur. Medical marijuana is an area of increased interest, but current evidence is insufficient to recommend its use for this indication.[3,27]

▶ *Benzodiazepines*

Benzodiazepines, especially lorazepam, are used to prevent and treat CINV.[8,14] Lorazepam is used as an adjunct to antiemetic agents.[14] Sedation and amnesia are common side effects. Respiratory depression can occur with high doses or when other central depressants such as alcohol are used concomitantly.

▶ *Serotonin Antagonists*

Serotonin is a neurotransmitter synthesized in neurons in the CNS and in enterochromaffin cells of the GI tract. Chemotherapeutic agents release 5-HT, which is a predominant mediator in nausea and vomiting.[28] This increase in 5-HT concentrations stimulates the visceral vagal nerve fibers and CTZ, thereby triggering nausea and vomiting. Selective 5-HT_3 receptor antagonists (ondansetron, granisetron, dolasetron, and palonosetron) prevent and treat nausea and vomiting due to stimulation of these receptors, especially for CINV and PONV.[3,4,29] These agents are well tolerated; the most common adverse effects are headache, somnolence, diarrhea, and constipation.[14] Dose-related QT changes (including torsades de pointes) have been reported, and ECG monitoring is recommended for patients with risk factors for QT prolongation who will receive ondansetron or dolasetron.[29] Although the labeling for granisetron and palonosetron does not include a recommendation for ECG monitoring, patients may still be at risk for QT changes.

Palonosetron is the first 5-HT_3 antagonist to be approved for preventing both acute and delayed CINV.[14] Compared to other 5-HT_3 antagonists, palonosetron has a longer serum half-life (40 hours compared to 4–9 hours) and a higher receptor-binding affinity, which may contribute to its efficacy in preventing delayed CINV.[30]

▶ *Neurokinin-1 Receptor Antagonists*

Substance P is a neurokinin neurotransmitter that binds to NK_1 receptors in the GI tract and the brain and is believed to mediate both acute and delayed nausea and vomiting.[3,31] Aprepitant was the first NK_1 receptor antagonist antiemetic and is effective for preventing acute and delayed CINV when used with a 5-HT_3 antagonist and a corticosteroid.[32] It is also effective for preventing

PONV.[4,33] Aprepitant has numerous drug interactions because it is an inhibitor and substrate of the CYP 3A4 metabolic pathway.[33]

Netupitant is the second NK$_1$ receptor antagonist; it is available only as a combination product with palonosetron (Akynzeo) for preventing acute and delayed CINV following moderately or highly emetogenic chemotherapy.[3] Rolapitant is the third NK$_1$ receptor antagonist.[34] It is available as an oral formulation that may be used in place of aprepitant or netupitant and is given as a single dose due to its long elimination half-life and does not have the same concerns for drug interactions associated with aprepitant and netupitant. None of the NK$_1$ antagonists are renally eliminated.

▸ *Olanzapine*

Olanzapine is an antipsychotic agent that has effects at D$_2$, 5-HT$_{2c}$, and 5-HT$_3$ receptors, among others. Current guidelines recommend the addition of olanzapine to combination therapy for prevention of CINV in patients receiving highly emetogenic chemotherapy.[3] When used for short-term treatment in this way, olanzapine is well tolerated with sedation on day 2 of chemotherapy the only reported significant adverse effect.

Chemotherapy-Induced Nausea and Vomiting

CINV is classified as (a) acute (within 24 hours after chemotherapy); (b) delayed (more than 24 hours after chemotherapy); or (c) anticipatory (prior to chemotherapy when acute or delayed nausea and vomiting occurred with previous courses).[3,8,14] Risk factors for CINV include poor emetic control with prior chemotherapy, female sex, low chronic alcohol intake, and younger age.[35]

Chemotherapeutic agents are classified according to their emetogenic potential, which aids in predicting CINV.[3,8] Cisplatin, high-dose cyclophosphamide (1.5 g/m^2 or more), or cyclophosphamide combined with an anthracycline are examples of highly emetogenic chemotherapeutic regimens. Lower doses of cyclophosphamide, ifosfamide, and carboplatin are examples of moderately emetogenic agents. Risk factors for anticipatory nausea and vomiting include poor prior control of CINV and a history of motion sickness or NVP.[3,14]

KEY CONCEPT A combination of antiemetics with different mechanisms of action is recommended to prevent acute CINV for patients receiving moderately or highly emetogenic chemotherapy (Table 21–3).[3,8,14] Patients receiving chemotherapeutic agents with low emetogenic potential should receive a single dose of a 5-HT$_3$ antagonist or an 8-mg dose of dexamethasone as CINV prophylaxis, and those receiving chemotherapy with minimal emetogenic risk do not require prophylaxis.

Delayed nausea and vomiting is more difficult to prevent and treat. It occurs most often with cisplatin- and cyclophosphamide-based regimens, especially if delayed nausea and vomiting occurred with previous chemotherapy courses.[8] Patients who had poorly controlled acute CINV in the past are at greatest risk for delayed CINV.[3,8,35]

Oral and IV antiemetics can be equally effective for CINV, depending on patient characteristics such as ability to take oral medications, dosage form availability, and cost.[3,14] Patients undergoing chemotherapy should have antiemetics available to treat breakthrough nausea and vomiting even if prophylactic antiemetics were given.[3,14] A variety of antiemetics may be used, including lorazepam, dexamethasone, methylprednisolone, prochlorperazine, promethazine, metoclopramide, 5-HT$_3$ antagonists, dronabinol, and olanzapine. If breakthrough CINV occurs despite prophylaxis, treatment with an antiemetic with a different mechanism of action is recommended.

Table 21–3

Recommended Drug Regimens for Prevention of CINV Based on Emetogenic Risk[3]

Emetogenic Risk	Acute CINV (Day 1)	Delayed CINV (Days 2–4)
Minimal	None	None
Low	Dexamethasone OR 5-HT$_3$ antagonist	None
Moderate[a,b]	5-HT$_3$ antagonist + dexamethasone	Dexamethasone (days 2 and 3) for agents with known risk for delayed nausea and vomiting
High (includes AC regimens)	NK$_1$ receptor antagonist + 5-HT$_3$ antagonist + dexamethasone[b] + olanzapine	If aprepitant[c] is used, continue days 2 and 3 Continue dexamethasone days 2–4 for non-AC highly emetogenic regimens Olanzapine (days 2–4)

[a] Add NK$_1$ receptor antagonist if using carboplatin and area under the curve is ≥ 4 mg/mL/min.

[b] If rolapitant is the NK$_1$ receptor used, use full dose (20 mg) dexamethasone on day 1. If aprepitant, fosaprepitant, or netupitant are used, dose-adjust dexamethasone (12 mg) on day 1.

[c] If fosaprepitant, netupitant/palonosetron combination or rolapitant are used as the NK$_1$ receptor antagonist on day 1, no subsequent doses required.

AC, anthracycline (daunorubicin, doxorubicin, epirubicin, or idarubicin) plus cyclophosphamide; CINV, chemotherapy-induced nausea and vomiting.

The best strategy for preventing anticipatory nausea and vomiting is to prevent acute and delayed CINV by using the most effective antiemetic regimens based on the emetogenic potential of the chemotherapy and patient factors. CINV should be aggressively prevented with the first cycle of therapy. If anticipatory nausea and vomiting occurs, benzodiazepines and behavioral therapy such as relaxation techniques may be tried.[8,14]

Postoperative Nausea and Vomiting

PONV is a common complication of surgery that can lead to delayed discharge and unanticipated hospitalization.[4] The overall incidence of PONV is 25% to 30%, but it can occur in 70% to 80% of high-risk patients.[4,5] Risk factors for PONV include patient factors (female sex, nonsmoking status, and history of PONV or motion sickness), anesthetic factors (volatile anesthetics, nitrous oxide, especially when administered for longer than one hour, or intraoperative or postoperative opioids), and surgical factors (duration and type of surgery).[4,5] Risk scores such as the Apfel simplified risk score allow practitioners to easily predict a patient's risk of experiencing PONV.[4] The Apfel risk score is based on four factors, each resulting in one point: (a) female sex, (b) history of PONV and/or motion sickness, (c) nonsmoking status, and (d) postoperative opioid use. A score of 0 to 1 corresponds to 10% to 20% risk of PONV (low risk), a score of 2 corresponds to 40% risk (medium risk), and a score of 3 to 4 corresponds to an 80% risk (high risk).

Patient Encounter 1

A 37-year-old man is having laparoscopic inguinal hernia repair surgery today.

PMH: GERD, hypertension, inguinal hernia

SH: Smokes five cigarettes/day, occasional alcohol, negative for illicit drugs

FH: Hypertension, dyslipidemia

Current meds: Lansoprazole 15 mg once daily, hydrochlorothiazide 25 mg once daily

VS: BP 124/84 mm Hg, HR 75 beats/min, RR 16 breaths/min, T 98.6°F (37.0°C)

Labs: All within normal limits
EKG shows normal sinus rhythm and a borderline QTc of 446 ms
General analgesia is planned for surgery and includes thiopental 4.5 mg/kg, atracurium 0.5 mg/kg, and fentanyl 0.05 mg followed by tracheal intubation. Postoperative orders include opioid analgesics for pain control.

What risk factors does this patient have for developing PONV?

What pharmacologic or nonpharmacologic PONV prevention or treatment options are recommended for this patient?

What treatment options would be recommended if he experiences PONV?

Patient Encounter 2

A 30-year-old woman who is 11 weeks pregnant with nausea and vomiting of pregnancy seeks your advice. She complains of frequent nausea and vomiting. She denies increased thirst or changes in urine output. She has not gained weight since her last appointment. She is tolerating small sips of water throughout the day to maintain hydration. She has been taking prenatal vitamins since before her pregnancy and has tried avoiding provoking stimuli, eating frequent small meals, and avoiding spicy and fatty foods. The patient's PUQE score is 7.

What type of nausea and vomiting is this patient experiencing?

What nonpharmacologic and pharmacologic treatment options may help prevent and treat this patient's nausea and vomiting?

Should this patient seek additional medical attention for her symptoms?

The first step in preventing PONV is reducing baseline risk factors when appropriate.[4,5] For example, the incidence of PONV may be less with regional anesthesia than general anesthesia, and nonsteroidal anti-inflammatory drugs may cause less PONV than opioid analgesics. Preventative antiemetic agents are administered based on a patient's risk for PONV.[4] A patient at low risk may not require prophylactic antiemetic medications, those at medium risk would benefit from one or two antiemetic agents, and those at high risk should receive a combination of two or more antiemetic agents as PONV prophylaxis.

KEY CONCEPT Some agents should be administered at induction of anesthesia (aprepitant, palonosetron, dexamethasone), whereas others are more effective when administered at the end of surgery (droperidol, 5-HT$_3$ receptor antagonists). Scopolamine should be administered the evening prior to surgery or 2 hours prior to surgery.[1,4] Aprepitant prevents PONV, but it is not more effective than other agents and is costly.[4,23] Combinations of antiemetics are recommended to prevent PONV for high-risk patients.[23] A 5-HT$_3$ antagonist plus droperidol or dexamethasone is an effective combination.[4,23] If PONV occurs despite appropriate prophylaxis, it should be treated with an antiemetic from a pharmacologic class not already administered.[23] If no prophylaxis was used, a low-dose 5-HT$_3$ antagonist should be used.[23]

Nausea and Vomiting of Pregnancy

KEY CONCEPT Nausea and vomiting affect the majority of pregnant women; the teratogenic potential of the therapy is the primary consideration in drug selection, followed by severity of the nausea and vomiting.[6] Risks and benefits of any therapy must be weighed by the health-care professional and the patient. The Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) is a thee-question assessment tool used to determine the severity of NVP. A score of 6 or less is classified as mild, 7 to 12 as moderate, and 13 or more as severe NVP.

Pyridoxine (vitamin B$_6$) 10 to 25 mg four times daily alone or in combination with an antihistamine such as doxylamine is first-line pharmacotherapy for NVP.[6,11] Combination products are available (Diclegis 10 mg/10 mg and Bonjesta 20 mg/20 mg) with a recommended dose of 20 mg/20 mg at bedtime. Pyridoxine is well tolerated, but doxylamine and other antihistamines may cause drowsiness.

Ondansetron has been used to treat severe NVP. Ondansetron readily crosses the human placenta during the first trimester. There is mixed evidence demonstrating the efficacy of ondansetron vs metoclopramide in preventing severe nausea and vomiting symptoms, and quality data on fetal safety are sparse. Although the safety of anticholinergics and metoclopramide have been established, data demonstrating efficacy are lacking.[6]

In rare instances (0.3%–3% of pregnancies), NVP progresses to hyperemesis gravidarum.[6] Enteral or parenteral nutrition might be used if oral liquids cannot be tolerated or if dehydration occurs. A corticosteroid such as methylprednisolone may be considered.

Patient Encounter 3

A 70-year-old man who presents to your practice is planning a 10-day Mediterranean cruise. He has a past medical history significant for benign prostatic hyperplasia and hypertension for which he takes tamsulosin 0.4 mg daily and lisinopril 10 mg once daily. He has experienced nausea and vomiting during boat rides in the past and states that a friend recommended he purchase "a patch" at his local pharmacy to prevent nausea and vomiting.

What recommendations for nonpharmacologic interventions would you give this patient to help prevent motion sickness?

What are the pharmacologic options for this patient to prevent or treat nausea and vomiting?

What potential adverse effects would you counsel this patient about?

Because methylprednisolone is associated with oral clefts in the fetus when used during the first trimester, corticosteroids should be reserved as a last resort and should be avoided during the first 10 weeks of gestation.[6,11]

Motion Sickness and Vestibular Disturbances

Nausea and vomiting can be caused by disturbances of the vestibular system in the inner ear because of infection, trauma, neoplasm, or motion.[16] Patients may experience dizziness and vertigo in addition to nausea and vomiting. If a patient is susceptible to motion sickness, preventive measures include minimizing exposure to movement, restricting visual activity, ensuring adequate ventilation, reducing the magnitude of movement, and taking part in distracting activities.[16]

KEY CONCEPT Because the vestibular system is replete with muscarinic type cholinergic and histaminic (H_1) receptors, anticholinergics and antihistamines are the most commonly used agents to prevent and treat motion sickness. Oral medications should be taken prior to motion exposure to allow time for adequate absorption. Once nausea and vomiting due to motion sickness occur, oral medication absorption may be unreliable, making the therapies ineffective. Transdermal scopolamine may be considered as a first-line option for patients who cannot tolerate oral medications or who require treatment for a prolonged period.[16] Drowsiness and reduced mental acuity are the most bothersome side effects of antihistamines and anticholinergics. Visual disturbances, dry mouth, and urinary retention can also occur.

OUTCOME EVALUATION

- The symptoms of simple nausea and vomiting are self-limited or relieved with minimal treatment. Monitor patients for adequate oral intake and alleviation of nausea and vomiting.
- Patients with complex nausea and vomiting may have malnourishment, dehydration, and electrolyte abnormalities.
- If the patient has weight loss, assess whether enteral or parenteral nutrition is needed.
- Assess for dry mucous membranes, skin tenting, tachycardia, and lack of axillary moisture to determine if dehydration is present.
- Obtain blood urea nitrogen (BUN), serum creatinine (SCr), calculated fractional excretion of sodium (FeNa), serum electrolytes, and arterial blood gases.
- Ask patients to rate the severity of nausea.
- Monitor the number and volume of vomiting episodes.
- Ask patients about adverse effects to the antiemetics used. Use this information to assess efficacy and tailor the patient's antiemetic regimen.

Abbreviations Introduced in This Chapter

CINV	Chemotherapy-induced nausea and vomiting
CTZ	Chemoreceptor trigger zone
D_2	Dopamine type 2 receptor
EPS	Extrapyramidal symptoms
FeNa	Fractional excretion of sodium
GERD	Gastroesophageal reflux disease
H_1	Histamine type 1 receptor
5-HT_3	5-Hydroxytryptamine (serotonin) type 3 receptors
NK_1	Neurokinin type 1 receptors
NVP	Nausea and vomiting of pregnancy
PONV	Postoperative nausea and vomiting

Pharmacist's Patient Care Process

Collect Information:

- Obtain a thorough patient history including the prescription, nonprescription, and herbal medications being used. Identify any substances that may be causing or worsening nausea and vomiting.

Assess the Information:

- Assess the patient to determine whether the nausea and vomiting is simple or complex and whether patient-directed therapy is appropriate.
- Determine which treatments for nausea and vomiting have been used in the past and their degree of efficacy.

Develop a Care Plan:

- Eliminate the underlying cause of nausea and vomiting if possible.
- Develop a treatment plan with the patient and other health-care professionals if appropriate.
- Choose treatments based on the underlying cause of nausea and vomiting, duration and severity of symptoms, comorbid conditions, medication allergies, presence of contraindications, risk of drug–drug interactions, and adverse-effect profiles.
- Use the oral route for mild nausea with minimal or no vomiting. Seek an alternative route (eg, transdermal, rectal, parenteral) if the patient is unable to retain oral medications due to vomiting.

Implement the Care Plan:

- Counsel the patient to avoid known triggers.
- Provide patient education regarding causes of nausea and vomiting, avoidance of triggers, potential complications, treatment options, medication adverse effects, and when to seek medical attention.
- Educate the patient about nonpharmacologic measures such as stimulus avoidance, dietary changes, acupressure or acupuncture, and psychotherapy.

Follow-up: Monitor and Evaluate:

- To assess efficacy, ask the patient whether nausea or vomiting is resolving with therapy. Assess whether treatment failure is due to inappropriate medication use or the need for additional or different treatments and proceed accordingly.
- Assess adverse effects by asking the patient what he or she has experienced. Patient observation or examination is also useful for diagnosing adverse effects such as EPS.

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22

Constipation, Diarrhea, and Irritable Bowel Syndrome

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Identify the causes of constipation.
2. Compare the features of constipation with those of irritable bowel syndrome (IBS) with constipation (IBS-C).
3. Recommend lifestyle modifications and pharmacotherapy for treatment of constipation.
4. Differentiate acute and chronic diarrhea.
5. Compare diarrhea caused by various infectious agents.
6. Appraise medication causes of diarrhea.
7. Construct pharmacotherapeutic strategies for treating diarrhea.
8. Identify the signs and symptoms of IBS with constipation (IBS-C), diarrhea (IBS-D), or mixed (IBS-M).
9. Compare and contrast the features of IBS-C, IBS-D, and IBS-M.
10. Establish treatment goals for IBS.
11. Evaluate the effectiveness of pharmacotherapy for IBS.

INTRODUCTION

Constipation, diarrhea, and irritable bowel syndrome (IBS) are disorders of the gastrointestinal (GI) tract that have various causes and symptoms. A thorough patient assessment is required to accurately identify the underlying causes and implement safe and effective treatment. Functional gastrointestinal disorders (FGIDs) have received increasing attention in recent years.[1] FGIDs are characterized by persistent and recurring GI symptoms due to abnormal GI tract function but without structural or biochemical abnormalities. As a result, many diagnostic tests (eg, X-rays, endoscopic examinations) are often negative. The Rome IV Foundation provides evidence-based definitions, diagnostic criteria, and classification of FGIDs.[1] This chapter is focused on the evaluation and management of constipation, diarrhea, and IBS.

CONSTIPATION

KEY CONCEPT Constipation, when not associated with symptoms of IBS-C, is characterized by the occurrence of fewer than three spontaneous stools per week. There may also be straining on defecation, lumpy or hard stools, sensation of incomplete evacuation, and the need to use manual maneuvers to facilitate defecation. Occasional constipation usually does not require medical evaluation or treatment. *Functional constipation* (FC) is defined as infrequent (fewer than three stools per week) or difficult passage of stools or both that lasts for 12 weeks or more and is accompanied by onset of symptoms at least 24 weeks prior to diagnosis. *Chronic idiopathic constipation* (CIC) is defined as continuing constipation with no known cause or known contributory illness.[2]

EPIDEMIOLOGY AND ETIOLOGY

Constipation affects people of all ages and occurs in approximately 16% of all adults and in one-third of adults aged 60 and older. In 2019, US sales of nonprescription laxative products totaled more than $1.4 billion.[3] It is estimated that CIC affects 9% to 20% of adults in the United States. A population-based survey determined that 37.6% of respondents had discussed their constipation symptoms with a primary care provider, gastroenterologist, or emergency room physician.[4] About 48% of respondents reported that they treated constipation with medication, with 93.5% of those using nonprescription medications alone, 1.3% using prescription medications alone, and 5.2% using both nonprescription and prescription medications.[4]

Constipation can be due to primary and secondary causes (Table 22–1). *Opioid-induced constipation* (OIC) is defined as a change from baseline bowel habits and patterns of defecation after initiating opioid therapy that is characterized by reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete bowel evacuation, or the patient's perception of stress related to bowel habits.[5] OIC can overlap with and worsen FC. OIC is associated with significant economic burden. In cancer patients taking opioids for pain, the incidence of OIC constipation approaches 94%.[5] Constipation is associated with significant socioeconomic costs and considerable quality-of-life ramifications.[5,6] Physiological, environmental, and demographic factors may play roles in the development of constipation. Some diseases and many medications are associated with constipation.[7,8]

Table 22–1

Some Causes of Constipation

Primary Causes

Normal-transit constipation
Slow-transit constipation (disturbances of neurogastroentero- and brain–gut interactions, inadequate caloric intake)
Defecatory or colonic/rectal evacuation disorders

Secondary Causes

Endocrine/metabolic conditions (diabetes mellitus, hypercalcemia, hypokalemia, hypomagnesemia, hypothyroidism, uremia)
Myopathies (amyloidosis, scleroderma)
Neurogenic conditions (brain trauma, stroke, Parkinson disease, multiple sclerosis, spinal cord injury, or tumor)
Mechanical obstruction (colon cancer, lesion compression, stricture, rectocele)
Medications (analgesics, anticholinergics, antidiarrheals, antihistamines, some antipsychotics and antidepressants, aluminum-containing products, calcium channel blockers, calcium-containing products, clonidine, diuretics, iron-containing supplements, ondansetron, phenothiazines)
Other (autonomic neuropathy, cardiac disease, cognitive impairment, diet, volume depletion, immobility, laxative abuse, postponing urge to defecate, deliberate suppression of defecation, psychological distress, perceptions about bowel frequency)

PATHOPHYSIOLOGY

Primary or idiopathic constipation is categorized as normal-transit constipation (NTC), slow-transit constipation (STC), or dyssynergic defecatory disorders (DD). In NTC, colonic motility is unchanged, and patients experience hard stools despite normal movements. In STC, motility is decreased or caloric intake is inadequate, resulting in infrequent, harder, and drier stools. All three conditions result in prolonged rectal storage of fecal residue and incomplete expulsion of feces from the rectum. Causes of DD may include inadequate relaxation of muscles or paradoxical contractions of the pelvic diaphragm, perineal membrane and deep perineal pouch (the pelvic floor), and the external anal sphincter during defecation.[2,9,10] Chronic constipation without an identifiable cause is often referred to as CIC.

Physiologic changes associated with OIC occur when opioids activate GI tract G-protein–coupled opioid μ, κ, and δ receptors. Activation of these receptors reduces acetylcholine release, which contributes to physiologic changes such as decreased propulsive activity; increased nonpropulsive contractions; decreased pancreatic, biliary, and gastric secretions; and increased anal tone. All of these changes may contribute to constipation.[11]

CLINICAL PRESENTATION AND DIAGNOSIS

A medical history is important to ascertain the frequency and character of bowel movements and the duration of symptoms (see accompanying box for the clinical presentation of constipation). It is important to understand the symptoms that the patient considers to constitute constipation. Dietary, hydration, and physical activity habits should also be determined to identify potential contributing factors. Family history should be assessed for the presence of inflammatory bowel disease (IBD) and colon cancer. A complete record of prescription medications, over-the-counter products, and dietary supplements is mandatory to identify drug-related causes.

KEY CONCEPT The diagnosis of constipation is based on clinical history (frequency of stools per week, consistency of stools, straining on defecation, sensation of incomplete evacuation, sensation of blockage or obstruction, and the need to apply manual maneuvers to facilitate passage of stool), physical examination, minimal laboratory tests, colonoscopy or other procedures, and specific tests to evaluate underlying pathophysiology.

Endoscopy is required to exclude cancer or strictures, especially in patients older than 50 years with weight loss greater than 10 pounds in 3 months, rectal bleeding, or anemia. Anorectal examination, manometry, radiography, colonoscopy, and other procedures may be useful in certain circumstances.

In most cases, the physical examination is normal, and no underlying cause of constipation is identified. However, evaluation may reveal one or more of the following conditions: (a) IBS-C; (b) STC with normal pelvic floor function and evidence of slow transit; (c) a defecatory disorder; (d) a combination of IBS-C and STC; (e) organic constipation (mechanical obstruction or adverse drug effect); and (f) secondary constipation (due to a metabolic disorder).[8]

Clinical Presentation and Diagnosis of Constipation

Symptoms of Constipation

- Infrequent bowel movements (fewer than three per week); straining; lumpy or hard stools; painful or difficult defecation; abdominal pain or distention; bloating; sensation of incomplete evacuation, anorectal obstruction, or blockage; and the need for manual maneuvers to facilitate defecations.
- Alarm (or "red flag") findings include worsening of constipation, sudden change in bowel habits after age 50, rectal bleeding in the absence of documented hemorrhoids or anal fissures, unintentional weight loss (more than 10% within 3 months), family history of colon cancer or family polyposis syndromes, anemia, or recent constipation onset without explanation. These findings require prompt medical evaluation and appropriate intervention.

Physical Examination

- The presence of central nervous system (CNS) or spinal cord lesions may suggest an underlying cause.
- Abdominal examination findings may include distention, hard stool in a palpable colon, or abdominal mass.
- Rectal examination may indicate fecal impaction, anal stricture, or rectal mass.

Laboratory Tests (to Identify Secondary Causes)

- Thyroid-stimulating hormone (hypothyroidism)
- Serum calcium (hypercalcemia)
- Glucose (diabetes mellitus)
- Serum electrolytes (dehydration, volume depletion)
- Urinalysis (dehydration)
- Complete blood count (anemia)

Other Tests

- Screening colonoscopy and other specialized tests may be conducted based on presenting signs and symptoms.

TREATMENT

Desired Outcomes

The primary goals for treating constipation are to: (a) educate the patient, (b) identify underlying causes, (c) treat or remove secondary causes, (d) relieve symptoms, and (e) restore normal bowel function.[1,8] Treatment of constipation depends on the characteristics, severity, and causes of symptoms.

Nonpharmacologic Therapy

KEY CONCEPT Nonpharmacologic measures including lifestyle and dietary modifications should usually be employed before recommending pharmacotherapy. The patient should be educated about possible causes of constipation and the appropriate use of nonpharmacologic measures. Medication use should be evaluated to identify possible contributing factors. Patients should be encouraged to schedule routine bathroom time after the morning or evening meal. It may be helpful to elevate the feet with a stool during defecation because that assists pelvic relaxation.

Increased dietary fiber intake or fiber supplementation (total 20–30 g/day) can improve NTC, whereas patients with STC or drug-induced constipation are unlikely to respond to increased fiber. High-fiber foods include beans, whole grains, bran cereals, fresh fruits, and vegetables such as asparagus, brussels sprouts, cabbage, and carrots.

There are two types of fiber: soluble and insoluble. Soluble fiber is dissolved by water and forms a gel that slows digestion. Some sources of soluble fiber include lentils, apples, nuts, flaxseed, and psyllium. Methylcellulose (eg, Citrucel with SmartFiber) is a soluble fiber. It is nonfermentable and less likely to cause bloating and gas. Calcium polycarbophil (eg, FiberCon) is mainly a soluble fiber. Wheat dextrin, a manufactured by-product of wheat (eg, Benefiber) contains only soluble fiber. Because Benefiber contains less than 20 parts per million of gluten, it is labeled as a gluten-free product. Psyllium is made from seed husks of the plantago ovata plant (eg, Metamucil). Psyllium contains 70% soluble fiber and some insoluble fiber.

Insoluble fiber does not dissolve in water and remains mostly intact as it decreases the time for food and feces to traverse the intestines. Insoluble fiber adds bulk to the diet and helps prevent constipation. Some food sources of insoluble fiber include whole wheat, corn bran, couscous, dark leafy green vegetables, and the skins of root vegetables such as potatoes. The beneficial effects of bulk-forming and osmotic products can be expected within 24 to 72 hours.

Adequate fluid intake is important, especially in patients with evidence of volume depletion. Adult men aged 19 years and over should ingest 3.7 L and women aged 19 and over should ingest 2.7 L of water daily. The thirst mechanism changes with age; keeping a daily intake diary may assist patients who need to be reminded to drink fluids. Increased exercise may improve symptoms of constipation.[1]

Biofeedback-aided pelvic floor training may be useful; patients are guided to demonstrate the ability to coordinate abdominal and pelvic floor motion during evacuation.

Surgery may be considered after all other approaches have failed and activities of daily living are compromised. Colectomy and ileorectal anastomosis may be considered in select patients with STC.

Pharmacologic Therapy

Table 22–2

Dosage Recommendations for Treatment of Constipation

Agent	Adults and Children Ages 12 and Over	Children Ages 6–11 Years
Agents That Cause Softening of Feces in 1–3 Days		
Bulk-forming agents/osmotic laxatives		
Methylcellulose	4–6 g/day PO	0.45–1.5 g PO per dose up to 3 g/day
Polycarbophil	4–6 g PO daily	On advice of practitioner
Psyllium	Varies with product	On advice of practitioner
Emollients		
Docusate sodium	50–360 mg PO daily	50–100 mg PO daily
Docusate calcium	50–360 mg PO daily	On advice of practitioner
Lactulose	15–30 mL PO daily	7.5 mL (5 g) PO daily
Mineral oil	15–30 mL PO daily	5–15 mL PO daily
Agents That Result in Soft or Semifluid Stool in 6–12 Hours		
Bisacodyl (oral)	5–15 mg PO daily	5–10 mg (0.3 mg/kg) PO daily
Bisacodyl Pico (sodium picosulfate)	5–10 mg (2–4 caps) PO at bedtime	Age 4–10: If recommended by MD
	5mg/5mL oral solution	2.5–5 mg PO at night Age under 4 years: not recommended
Senna	Dose varies with formulation	6–25 mg PO once or twice daily
Agents That Cause Watery Evacuation in 1–6 Hours or Less		
Magnesium citrate	120–300 mL PO	100–150 mL PO
Magnesium hydroxide	30–60 mL PO (15–30 mL of concentrate PO)	2.5–5 mL PO up to four times
Magnesium sulfate	10–30 g PO	5–10 g PO
Bisacodyl (suppository)	10 mg rectally	5 mg rectally (1/2 suppository)
Sodium picosulfate, magnesium oxide, anhydrous citric acid (Clenpiq)	Split-dose regimen: First dose during the evening before the colonoscopy. Second dose the next day in the morning prior to colonoscopy. Additional liquids must be consumed	Safety not established in children

KEY CONCEPT Oral laxatives are the primary pharmacologic intervention for relief of most forms of constipation, including OIC; several different drug classes are available (Table 22–2). Patients with OIC who are refractory to traditional laxatives should be treated with the peripherally-acting μ-opioid receptor-antagonists naldemedine, naloxegol, or methylnaltrexone.[11]

▶ *Bulk Producers*

These agents are either naturally derived (psyllium), semisynthetic (polycarbophil), or synthetic (methylcellulose) fiber supplements. They act by swelling in intestinal fluid, forming a gel that aids in fecal elimination and promoting peristalsis. They may cause flatulence (less commonly with methylcellulose), bloating, distention, and abdominal cramping. Fiber supplements may result in less improvement in patients with delayed colon transit constipation and/or obstruction. Bulk-forming or fiber laxatives must be taken with sufficient water (240 mL/dose) to avoid becoming lodged in the esophagus and producing obstruction or worsening constipation. Hypersensitivity reactions may occur and rarely may be manifested as an anaphylactic reaction.

▶ *Osmotics*

Lactulose, sorbitol, and glycerin are osmolar sugars. These products cause water to enter the lumen of the colon and may stimulate peristalsis. Lactulose acidifies colonic contents, increases water content of the gut, and softens the stool. Glycerin causes local irritation and possesses hyperosmotic action. Glycerin may be administered rectally and can cause rectal discomfort. Sorbitol can cause intestinal irritation and may affect blood glucose levels in diabetic patients. Osmotic agents may cause flatulence, abdominal cramping, and bloating. Polyethylene glycol (PEG) 3350 (MiraLAX) is used to treat occasional constipation and expected to produce a bowel movement within 1 to 3 days. In patients with kidney disease, this over-the-counter product should be used only on the advice and supervision of a physician.

PEG 3350 with electrolytes, a prescription product (eg, GoLYTELY, Colyte), is used for acute complete bowel evacuation prior to GI examination. The patient is required to drink large volumes of liquid, which can cause nausea and distention. For this reason, its use has been largely supplanted by newer colonoscopy preparations that require ingestion of much less fluid volume.

▶ *Lubricants*

Lubricant laxatives coat the stool, allowing it to be expelled more easily. The oily film covering the stool also keeps the stool from losing its water to intestinal reabsorption processes. Oral mineral oil (liquid petrolatum) is a nonprescription heavy oil that should be used with caution, if at all, because it can be aspirated into the lungs and cause lipoid pneumonia. This is of particular concern in the young and elderly. It may also inhibit absorption of fat-soluble vitamins.

▶ *Stimulant Laxatives*

Diphenylmethane derivatives (eg, bisacodyl) and anthraquinones (eg, senna) have a selective action on the nerve plexus of intestinal smooth muscle leading to enhanced motility. Enteric-coated bisacodyl tablets should be swallowed whole to avoid gastric irritation and vomiting. Ingestion should be avoided within 1 to 2 hours of antacids, H_2-receptor antagonists, proton pump inhibitors, and milk. Bisacodyl oral tablets, rectal suppository, and enema products are available. The onset of effect is more rapid with rectal administration. The effects can be harsh (cramping), depending on the dose taken.

Sodium picosulfate (eg, Dulcolax Pico) is a stimulant laxative used for short-term relief of constipation. When used in combination preparations with magnesium oxide and anhydrous citric acid, which form magnesium citrate (eg, Clenpiq), it is indicated for colonic cleansing prior to colonoscopy in adults and children aged 9 years and older. There are no data regarding safety of sodium picosulfate in pregnant women.[12]

Castor oil is used less frequently; it is pregnancy category X and associated with uterine contractions and rupture. Use of castor oil in breastfeeding is considered “possibly unsafe.”

▶ *Emollients*

Also known as surfactants and stool softeners, emollients (eg, salts of docusate) act by increasing the surface-wetting action on the stool leading to a softening effect. They reduce friction and make the stool easier to pass. The onset of action of stool softeners is longer than with most stimulants and may take up to 72 hours. These agents tend to be less effective in treating constipation of long duration.

▶ *Saline Agents*

Salts of sodium, magnesium, and phosphate pull water into the lumen of the intestines resulting in increased enteral pressure. Magnesium and phosphate may accumulate in patients with renal dysfunction. Principal concerns with sodium phosphate derivatives include dehydration, hypernatremia, hyperphosphatemia, acidosis, hypocalcemia, and worsening renal function. Older persons and patients with heart failure and renal dysfunction should be advised to avoid saline agents. Nonprescription oral sodium phosphate solutions are no longer available because of the risk of acute phosphate nephropathy, a form of acute kidney injury.

Newer saline combination products containing sodium sulfate, potassium sulfate, and magnesium sulfate (eg, Suprep) are much safer and are widely used as precolonoscopy preparations.

▶ *Intestinal Secretagogues*

Lubiprostone (Amitiza) This oral agent is derived from prostaglandin E_1 and acts locally on intestinal chloride channels to increase intestinal fluid secretion, resulting in increased intestinal motility and passage of stool.[11] It is approved for treatment of CIC in adults, OIC in adult patients with chronic noncancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation, and in irritable bowel syndrome with constipation (IBS-C) in women at least 18 years old (Table 22–3). Effectiveness for treating OIC in patients taking methadone has not been established. In patients taking diphenylheptane opioid derivatives (eg, methadone), a dose-dependent decrease in lubiprostone effectiveness can occur. Lubiprostone is contraindicated in patients with known or suspected mechanical GI obstruction. Common adverse effects include nausea, diarrhea, syncope, hypotension, dyspnea, bowel obstruction, headache, abdominal distension and pain, and flatulence. The effectiveness of lubiprostone has not been established in children aged 6 years and older. The capsule should be swallowed whole and not be chewed or broken apart.[13,14]

Linaclotide (Linzess) The parent compound and its active metabolite activate guanylate cyclase-C (GC-C) act locally by increasing intracellular and extracellular concentrations of cyclic guanosine monophosphate (GMP). Cyclic GMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, resulting in increased interstitial fluid and intestinal transit.[15] Linaclotide is indicated for treatment of IBS-C and CIC in adults only.

The linaclotide dose for CIC is 145 mcg is administered once daily on an empty stomach at least 30 minutes before the first

Table 22–3

Medications for Treatment of Opioid-Induced Constipation

Agent	Adults and Children Ages 12 and Over
Lubiprostone	24 mcg PO twice daily with food and water
Methylnaltrexone bromide	Given subcutaneously every other day based on body weight: 12 mg if 62–114 kg; 8 mg if 38–61 kg; other doses based on weight if outside these parameters
Naloxegol	25 mg PO once daily in the morning on an empty stomach or if not tolerated 12.5 mg PO daily
Naldemedine	0.2 mg PO once daily with or without food

[a] Safety and efficacy have not been established in children younger than age 12.

meal of the day; 72 mcg once daily can be used based on patient presentation and tolerability (Table 22–3). The capsule should be swallowed whole and not be broken or chewed.

Adverse effects of linaclotide include diarrhea, headache, fatigue, dehydration, abdominal pain, flatulence, and abdominal distention. Loose stools and greater stool frequency may occur after administration with a high-fat breakfast. Patients should be monitored for fluid and electrolyte loss. Linaclotide is classified as pregnancy category C.

Plecanatide (Trulance) This medication functions as a guanylate cyclase-C (GC-C) agonist. It is indicated for treatment of CIC and IBS-C in adults. The efficacy and safety of plecanatide have not been established in children less than 18 years of age, and it should be avoided in persons aged 6 to 18 years. It is contraindicated in children under the age of 6 years because increased fluid secretion may lead to serious dehydration. It is also contraindicated in patients with known or suspected mechanical GI obstruction.[16]

The recommended adult dose of plecanatide is 3 mg orally once daily. The tablet can be given with or without food and should be swallowed whole. For adults with swallowing difficulties, the tablets can be crushed and administered orally either in applesauce or with water or given with water via a nasogastric or gastric feeding tube.

The major adverse effect associated with plecanatide is diarrhea, which may lead to discontinuation in some patients. Less common adverse effects include sinusitis, upper respiratory tract infection, abdominal distention, flatulence, abdominal tenderness, and increased hepatic enzymes. Although there are insufficient data on potential harm in pregnancy, plecanatide and its active metabolite are absorbed negligibly, and maternal use is not expected to result in fetal drug exposure. No human lactation studies have yet been conducted.[16]

▶ *Peripherally Acting μ-Opioid Receptor Antagonists (PAMORAs)*

PAMORAs are prescribed for treatment of OIC. There are currently three antagonists of opioid binding at the μ-opioid receptor that have negligible ability to cross the blood–brain barrier: naldemedine, methylnaltrexone bromide, and naloxegol (Table 22–3). They function as peripherally acting μ-opioid receptor antagonists (PAMORAs) in tissues such as the GI tract, thereby decreasing the constipating effects of opioids without diminishing the opioid analgesic effects in the CNS. They are indicated for treatment of OIC in adults with chronic pain that is not caused by active cancer (including chronic pain related to prior cancer or its treatment) who do not require frequent (eg, weekly) opioid dosage escalation.[11] The opioid analgesic regimen does not need to be altered before starting a PAMORA. Patients should be near toilet facilities after a PAMORA is administered. Patients receiving opioids for less than 4 weeks may be less responsive to these agents. All maintenance laxative therapy should be discontinued before starting a PAMORA; laxatives may be resumed if there is suboptimal response to the PAMORA after 3 days. Concomitant PAMORA use with other opioid antagonists can result in additive adverse effects and should be avoided. PAMORA treatment should be stopped if opioid therapy is discontinued.

The most common PAMORA adverse effects are abdominal pain, nausea, diarrhea, flatulence, and vomiting. GI perforation has been reported in patients with other conditions that reduce the structural integrity of the GI tract wall (eg, peptic ulcer disease, Crohn disease); the PAMORA should be discontinued if severe, persistent, or worsening abdominal pain occurs. Symptoms of opioid withdrawal may occur (sweating, chills, diarrhea, abdominal pain, anxiety, yawning) in patients physically dependent on opioids.[11]

Naldemedine (Symproic) is a derivative of naltrexone that contains an added side chain that increases molecular weight and reduces its ability to cross the blood–brain barrier. It has binding affinities for μ-, δ-, κ-opioid receptors.[17] The recommended dose is 0.2 mg orally once daily with or without food.

Concomitant use of strong CYP3A inducers such as rifampin should be avoided because decreased naldemedine concentrations can occur. On the other hand, increased naldemedine concentrations can occur when moderate (eg, fluconazole) or strong (eg, itraconazole) CYP3A4 inhibitors are used concomitantly; patients should be monitored for adverse reactions. Naldemedine is also a substrate of the P-glycoprotein (P-gp) efflux transporter; patients taking P-gp inhibitors (eg, amiodarone, captopril, cyclosporine, and verapamil) should be monitored for adverse effects due to increased naldemedine concentrations.[17]

Naloxegol (Movantik) is a pegylated derivative of naloxone. The recommended dose is 25 mg orally once daily on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours after the meal. The dose may be reduced to 12.5 mg daily if the larger dose is not tolerated. The starting dose should also be reduced to 12.5 mg daily in patients with moderate-to-severe renal impairment. If a patient cannot swallow the tablet whole, it may be crushed to a powder, mixed with 4 oz (120 mL) of water, and administered immediately; the glass should then be refilled with 4-oz water, stirred, and the contents drunk. Patients should avoid consumption of grapefruit and grapefruit juice because these foods may increase plasma naloxegol concentrations.

Naloxegol is contraindicated in patients receiving strong CYP3A4 inhibitors (eg, clarithromycin, ketoconazole) and should be avoided if possible in patients taking moderate CYP3A4 inhibitors (eg, diltiazem, erythromycin, and verapamil) due to increased naloxegol concentration that may increase the risk of adverse reactions.[18]

Methylnaltrexone Bromide (Relistor) is a quaternary amine derivative of naltrexone. The recommended oral dose is 450 mg (3 × 150-mg tablets) once daily with water on an empty stomach at least 30 minutes before the first meal of the day; there is a subcutaneous (SC) product that can also be used for treating OIC in adults with chronic noncancer pain; the dose is 12 mg SC once daily. The SC injection is also indicated for treatment of OIC in adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care. The SC injection is usually given every other day as needed; the dose is weight-based for this indication (refer to product labeling). The oral or SC methylnaltrexone dose must be reduced in patients with moderate to severe renal or hepatic dysfunction.[19]

Treatment Recommendations

The conventional effective, safe, and inexpensive modalities (fluid intake; dietary and supplemental fiber; stool softeners; and saline, stimulant, or osmotic laxatives) should be attempted before agents such as secretagogues are prescribed. The μ-receptor antagonists are indicated only for treatment of OIC.[11]

Patients who are not constipated but need to avoid straining (eg, patients with hemorrhoids, hernia, or myocardial infarction) may benefit from stool softeners or mild laxatives such as PEG 3350.

Pregnant women should be advised to eat regular meals that are balanced among fruits, vegetables, and whole grains and maintain adequate water intake to avoid constipation. Bulk producers and stool softeners are probably safe during pregnancy because they are poorly absorbed. Lactulose and magnesium products are pregnancy category B. Magnesium-based antacids have minimal absorption and are considered low risk in pregnant women. Long-term use of magnesium citrate should be avoided (pregnancy category B).

Patient Encounter 1

A 30-year-old woman with a history of iron-deficiency anemia and constipation was admitted to the hospital after a fall. The patient is status-post exploratory laparoscopic surgery. Presently, she is being treated for acute pain and is being discharged to home. Medication profile includes ferrous sulfate 325 mg orally three times a day, ibuprofen 400 mg orally every 6 hours as needed for pain equal to 4/10 or 5/10, oxycodone/acetaminophen 5 mg/325 mg 1 tablet orally every 6 hours as needed for pain equal to 6/10 or 7/10, and 2 tablets orally every 6 hours as needed for pain equal to 8 to 10/10.

What general approach to this patient should be employed?

What are the possible contributing causes of her constipation?

What nonpharmacologic and pharmacologic therapies would be appropriate for her constipation?

Laxatives may provide relief for constipation occurring during the postpartum period when the mother is not breastfeeding.

Children younger than 6 years old should be evaluated by a health-care provider before being given a laxative because they may not be able to describe their symptoms well. Evaluation of the patients' ability to recognize and self-report constipation symptoms should be considered. Treating secondary causes may resolve constipation without the use of laxatives. As in adults, children benefit from a balanced diet and adequate water intake.

Because many older persons experience constipation, laxative use is sometimes viewed as a normal part of daily life. However, oral ingestion of mineral oil can present a hazard to bedridden individuals because inhalation of oil droplets can lead to pneumonia. Lactulose may be a better choice in this situation. Regular use of any laxative that affects fluid and electrolytes may result in significant adverse effects.

Patients with the following conditions should use laxatives only under the supervision of a health-care provider: (a) colostomy; (b) diabetes mellitus (some laxatives contain sugars such as dextrose, galactose, and/or sucrose); (c) heart disease (some products contain sodium); (d) kidney disease; and (e) swallowing difficulty (bulk-formers may produce esophageal obstruction). Saline laxatives containing magnesium, potassium, or phosphates should be used cautiously in persons with reduced kidney function. Monitor appropriate serum electrolyte concentrations in patients with unstable renal function evidenced by changing serum creatinine or creatinine clearance.

OUTCOME EVALUATION

- Ask the patient about symptom improvement to determine effectiveness of laxative therapy. Patients should have an increase in stool frequency to three or more well-formed stools per week. Patients should report reduced defecation time or the absence of excessive straining.
- When acute overuse or chronic misuse of saline or stimulant laxatives is suspected, electrolyte disturbances should be evaluated (eg, hypokalemia, hypernatremia, hyperphosphatemia, and hypocalcemia).
- Some laxatives (eg, bulk producers) contain significant amounts of sodium or sugar and may be unsuitable for salt-restricted or diabetic patients. Monitoring of fluid retention (edema) and blood pressure changes is indicated in patients on sodium-restricted diets. Glucose monitoring may be required in diabetic patients with chronic use. The use of low-sodium or sugar-free products may be indicated.
- All laxatives are contraindicated in patients with undiagnosed abdominal pain, nausea, or vomiting. Patients should consult their health-care providers if changes in bowel habits persist for more than 14 days or if laxative use for 7 or more days results in no effect.

Patient Care Process for Constipation

Collect Information:

- Document the patient's age, bowel movement frequency, medical conditions, and medication use.
- Ask about symptoms to determine if patient-directed therapy is appropriate or if physician evaluation is required. Determine type, frequency, and duration of symptoms; the presence or absence of abdominal pain; and exclude the presence of alarm symptoms.
- Review available information to determine potential causes and type of constipation. List factors that seem to make it better or worse. Assess dietary habits, fluid intake, and level of physical activity. The use of bowel and medication diary may help identify patterns. The use of the Bristol Stool Form Scale may be considered (see https://en.wikipedia.org/wiki/Bristol_stool_scale).

Assess the Information:

- Obtain a thorough history of prescription medication, nonprescription product, and dietary supplement use. Determine what treatments have been helpful in the past, whether the patient is taking any medications that may contribute to constipation, usual diet, and fluid intake. Assess for the presence of adverse drug reactions, drug allergies, and drug interactions.
- Assess the presence of pain to help differentiate functional constipation condition from possible IBS-C.

Develop a Care Plan:

- Recommend administration of soluble dietary fiber such as psyllium, then an osmotic agent such as PEG, and then a magnesium-based or stimulant/stool softener-based product.
- Provide patient education about constipation, dietary modifications, and drug therapy. Consider asking, "Do you take the time to have a bowel movement?"

Implement the Care Plan:

- Educate the patient about causes of constipation and recommend ways to avoid it.
- Counsel the patient on appropriate laxative use, when to expect onset of relief, need for adequate fluid intake, and to seek medical attention if there is no improvement with laxative use in 3 or more days or if symptoms worsen.
- Advise the patient to seek medical attention if alarm symptoms occur.

Follow-up: Monitor and Evaluate:

- Develop a plan to assess the effectiveness of laxative use. Include dosing, monitoring parameters (eg, improvement in symptoms/complaints), and recommended duration of therapy.

DIARRHEA

The definition of diarrhea is based on two characteristics of stool: frequency and consistency.[2,20] Diarrhea is defined as the increased frequency of passing abnormally liquid or unformed stools. Functional diarrhea is the presence of loose or watery stools, without predominant abdominal pain or bothersome bloating, occurring in more than 25% of stools. The symptoms must be present for the last 3 months with symptom onset at least 6 months before the diagnosis is made. Patients meeting the criteria for IBS-D should be excluded.[2,21,22] Diarrhea is defined as acute if it lasts less than 2 weeks, persistent if it lasts from 2 to 4 weeks, and chronic if it lasts longer than 4 weeks. The World Health Organization (WHO) describes three levels of severity: (a) mild (diarrhea three or more times a day with occasional abdominal discomfort); (b) moderate (diarrhea three or more times a day with painful abdominal cramps and thirst); and (c) severe (diarrhea three or more times a day with severe abdominal cramps, thirst, nausea, and tiredness).[21] Diarrhea can also be classified as watery.[22] Contributors to diarrhea include IBD, colitis, and infection.[23] Patients presenting with diarrhea should be evaluated for these conditions as well as functional diarrhea and IBS-D. The evidence to support the use of laboratory tests with functional diarrhea is uncertain, and presently no tests exist that support the confirmative diagnosis of IBS-D.[24,25]

EPIDEMIOLOGY AND ETIOLOGY

The WHO reported that in 2016 diarrhea was the ninth leading cause of death globally (> 1.3 million deaths). Worldwide, diarrhea is a significant area of concern for children aged 5 years and under in resource-limited regions.[26] The incidence and prevalence of diarrhea are difficult to quantify. Prevalence rates of functional diarrhea reported from different countries range from 1.5% to 17%. Although it has not been well studied, incidence rates of diarrhea may be lower in regions where higher level sanitation systems are available and utilized.[26]

Acute Diarrhea

Acute diarrhea generally involves the sudden onset of three or more loose or liquid stools above baseline in a 24-hour period. More than 90% of cases of acute diarrhea are caused by infectious agents. Acute diarrheal infection is also referred to as gastroenteritis. Most infectious diarrheas are acquired by fecal–oral transmission or via ingestion of food or water contaminated with human or animal fecal pathogens.[27] Many of these cases are accompanied by abdominal pain and cramps, bloating, flatulence, passage of bloody stools, tenesmus, fecal urgency, fever, and vomiting. Some acute GI infections may cause vomiting as a predominant symptom with little to no diarrhea. The remaining 10% of acute diarrhea cases are caused by medications, toxic ingestions, ischemia, food intake, and other conditions. Acute diarrhea is a leading cause of outpatient visits and hospitalizations and has a direct negative impact on quality of life.

Viruses cause a large proportion of acute diarrhea cases. Common culprits include Rotavirus, Norwalk, and adenovirus. Bacterial causes include *Escherichia coli*, *Salmonella* species, *Shigella* species, *Vibrio cholerae*, and *Clostridioides difficile* (especially if antibiotics had been administered). The term *dysentery* describes some of these bacterial infections when associated with serious occurrences of bloody diarrhea.[27]

Acute or persistent diarrheal conditions can also result from parasites and protozoa such as *Entamoeba histolytica*, *Microsporidium*, *Giardia lamblia*, and *Cryptosporidium parvum*. Most of these infectious agents can cause **traveler's diarrhea**, a common condition that can afflict travelers worldwide. It usually occurs during or just after travel following the ingestion of food or water that is contaminated with feces. It has an abrupt onset but usually subsides within 2 to 3 days (see Chapter 80, Gastrointestinal Infections, for more detailed information on traveler's diarrhea).

Brainerd diarrhea may be associated with subtle distal small intestine or proximal colonic inflammatory changes and is believed to be caused by an infectious agent. It is described as an abrupt-onset diarrhea that persists for 4 weeks and may last 1 to 3 years. It is named after Brainerd, Minnesota, the community where the first outbreak occurred in 1983.

Noninfectious causes of acute diarrhea include drugs and toxins, laxative abuse, food intolerance, IBS, IBD, ischemic bowel disease, lactase deficiency, vitamin B_{12} deficiency anemia, diabetes mellitus, malabsorption, fecal impaction, diverticulosis, and celiac sprue.[23]

Lactose intolerance is a gastrointestinal disorder that is due to the inability to digest lactose into glucose and galactose. Symptoms include loose stools, **borborygmus**, flatulence, abdominal pain and bloating, and nausea. Low levels of the enzyme needed to digest lactose is a common form of disaccharidase deficiency. Lactose intolerance is responsible for many cases of acute diarrhea, especially in persons of African descent, Asians, South Americans, and Native Americans. Possible food-related causes include fat substitutes, dairy products, and products containing nonabsorbable carbohydrates.

The diarrhea of IBS is sudden, perhaps watery but likely loose, usually accompanied by urgency, bloating, and abdominal pain often in the morning or immediately following a meal. IBD is typically associated with the sudden onset of bloody diarrhea accompanied by urgency, crampy abdominal pain, and fever. Patients who experience bowel ischemia may develop bloody diarrhea, particularly if they progress to shock.[24,25]

In the United States, high-risk groups for acquiring acute diarrhea include travelers, consumers of certain foods, immunodeficient persons, daycare attendees and their family members, and institutionalized persons.

Chronic Diarrhea

Chronic diarrhea is much less likely to be infectious and usually results from functional or inflammatory bowel disorders, endocrine disorders, malabsorption syndromes, and drugs (including laxative abuse). Daily watery stools may not occur with chronic diarrhea. Diarrhea may be either intermittent or continual.[22,24]

PATHOPHYSIOLOGY

In patients who present with watery diarrhea, abnormal physiological control of intestinal fluid and electrolyte transport mechanisms or derangement in barrier properties may occur. The inability to sufficiently absorb solutes or the impact active secretion of solutes into the gut lumen or both may occur. In addition, the integrity of the intestinal epithelial barrier function contributes to control of the ability to dehydrate the stool. These actions influence the amount of fluid found within the intestinal lumen. Intestinal cellular mechanisms of fluid transport are dependent upon sodium secretion and chloride absorption. The absence of the transporter proteins due to genetic coding, the presence of inflammatory cytokines, and the presence of single nucleotide polymorphisms may influence the volume of fluid collected within the small and large intestines, thus resulting in the development of watery diarrhea.[20,24,25] Sodium secretion is also affected

Table 22–4

Selected Drugs and Substances That May Cause Acute Diarrhea

Drugs			
Antibiotics	Hydralazine	Metformin	Sorbitol
Colchicine	Laxatives	Misoprostol	Theophylline
Digitalis	Mannitol	Quinidine	Thyroid products
Dietary Supplements			
St. John's wort	Echinacea	Ginseng	Aloe vera
Poisons			
Arsenic	Cadmium	Mercury	Monosodium glutamate

by the expression of intestinal epithelial sodium channels.[20] Factors that increase active chloride secretion include bile acid malabsorption, the presence of mutations in the guanylate cyclase 2C gene that encodes for chloride secretagogues such as guanylin and uroguanylin, and other mechanisms.

Disruption of barrier permeability function of the junctions that link adjacent intestinal epithelial cells through pores can occur. During inflammatory processes, improper increased contraction may contribute to inappropriate epithelial leakage. It is proposed that reduced barrier permeability in the presence of disruption of ion movement and fluid collection in the intestinal lumen can cause leakage of adsorbed solutes into the lumen and interfere with absorptive transport.[20]

Diarrhea may be attributed to a single or to multiple overlapping mechanisms. For example, malabsorption syndromes and traveler's diarrhea are associated with both secretory and osmotic mechanisms.[20]

Medications are a common cause of diarrhea (Table 22–4). Drug-induced diarrhea can occur by several mechanisms. First, water can be drawn into the intestinal lumen osmotically (eg, saline laxatives). Second, the intestinal bacterial ecosystem can be upset leading to the emergence of invasive pathologic organisms triggering secretory and inflammatory processes (eg, antibiotic use). Third, some drugs increase intestinal motility. Other drugs produce diarrhea through undetermined mechanisms (eg, procainamide, colchicine). Discontinuation of the offending drug may be the only measure needed to ameliorate diarrhea.

CLINICAL PRESENTATION AND DIAGNOSIS

Patients with diarrhea should be questioned about the onset of symptoms, recent travel, diet, source of water, and medication use; see accompanying box for the clinical presentation of diarrhea. Other important considerations include duration and severity of the diarrhea and the presence of abdominal pain or vomiting; blood in the stool; stool consistency, appearance, and frequency; and weight loss. Although most cases of diarrhea are self-limited, infants, children, elderly persons, and immunocompromised patients are at risk for increased morbidity.

The diagnostic criterion for functional diarrhea is the presence of loose or watery stools without predominant abdominal pain or bothersome bloating, occurring in more than 25% of stools. The criterion needs to be fulfilled for the prior 3 months with the symptom onset at least 6 months before diagnosis. Patients meeting criteria for diarrhea-predominant IBS should be excluded.[24,25]

Findings on physical examination can assist in determining hydration status and disease severity. The presence of blood in the stool suggests an invasive organism, an inflammatory process, or perhaps a neoplasm. Large-volume stools suggest a small-intestinal disorder, whereas small-volume stools suggest a colon or rectal disorder. Further investigation should be performed in patients who present with diarrhea in the presence of alarm symptoms such as unintentional weight loss, diarrhea awakening the patient, recent antibiotic use, hematochezia (in the absence of documented bleeding hemorrhoids or anal fissures), very frequent bowel movement (> 6–10 daily), high volume diarrhea (> 250 mL of feces daily), evidence of malnutrition, family history of new or abnormal growth of colorectal tissue, celiac disease, or IBD. Patients with prolonged or severe symptoms may require colonoscopic evaluation to identify the underlying cause.[24,25]

Clinical Presentation of Diarrhea

Signs and Symptoms of Acute Diarrhea

- Acute diarrhea presents abruptly as loose, watery, or semiformed stools.
- Abdominal cramps and tenderness, rectal urgency, nausea, bloating, and fever may be present.
- Patients infected with invasive organisms may have bloody stools and severe abdominal pain.

Laboratory Tests in Acute Diarrhea

- Stool cultures can help identify infectious causes. Methods using real-time polymerase chain reaction shorten the reporting time.
- Stool may be analyzed for mucus, fat, osmolality, fecal leukocytes, and pH. Mucus fragments suggest colonic involvement; fat in the stool suggests malabsorption. Fecal leukocytes are present in inflammatory diarrheas including bacterial infections. Stool pH (normally > 6) is decreased by bacterial fermentation processes.
- Assessment of stool volume and electrolytes in large-volume watery stools may identify osmotic or secretory diarrhea.
- CBC and blood chemistries to determine extent of vitamin and electrolyte deficiencies may be helpful when symptoms persist. Findings of anemia, leukocytosis, or neutropenia offer further clues to the underlying cause.

Signs and Symptoms of Chronic Diarrhea

- Presenting symptoms may be severe or mild. Weight loss can be demonstrated, and weakness may be present.
- Dehydration may manifest as decreased urination, dark-colored urine, dry mucous membranes, increased thirst, and tachycardia.

Laboratory Tests in Chronic Diarrhea

- Tests described for acute diarrhea are also useful to diagnose chronic diarrhea; the differential diagnosis is more complicated. Results can help categorize the diarrhea as watery, inflammatory, or fatty, narrowing the focus on a primary disorder.
- Colonoscopy allows visualization and biopsy of the colon and is preferred when there is blood in the stool or if the patient has acquired immune-deficiency syndrome.

TREATMENT

Acute diarrhea is generally self-limited, lasting 3 to 4 days even without treatment. Most healthy adults with diarrhea do not develop significant dehydration or other complications and can self-medicate symptomatically if necessary. KEY CONCEPT Dehydration can occur when diarrhea is severe and oral intake is limited, particularly in older persons and infants. Evidence of dehydration includes increased thirst, dry mouth, dry skin, reduced skin elasticity, infrequent urination, reduced urine volume, orthostatic hypotension with rapid pulse, lightheadedness, tachypnea, fatigue, muscle cramps, muscle weakness, and sunken eyes. Clinical laboratory abnormalities may include increased blood urea nitrogen/serum creatinine ratio, hemoglobin and hematocrit, serum sodium concentration, and serum osmolality. Assessment of medication use history (eg, diuretics) is also important for dehydration assessment.

Children are more susceptible to dehydration (particularly when vomiting occurs) and may require medical attention early in the course, especially if younger than 3 years. Physician intervention is also necessary for older patients who are sensitive to fluid loss and electrolyte changes due to concurrent chronic illness.

Patients should seek medical attention in the following circumstances: (a) moderate to severe abdominal tenderness, distention, or cramping; (b) bloody stools; (c) evidence of dehydration; (d) high fever (38.3°C or 101°F or higher); (e) evidence of weight loss greater than 5% of total body weight; and (f) diarrhea that lasts longer than 48 hours.[27]

Desired Outcomes

The goals of treatment for diarrhea are to relieve symptoms, maintain hydration, treat the underlying cause(s), and maintain nutrition. KEY CONCEPT The primary treatment of acute diarrhea includes fluid and electrolyte replacement, dietary modifications, and drug therapy.

Nonpharmacologic Therapy

▶ *Fluid and Electrolytes*

Fluid replacement is not a treatment to relieve diarrhea but rather an attempt to restore fluid balance. In many parts of the world where diarrheal states are frequent and severe, fluid replacement is accomplished using oral rehydration solution (ORS), which are a measured mixture of water, salts, and glucose. The solution recognized by the WHO consists of 75 mEq/L (mmol/L) sodium, 75 mmol/L glucose, 65 mEq/L (mmol/L) chloride, 20 mEq/L (mmol/L) potassium, and 10 mEq/L (3.3 mmol/L) citrate, having a total osmolarity of 245 mOsm/L (mmol/L). A simple solution can be prepared from 1 L water mixed with eight teaspoonfuls of sugar and one teaspoonful of table salt.[28] Some commercial products include Pedialyte, Rehydralyte, and CeraLyte.

Consistent intake of water (perhaps by slowly sipping), along with eating as tolerated, should restore lost fluids and salt for typical diarrhea sufferers. Patients may also replace lost fluid by drinking flat soft drinks such as ginger ale, tea, fruit juice, broth, or soup. Although sports drinks may be used to treat dehydration, caution should be exercised so they are not viewed as a casual panacea. Severe diarrhea may require the use of parenteral solutions, and parenteral products should be used if patients are vomiting or unconscious.[27]

▶ *Dietary Modifications*

During an acute diarrheal episode, patients typically eat less as they focus on the diarrhea. Both children and adults should attempt to maintain nutrition because food helps replete lost nutrients and fluid volume. However, food-related fluid may not be sufficient to compensate for diarrheal losses. Some foods may be inappropriate if they irritate the GI tract or if they are implicated as the cause of the diarrhea. Patients with chronic diarrhea may find that increasing bulk in the diet may help (eg, rice, bananas, whole wheat, and bran).

Pharmacologic Therapy

The goal of drug therapy is to control symptoms, enabling the patient to continue with as normal a routine as possible while avoiding complications (Table 22–5). Most infectious diarrheas are self-limited or curable with anti-infective agents.[27]

▶ *Adsorbents and Bulk Agents*

Attapulgite adsorbs excess fluid in the stool with few adverse effects; it is available in Canada but not the United States. Calcium polycarbophil is a hydrophilic polyacrylic resin (widely available in the United States) that also works as an adsorbent, binding about 60 times its weight in water and leading to formation of a gel that enhances stool formation. Neither attapulgite nor

Table 22–5

Pharmacotherapy for Diarrhea

Drug	Usual Oral Dose	Type of Diarrhea
Calcium polycarbophil (OTC)	Adults: 1000 mg four times daily PO or after each loose stool, not to exceed 12 tablets per day Children 6–12 years: 500 mg PO three times daily Children 3–6 years: 500 mg twice daily	Chronic
Loperamide (OTC, RX)	Adults: 4 mg initially, then 2 mg PO after each subsequent loose stool. Maximum: 8 mg in 24 hours (OTC), 16 mg in 24 hours (RX) Children maximum daily doses: Age 2–5: 3 mg Age 6–8: 4 mg Age 8–12: 6 mg	Acute and chronic
Diphenoxylate/atropine (RX)	Adults: Two tablets (5 mg) initially, then one tablet PO every 3–4 hours, not to exceed 20 mg in 24 hours Children 2–12 years: Oral solution (avoid tablets) 0.3–0.4 mg/kg/day in divided doses. Do not administer to children younger than 2 years	Acute and chronic
Bismuth subsalicylate (OTC) (Kaopectate, PeptoBismol)	Adults and children 12 years and over: 524 mg/30 mL PO every 30–60 minutes as needed; Do not exceed 8 doses (240 mL or 16 tablets) per day Children: Consumers should speak with a physician before giving to children under 12 years of age	Traveler's and nonspecific acute diarrhea

OTC, over the counter; PO, by mouth; RX, prescription only.

polycarbophil is systemically absorbed. Calcium polycarbophil is effective in reducing fluid in the stool. However, caution must be exercised because it can also adsorb nutrients and other medications, thereby reducing their benefits. Its administration should be separated from other oral medications by 2 to 3 hours. Psyllium and methylcellulose products may also be used to reduce fluid in the stool and relieve chronic diarrhea.

▶ *Antiperistaltic (Antimotility) Agents*

Antiperistaltic drugs prolong intestinal transit time, thereby reducing the number of stools and the amount of fluid lost in the stool. The two drugs in this category are loperamide HCl (available over-the-counter as Imodium A–D and generically) and diphenoxylate HCl with atropine sulfate (available by prescription as Lomotil and generically). The atropine is included only as an abuse deterrent; when taken in large doses, the unpleasant anticholinergic effects of atropine negate the euphoric effect of diphenoxylate. Both loperamide and diphenoxylate are effective in relieving symptoms of acute noninfectious diarrhea and are safe for most patients experiencing chronic diarrhea. These products should be discontinued in patients whose diarrhea worsens despite therapy.

Loperamide is considered safe when used in recommended doses. When excessive doses are ingested, severe problems such as cardiac arrhythmias and death can occur.[29] Loperamide misuse and abuse has been reported.[30] Coadministration of potent CYP450 3A4 inhibitors (eg, azole antifungals, clarithromycin, conivaptan, delavirdine, erythromycin, nefazodone, protease inhibitors, and telithromycin) and 2C8 inhibitors (eg, gemfibrozil, clopidogrel) with loperamide may increase plasma loperamide concentrations and adverse effects. Patients who have ingested large doses of loperamide alone or with medications that can enhance loperamide effect may experience dizziness, lightheadedness, fainting, palpitations, irregular heart rhythm, shortness of breath, or syncope and should be advised to discontinue loperamide and seek medical attention.[29,30]

▶ *Antisecretory Agents*

Bismuth subsalicylate (BSS) is thought to have antisecretory and antimicrobial effects and used to treat acute diarrhea. Although it passes largely unchanged through the GI tract, the salicylate portion is absorbed in the stomach and small intestine. For this reason, BSS should not be given to people who are allergic to salicylates, including aspirin. Patients taking BSS should be informed that their stool will turn black. Caution should be exercised with regard to the total dose given to patients taking salicylates for other reasons to avoid salicylism. Signs and symptoms of salicylism include nausea, vomiting, tinnitus, hypotension, hyperventilation, wheezing, hyperactivity, agitation, hallucinations, fever, confusion, bleeding seizures, rhabdomyolysis, renal failure, and respiratory failure.

Octreotide is an antisecretory agent used for severe secretory diarrhea associated with cancer chemotherapy, human immunodeficiency virus, diabetes, gastric resection, and GI tumors. It is administered as a subcutaneous or IV bolus injection in an initial dose of 50 mcg three times daily to assess the patient's tolerance to GI adverse effects. Possible adverse effects include nausea,

Patient Encounter 2

A 42-year-old male account executive visited an urgent care center complaining of a history of heartburn usually after eating, which usually worsens at night, trouble swallowing, and a sensation of a lump in his throat. He stated that about 28 days ago he started over-the-counter self-treatment with omeprazole 20 mg, and about 7 days ago he began experiencing repeated bouts of diarrhea. He admitted that at times he takes twice as much medication as recommended.

Assess the likelihood that his diarrhea is due to Clostridioides difficile–associated diarrhea.

Identify findings that suggest the presence of dehydration.

Discuss potential treatment measures for this patient.

Patient Care Process for Diarrhea

Collect Information:

- Determine symptoms, severity, frequency, and exacerbating factors.
- Review hydration status.
- Determine if patient-directed therapy is appropriate or a referral is needed.
- Inquire about recent foreign travel.
- Obtain history of prescription, nonprescription, and dietary supplement use.

Assess the Information:

- Review current therapy as potential cause(s) of diarrhea.
- Determine if any diarrhea treatments have been attempted, including home remedies.
- Assess need for medical evaluation if patient is pregnant, breastfeeding, younger than 3 years or older than 70 years, or has multiple medical conditions.

Develop a Care Plan:

- If home care is recommended, provide clear instructions about how to proceed if symptoms do not improve or new symptoms emerge.
- Discuss the importance of maintaining nutrition by diet modification.
- Educate the patient about: (a) acute and chronic diarrhea causes, (b) possible complications, (c) treatment goals, (d) the medication used to manage diarrhea, and (e) if appropriate, the circumstances when antibiotics are necessary.

Implement the Care Plan:

- Educate the patient about diarrhea and its likely causes.
- Advise the patient to seek medical attention if diarrhea does not resolve.

Follow-up: Monitor and Evaluate:

- Although most diarrheal episodes resolve with minimal intervention, individuals with a protracted course should be followed until symptoms have abated or are under control. Pay special attention to the very young, the aged, and those who are medically compromised.
- Refer the patient for medical attention if needed.

bloating, pain at the injection site, and gallstones (with prolonged therapy).

▶ *Probiotics, Prebiotics, and Synbiotics*

Probiotics are dietary supplements containing bacteria (*Saccharomyces boulardii*, *Lactobacillus* species, *Bifidobacterium bifidum*, and others) that may promote health by enhancing the normal microflora of the GI tract while resisting colonization by potential pathogens.[31] Probiotics can be taken in tablets, gummies, capsules, powders, and liquids. Prebiotics are nondigestible food ingredients that are fermentable in the colon and stimulate potentially health-promoting bacteria such as bifidobacteria and lactobacilli. Synbiotics are formed when prebiotics and postbiotics are joined.[31]

Yogurt may provide relief from diarrhea due to lactose intolerance. The *Lactobacillus acidophilus* in yogurt, cottage cheese, and acidophilus milk may improve digestion of lactose and may prevent or relieve diarrhea related to lactose deficiency and milk intake. Although lactase is not a probiotic, lactase tablets may also be used to prevent diarrhea in susceptible patients.

Fecal microbiota transplantation (FMT) for treatment of diarrhea is under investigation. In 2020, the FDA issued a safety alert regarding the use of fecal microbiota for transplantation and the potential risk of serious adverse reactions, which were likely due to transmission of the pathogenic organisms thereby increasing the potential risk of serious life-threatening infections.[32] The FDA was made aware of six infections caused by enteropathogenic *E. coli* (EPEC) and Shigatoxin-producing *E. coli* (STEC) in patients being treated for *C. difficile* infection unresponsive to standard therapies.[32] Although risk of transmission is unknown and presently there is limited information about the availability and sensitivity of direct stool tests, the FDA also issued a safety alert regarding additional safety precautions pertaining to SARS-CoV2 and COVID-19 related to the transplantation of fecal microbiota.[33]

OUTCOME EVALUATION

- Monitor the patient with diarrhea from the point of first contact until symptoms resolve, keeping in mind that most episodes are self-limiting.
- Question the patient to determine whether symptom resolution occurs within 48 to 72 hours in acute diarrhea.
- Monitor for the maintenance of hydration, particularly when symptoms continue for more than 48 hours. Ask about increased thirst, decreased urination, dark-colored urine, dry mucous membranes, and rapid heartbeat, which suggest dehydration especially when nausea and vomiting are present.
- Monitor for symptom control in patients with chronic diarrhea.
- When antibiotics are used, monitor for completion of the course of therapy.

IRRITABLE BOWEL SYNDROME

KEY CONCEPT IBS is a functional bowel disorder (FBD) in which recurrent abdominal pain is associated with defecation or a change in bowel habits. In the absence of alarm symptoms such as rectal bleeding, family history of colon cancer, or unintentional weight loss, disordered bowel habits such as constipation, diarrhea, or a mix of constipation and diarrhea and symptoms of abdominal bloating/distention are usually present. IBS is classified into one of four types: (a) constipation predominant (IBS-C), (b) diarrhea predominant (IBS-D), (c) mixed with both constipation and diarrhea (IBS-M), or (d) unsubtyped (IBS-U; hard or lumpy stools less than 25% of the time and loose or watery stools less than 25% of the time). IBS is associated with frequent fluctuation in symptoms, loss of productivity, and decreased quality of life.[2,24,25]

EPIDEMIOLOGY AND ETIOLOGY

The diagnosis of IBS is considered a diagnosis of exclusion.[24,34] While pooled global population-based data estimated the prevalence of IBS to be between 7% and 21%, the prevalence of IBS in places like North America is estimated to be about 12%.[24,35]

A meta-analysis found that more than 10% of patients who were diagnosed with infectious enteritis later developed IBS. Although there were some differences in the studies analyzed, the risk was four times higher than in patients who did not have a diagnosis of infective enteritis. The authors also found that women who developed severe enteritis are at increased risk for developing IBS. Other patients at risk for developing enteritis included those experiencing psychological distress and users of antibiotics during enteritis.[36]

PATHOPHYSIOLOGY

Enteric nerves control intestinal smooth muscle action and are connected to the brain by the autonomic nervous system. IBS is thought to result from dysregulation of this "brain–gut axis." The enteric nervous system is composed of two ganglionated plexuses that control gut innervation: the submucous plexus (Meissner plexus) and the myenteric plexus (Auerbach plexus). The enteric nervous system and the CNS are interconnected and interdependent. Several neurochemicals mediate their function, including serotonin (5-hydroxytryptamine or 5-HT), acetylcholine, substance P, and nitric oxide.[37]

Serotonin is particularly important because the GI tract contains the largest amounts in the body. Two 5-HT receptor subtypes, 5-HT_3 and 5-HT_4, are involved in gut motility, visceral sensitivity, and gut secretion. The 5-HT_3 receptors slow colonic transit and increase fluid absorption, whereas 5-HT_4 receptor stimulation accelerates colonic transit.

Although no single pathologic defect accounts for the pattern of exacerbation and remission in IBS, CNS abnormalities, dysmotility, visceral hypersensitivity, and other factors have been implicated.[37]

The passage of fluids into and out of the colon is regulated by epithelial cells. In IBS, the colonic lining (epithelium) appears to function properly. However, increased movement of the contents in the colon can overwhelm its absorptive capacity. Disturbed intestinal motility appears to be a central feature of IBS and leads to altered stool consistency. Studies suggest that the colon of IBS sufferers is abnormally sensitive to normal stimuli. Enhanced visceral sensitivity manifests as pain, especially related to gut distention.[37]

Some IBS patients demonstrate sensitivity to common foods such as wheat, beef, pork, soy, and eggs. Evidence suggests that an immune component may be involved in IBS patients who experience bloating and dysmotility-like dyspepsia and that gender specificity exists.

CLINICAL PRESENTATION AND DIAGNOSIS

Refer to the accompanying box for the clinical presentation of IBS. **KEY CONCEPT** The diagnosis of IBS is made by symptom-based criteria, the absence of alarm symptoms, and the exclusion of organic disease. Patient diagnosis is categorized by the predominant disorder (IBS-C, -D, -M, or -U).

IBS is diagnosed by obtaining a thorough history to distinguish the characteristic symptoms of IBS from other conditions having similar symptoms, physical examination including anorectal examination, limited diagnostic tests, and careful follow-up. Patients should be questioned about the frequency, consistency, color, and size of stools. Because of the functional nature of IBS, a patient may present with symptoms of upper GI problems such as gastroesophageal reflux disease or with excessive flatulence. Patients should also be questioned about diet to establish any symptom relationship to meals or specifically after consumption of certain foods.

Barium enema, sigmoidoscopy, or colonoscopy may be indicated in the presence of red flag symptoms (fever, weight loss, bleeding, anemia, and persistent severe pain), which often point to a potentially serious non-IBS problem. A barium enema may identify polyps, diverticulosis, tumors, or other abnormalities that might be responsible for the symptoms. Furthermore, barium enema may detect exaggerated haustral contractions, which can impede stool movement and contribute to constipation. Flexible sigmoidoscopy can identify obstructions in the rectum and lower colon, whereas colonoscopy can evaluate the entire colon for organic disease.

The Rome IV diagnostic criteria for IBS include symptoms of recurrent abdominal pain occurring on average at least 1 day per week in the last 3 months, associated with two or more of the following: (a) related to defecation, (b) associated with a change in frequency of stool, or (c) associated with a change in form (appearance of stool). These findings should exist for the last 3 months with symptom onset at least 6 months prior to diagnosis.[1]

TREATMENT

Desired Outcomes

KEY CONCEPT The principal goal of IBS treatment is to reduce or control symptoms. The treatment strategy is based on: (a) the prevailing symptoms and their severity, (b) the degree of functional

Clinical Presentation of IBS

Symptoms

- Patients report a history of abdominal pain or discomfort that is relieved with defecation. Symptom onset is associated with change in frequency or appearance of stool. Some persons experience hard, dry stools; others have loose or watery stools. Stools may be small and pellet-like or narrow and pencil-like in appearance.
- KEY CONCEPT Symptoms can typically be categorized as either IBS-D or IBS-C. Patients with IBS-D usually report more than three loose or watery stools daily. Those with IBS-C usually have fewer than three bowel movements per week; stools are typically hard and lumpy and accompanied by straining. However, stool frequency may be normal in many cases.
- IBS-C can often be distinguished from functional constipation by the presence of abdominal pain and discomfort. Although pain and discomfort may be present in some patients with functional constipation, it is an expected feature of IBS.
- Some patients report alternating episodes of diarrhea and constipation (IBS-M).
- Patients with IBS-U report hard or lumpy stools less than 25% of the time and loose or watery stools less than 25% of the time.
- Other common symptoms include: (a) feelings of incomplete evacuation, (b) abdominal fullness, (c) bloating, (d) flatulence, (e) passage of clear or white mucus with stool, and (f) occasional fecal incontinence.
- Periods of normal stools and bowel function are punctuated by episodes of sudden symptoms.
- Symptoms are often exacerbated by stress.
- Left lower quadrant abdominal pain is often brought on or made worse by eating. Passage of stool or flatus may provide some relief.
- Patients with IBS may experience comorbidities outside the GI tract such as fibromyalgia, sleep disturbances, headaches, dyspareunia, and temporomandibular joint syndrome.

Signs

- The physical examination is often normal in IBS.
- The patient may appear to be anxious.
- Palpation of the abdomen may reveal left lower quadrant tenderness, which may indicate a tender sigmoid colon.
- Abdominal distention may be present in some cases.
- The following "red flag" or alarm features are *not* associated with IBS and may indicate inflammatory bowel disease, cancer, or other disorders: fever, weight loss, bleeding, anemia, and persistent severe pain.

Laboratory Tests

- In most cases, laboratory testing reveals no abnormalities, but certain tests can help identify other causes for the patient's symptoms:
- CBC may identify anemia, which may suggest blood loss and an organic source for GI symptoms.
- Serum electrolytes and chemistries may indicate metabolic causes of symptoms.
- Thyroid-stimulating hormone (TSH) should be ordered when thyroid dysfunction is suspected. Hypothyroidism may be responsible for constipation and related symptoms.
- Stool testing for ova and parasites may identify *Clostridioides difficile* and amoebae as possible causes of diarrhea rather than IBS.
- Fecal leukocytes can be found in inflammatory diarrhea, especially when due to invasive microorganisms.
- A positive stool guaiac test indicating blood in the GI tract does not support a diagnosis of IBS.
- An elevated erythrocyte sedimentation rate is consistent with a systemic inflammatory process such as inflammatory bowel disease rather than IBS.
- Testing for lactase deficiency can confirm the presence of lactose intolerance, which may explain the symptoms.

Patient Encounter 3

A 25-year-old man presents to the clinic complaining of headaches, sleep disturbances, cramping abdominal pain, bloating, excessive flatulence, and small amounts of hard, dry stools. When asked to show where his abdomen hurts, he pointed to both his lower left and lower right abdomen. He indicated that the pain seemed to lessen after a bowel movement. Further, he stated that the symptoms have become worse over the last month with dry stools that make it difficult to defecate. He stated that he sometimes will go a few days without a single bowel movement. About 4 months ago, he was diagnosed with fibromyalgia and was started on pregabalin. He stated that the pregabalin has helped.

Identify symptoms characteristic of IBS in this patient.

Discuss how this patient fits within the typical epidemiologic profile of patients with IBS.

impairment, and (c) the presence of psychological components. A standard treatment regimen is not possible because of the heterogeneous nature of the IBS patient population. Patients suffering from IBS can benefit from clinician support and reassurance.

Nonpharmacologic Therapy

▶ *Diet and Other General Modifications*

Dietary modification is a standard therapeutic modality. Food hypersensitivities and adverse effects have been associated with IBS, especially IBS-D. Elimination diets are the most commonly used strategy, usually focusing on milk and dairy products, fructose and sorbitol, wheat, and beef. Flatulence may be controlled by reducing gas-causing foods (beans, celery, onions, prunes, bananas, carrots, and raisins). Response to elimination diets varies widely, but they may be useful in individual patients. Care should be taken to avoid nutritional deficits while attempting to eliminate offending foods.

The low FODMAP diet is said to control IBS symptoms in some patients. FODMAPs are carbohydrates (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) that are poorly absorbed and quickly fermented by bacterial action in the gut. The gas by-product of the bacterial action is thought to contribute to IBS symptoms.[38]

The American Gastroenterological Association (AGA) Clinical Practice Guidelines on the role of probiotics in managing GI disorders made no recommendation about the use of probiotics in symptomatic children and adults with IBS because of the variability in clinical trial methodology; the guidelines further state that probiotics should be used only in the context of a clinical trial.[31]

Pharmacologic Therapy

The recommendations that follow are based on the 2014 AGA Institute Guideline on the Pharmacological Management of Irritable Bowel Syndrome.[39,40] New guidelines were expected to be published in 2021, so readers should refer to the newer guidelines when available.

▶ *Agents for Pain and Bloating*

Botanicals Peppermint oil is widely advocated; it acts as an antispasmodic agent due to its ability to relax GI smooth muscle. However, it also relaxes the lower esophageal sphincter, which could allow the reflux of gastric contents into the esophagus. The usual dose is one to two enteric-coated capsules containing 0.2 mL of peppermint oil two to three times daily. *Matricaria recutita*, known as German chamomile, is also purported to have antispasmodic properties. It is taken most often as a tea up to four times a day. Benzodiazepine, alcohol, and warfarin users should be cautioned against taking this product because it can cause drowsiness, and it contains coumarin derivatives. Primrose oil is used by some patients, but evidence of effectiveness is lacking.

Patient Encounter 3, Part 2

Upon further questioning, the patient recalled experiencing similar symptoms about 2 years ago when he thought he would have to leave school because of dwindling finances. He did not seek medical attention then because he did not have health insurance. He is a full-time student who is self-financing his higher education. His diet consists mostly of fast food.

PMH: Insomnia, headaches, fibromyalgia

FH: None

SH: Has a glass of wine occasionally with dinner

Meds: Duloxetine 30 mg orally once daily as needed for fibromyalgia; melatonin 3 mg one tablet 1 to 2 hours before bedtime as needed for insomnia; acetaminophen/aspirin/caffeine tablets two tablets every 6 hours as needed for headache; loperamide 2 mg as needed for diarrhea; bisacodyl 10 mg as needed for constipation.

Allergies: No known drug allergies

PE:

General: thin appearing; somewhat anxious and nervous when speaking

VS: BP 128/70 mm Hg; pulse 86 beats/min; RR 18 breaths/min; T 97.4°F (36.3°C); Ht. 5′4″ (163 cm); Wt. 140 lbs. (63 kg)

Integ: Skin appears dry and scaly

HEENT: PERRLA, EOMI

Ext: Normal, no swelling

Chest: Clear to A and P bilaterally

CV: RRR

Abd: (+) BS, tender LLQ and LRQ

Rectal: No abnormalities, negative stool guaiac test

Which of this patient's findings are indicative of IBS?

Propose a comprehensive treatment approach to IBS in this patient. Where appropriate, consider the presence and influence of comorbidities.

▶ *Agents for Constipation Predominance (IBS-C)*

Bulk Producers These agents may improve stool passage in IBS-C but are unlikely to have a favorable effect on pain or global IBS symptoms. Psyllium may increase flatulence, which can worsen discomfort in some patients. Methylcellulose products are less likely than psyllium to increase gas production. Although fiber-based supplement use is common in IBS-C, methylcellulose may be dose adjusted in diarrhea to increase stool consistency.

Osmotic Laxatives More studies are needed to determine the evidence of benefit on quality of life, number of stools, symptom improvement, and the ability to continue therapy in patients with IBS-C with use of polyethylene glycol 3350 (PEG) or PEG 3350 with electrolytes. The 2014 AGA practice guideline suggests the use of laxatives over no treatment for patients with IBS-C.[39]

Linaclotide (Linzess) This drug is a guanylate cyclase-C (GC-C) agonist indicated for treatment of IBS-C in adults. In IBS-C, the recommended linaclotide dose is 290 mcg orally once daily. Linaclotide relieves the abdominal pain, bloating, and constipation associated with IBS-C while exhibiting a low tendency for systemic side effects. However, diarrhea may lead to discontinuation in some patients. Clinical trials have demonstrated symptom relief and improved quality of life in treated patients. Studies of linaclotide had high overall quality of evidence across all critical outcomes such as abdominal pain response, spontaneous complete bowel movement response, improvement in quality of life, and improvement in stool consistency and urgency. The 2014 AGA practice guideline recommends the use of linaclotide over no treatment in patients with IBS-C.[39,40]

Lubiprostone (Amitiza) This agent is also FDA approved for treatment of IBS-C, but only in women age 18 years and older. Lubiprostone is generally well tolerated in such patients. It is typically given in smaller doses than those used in CIC. However, as with treatment for constipation, nausea may limit its use. Diarrhea leading to treatment discontinuation may occur. Recent evidence indicated a moderate degree of symptom relief and improvement in quality of life with lubiprostone use. No clinical studies currently exist that compare the beneficial effects or harm associated with the use of linaclotide versus lubiprostone. In patients with IBS-C the 2014 AGA practice guideline suggests use of lubiprostone over no drug treatment.[39,40]

Plecanatide (Trulance) This guanylate cyclase-C agonist is indicated for treatment IBS-C.[41] Plecanatide and its active metabolite act locally on the luminal surface of the intestinal epithelium to increase the availability of intra- and extracellular cyclic GMP. In animal models, increased availability of cyclic GMP has been associated with decreased activity of pain-sensing nerves of visceral pain and stimulation of secretion of chloride and bicarbonate via activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel into the intestinal lumen, resulting in increased intestinal fluid and accelerated transit. Due to risk of serious dehydration, plecanatide is contraindicated in patients less than 6 years of age, and its use should be avoided in patients aged 6 to 18 years of age. The safety and efficacy of plecanatide in patients less than 18 years of age has not been established. The recommended adult dosage for treating IBS-C is one 3-mg tablet orally once daily. The tablet should be swallowed whole and can be taken with or without food. Diarrhea leading to discontinuation is the most common adverse reaction associated with plecanatide. Most cases of diarrhea occurred within the first 4 weeks of therapy, but severe diarrhea has been reported within the first day of treatment. Less commonly reported adverse effects included nausea, nasopharyngitis, upper respiratory tract infection, urinary tract infection, and dizziness. Increased liver alanine aminotransferase (ALT) levels have been reported.[41]

Tegaserod maleate (Zelnorm) is indicated for the treatment of adult women younger than 65 years of age who are diagnosed with IBS-C.[42] It acts by enhancing intestinal secretion and motility through its partial 5-hydroxytryptamine (5-HT$_4$) receptor partial agonist activity. The recommended dosage is 6 mg taken twice daily orally at least 30 minutes before meals. Tegaserod should be discontinued if patients do not achieve adequate symptom control after 4 to 6 weeks of treatment. Tegaserod is contraindicated in patients with a history of serious cardiac conditions, ischemic colitis, or other forms of intestinal ischemia, severe renal impairment (eGFR< 15 mL/min/1.73 m^2), or end-stage renal disease. It is also contraindicated in moderate or severe hepatic impairment (Child-Pugh B or C), a history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions and hypersensitivity to tegaserod. The benefit of tegaserod use lasts about 90 days. Before tegaserod is prescribed, the potential risks of tegaserod treatment must be balanced with expectations in improvements in symptoms of IBS-C. Discontinue treatment in patients who experience a myocardial infarction, stroke, transient ischemic attack, or angina. Evaluate the risks and benefits of continued treatment in patients who develop clinical or other evidence of cardiovascular ischemic heart disease and/or experience changes in health status that could increase cardiovascular risk during treatment. Patients with ischemic colitis should be monitored for rectal bleeding, bloody diarrhea, and new or worsening abdominal pain; discontinue tegaserod if symptoms develop. Volume depletion associated with diarrhea can occur. Instruct patients to discontinue tegaserod and contact their health-care provider if severe diarrhea, hypotension, or syncope occur. Monitor patients for clinical worsening of depression and emergence of suicidal thoughts and behaviors, especially during the initial few months of treatment. Instruct patients to immediately discontinue tegaserod and contact their health-care provider if their depression is persistently worse or they are experiencing emergent suicidal thoughts or behaviors. Adverse reactions include headache, abdominal pain, alopecia, nausea, diarrhea, flatulence, dyspepsia, and dizziness. Available data from case reports indicated that use in pregnant women has not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.[42]

▶ *Agents for Diarrhea Predominance (IBS-D)*

Loperamide This antidiarrheal inhibits peristalsis and fluid secretion, thereby improving stool consistency and reducing the number of stools. Consequently, it is most useful in patients who have diarrhea as a prominent symptom. However, it does not lessen abdominal pain and can occasionally aggravate pain. Recent evidence indicates that the level of symptom relief and improvement in quality of life with loperamide is very low. As described in the Diarrhea section, excessive dosing can result in serious cardiovascular adverse effects; patients should be instructed not to exceed the maximum recommended dose of 8 mg (OTC) or 16 mg (prescription) daily.[30] In patients with IBS-D, the 2014 AGA practice guideline suggests that loperamide should be used over no drug treatment.[39]

Antispasmodics Dicyclomine and hyoscyamine have been among the most frequently used medications for treating abdominal pain in patients with IBS (Table 22–6). They have shown improvement in global symptoms and abdominal pain associated with IBS. Nevertheless, the overall quality of evidence across all critical outcomes for antispasmodics is low. The 2014 AGA practice guideline suggests the use of antispasmodics over no drug in patients with IBS.[39]

Side effects include dry mouth, dizziness, blurred vision, constipation, urinary retention, and (rarely) psychosis. Although their effectiveness remains unconfirmed, these drugs may deserve a trial in patients with intermittent postprandial pain.

Antidepressants Tricyclic antidepressants (TCAs) (eg, amitriptyline, desipramine, trimipramine, and doxepin) may help patients with IBS who predominantly experience abdominal

Table 22–6

Pharmacologic Treatments for IBS

Generic Name	Dose
Antispasmodics	
Dicyclomine	10–20 mg PO every 4–6 hours as needed
Hyoscyamine	0.125–0.25 PO mg or sublingually every 4 hours as needed
Propantheline bromide	15 mg PO three times a day (before meals) and 30 mg at bedtime
Clidinium bromide plus chlordiazepoxide HCl	5–10 mg PO three to four times a day
Hyoscyamine, scopolamine, atropine, phenobarbital	One to two tablets PO three to four times daily
Tricyclic Antidepressants	**In IBS with Diarrhea:**
Amitriptyline	50–150 mg PO daily
Doxepin	10–150 mg PO daily
Selective Serotonin-Reuptake Inhibitors	**In IBS with Constipation:**
Paroxetine (others can be used)	10–40 mg PO daily
Bulk-Forming Laxatives	
Psyllium	2.5–4 g PO daily
Methylcellulose	4–6 g PO daily
Antimotility Agents	
Loperamide	4 mg PO; then 2 mg PO after each loose stool; daily maximum: 8 mg (OTC) or 16 mg (RX)
5-HT$_3$ Receptor Antagonist	
Alosetron[a]	0.5 mg PO two times a day for 4 weeks; then assess appropriate dose
5-HT$_4$ Receptor Agonist	
Tegaserod maleate[a]	6 mg PO twice daily
Guanylate Cyclase-C (GC-C) Agonist	
Linaclotide	290 mcg PO once daily
Plecanatide	3 mg PO once daily
Nonabsorbable antibiotic	
Rifaximin	550 mg PO three times daily for 14 days; patients who experience symptom recurrence can be retreated up to two times with the same dosage regimen
Mu-Opioid Receptor Agonist	
Eluxadoline	100 mg PO twice daily with food; 75 mg PO twice daily is recommended for select patients (eg, hepatic impairment)
Chloride Channel Activator	
Lubiprostone	8 mcg PO twice daily with food and water

[a] Withdrawn from general use; available only on a restricted basis.

pain. They modulate pain principally through effects on neurotransmitter reuptake, especially norepinephrine and serotonin. Their effectiveness in functional GI disorders seems independent of mood-altering effects normally associated with these agents. Continued TCA therapy may be limited by adverse effects. The overall effect of TCAs on quality of life, symptom relief, and presence of adverse events leading to treatment discontinuation is reported as low. In patients with IBS, the 2014 AGA practice guideline suggests the use of tricyclic antidepressants over no drug treatment.[39]

The selective serotonin-reuptake inhibitors (SSRIs) paroxetine, fluoxetine, and citalopram are potentially useful due to the significant effect of serotonin in the gut. SSRIs principally act on 5-HT$_1$ or 5-HT$_2$ receptors, but they can also have some effect on gut-predominant 5-HT$_3$ and 5-HT$_4$ receptors, perhaps reducing visceral hypersensitivity. Serotonin–norepinephrine reuptake inhibitors (SNRIs) do not offer improvement of abdominal pain and no improvement in global relief of symptoms within a 6- to 12-week treatment period. Recent evidence indicates that the use of SSRIs in IBS patients in relationship to the overall quality of evidence across all critical outcomes was rated as low. The 2014 AGA practice guideline suggests against using SSRIs for patients with IBS.[39]

Rifaximin (Xifaxan) Semisynthetic antibacterial agent is structurally similar with rifampin. It has very low systemic absorption and is FDA approved for treatment of IBS-D in adults.[43] Research suggests bacterial overgrowth plays a role in producing bloating experienced by some IBS patients. Rifaximin is not to be used in patients with diarrhea accompanied by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*. It should be used with caution in patients with severe (Child-Pugh Class C) hepatic impairment. Rifaximin has proven to be better than placebo in relieving bloating, and its lack of absorption reduces the likelihood of adverse effects. The overall quality of evidence across outcomes such as pain relief, stool consistency, and the return of complete spontaneous bowel movements is moderate.[39]

For treatment of IBS-D, rifaximin 550-mg tablets are administered orally three times daily for 14 days.[43] The same regimen can be repeated up to two times in patients who experience recurrence. Potential adverse reactions include nausea, increased ALT and creatine kinase (CK) enzymes, *C. difficile*–associated colitis, myalgia, and hypersensitivity reactions including exfoliative dermatitis, rash, swelling of the face and tongue, and difficulty swallowing. Hypersensitivity reactions can occur within 15 minutes of rifaximin ingestion. Rifaximin use for treatment of IBS-D has not been studied in pregnant women or children under the age of 18. Caution should be used in patients with liver dysfunction. The 2014 AGA practice guideline suggests the use of rifaximin in patients with IBS-D over no drug therapy.[39]

Alosetron (Lotronex) Stimulation of 5-HT_3 receptors triggers hypersensitivity and hyperactivity of the large intestine. Alosetron, a selective 5-HT_3 antagonist, blocks these receptors and is indicated only for women with severe IBS-D who have: (a) chronic IBS symptoms (6 months or longer); (b) no anatomic or biochemical abnormalities of the GI tract; and (c) not responded adequately to conventional therapy. The recommended starting dose is 0.5 mg twice daily, increasing to 1 mg twice a day after 4 weeks if the starting dosage is well tolerated but does not adequately control IBS symptoms. The most common adverse effects are constipation, abdominal discomfort and pain, nausea, and GI discomfort and pain. Alosetron labeling contains a black box warning related to serious GI adverse reactions, including ischemic colitis and serious complications of constipation that have resulted in hospitalization and, rarely, blood transfusion, surgery, and death. The 2014 AGA practice guideline suggests that in patients diagnosed with IBS-D alosetron use may improve global symptoms over no drug treatment.[39]

Eluxadoline (Viberzi) This μ-opioid receptor agonist reduces bowel contractions and is FDA approved for treatment of adults with IBS-D.[44] The recommended dose is 100 mg orally twice daily taken with food. The dose can be reduced to 75 mg twice daily with food in patients who cannot tolerate the 100-mg dose and in patients with mild or moderate hepatic impairment.[45] The most common adverse effects are constipation, nausea, and abdominal pain. It is contraindicated in persons who drink more than three alcoholic beverage per day because these patients are at increased risk for acute pancreatitis.[45] Eluxadoline should not be used in patients without a gallbladder because these patients are at increased risk of developing pancreatitis and/or sphincter of Oddi spasm. Eluxadoline is a Schedule IV controlled substance.

OUTCOME EVALUATION

- Monitor for adequate symptom relief. Patients whose pain does not respond to drug therapy may have a psychological comorbid condition requiring psychiatric intervention.
- Monitor for relief of pain if initially present. Monitor IBS-C or IBS-D patients for stool frequency, appearance, and size relative to normal characteristics. As stools normalize, associated symptoms such as bloating and abdominal distention should resolve.
- For IBS-C and IBS-M patients taking bulk producers, monitor for relief of constipation. Hard stools should soften within 72 hours.
- Monitor antidepressant and antispasmodic therapy for relief of abdominal pain and potential adverse effects.
- Assess 5-HT_4 receptor agonists for relief of crampy abdominal pain and bloating.
- Monitor linaclotide for treatment-limiting diarrhea in IBS-C.
- Evaluate 5-HT_3 receptor antagonists (alosetron) for relief of abdominal pain and fecal incontinence. Monitor for constipation.
- Expect antimotility agents to reduce stool frequency and control diarrhea within 18 to 36 hours unless severe.
- Monitor CBC, serum electrolytes and chemistries, stool guaiac, and erythrocyte sedimentation rate yearly for changes that might signal an overlapping organic problem.
- Refer for medical evaluation any patient presenting with red flag signs (eg, fever, weight loss, bleeding, anemia, and persistent severe pain).

Patient Care Process for IBS

Collect Information:

- Determine the type, severity, and frequency of symptoms and possible exacerbating factors.
- Obtain a thorough current history of prescription, nonprescription, and dietary supplement use.

Assess the Information:

- Determine if any IBS treatments have been attempted and their effectiveness.
- Establish whether self-care is appropriate or a medical referral is needed.

Develop a Care Plan:

- Determine whether the patient has received prior education about IBS, lifestyle modifications, drug therapy for IBS, and symptom prevention measures. If necessary:
- Explain medication use relative to symptom intensity
- Describe potential adverse effects
- List drugs that may interact with the therapy

Implement the Care Plan:

- Provide patient education about IBS and the treatment selected.

Follow-up: Monitor and Evaluate:

- Encourage patients to report every professional interaction since their last encounter to remain current with all treatment recommendations.
- Be vigilant for the occurrence of red flag symptoms.

Abbreviations Introduced in This Chapter

BSS	Bismuth subsalicylate
CBT	Cognitive behavioral therapy
CIC	Chronic idiopathic constipation
FBD	Functional bowel disorder
FGID	Functional gastrointestinal disorder
FMT	Fecal microbiota transplantation
GMP	Guanosine monophosphate
IBS	Irritable bowel syndrome
IBS-C	Irritable bowel syndrome with constipation
IBS-D	Irritable bowel syndrome with diarrhea
IBS-M	Irritable bowel syndrome with constipation and diarrhea (mixed)
NTC	Normal-transit constipation
OIC	Opioid-induced constipation
ORS	Oral rehydration solution
STC	Slow-transit constipation
PAMORA	Peripherally acting μ-opioid receptor antagonist
TCA	Tricyclic antidepressant
TD	Traveler's diarrhea

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23 Portal Hypertension and Cirrhosis

Laurajo Ryan

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the pathophysiology of cirrhosis and portal hypertension.
2. Identify signs and symptoms of cirrhosis.
3. Identify laboratory abnormalities that result from liver disease and describe the associated pathophysiology.
4. Describe the consequences associated with cirrhosis and decreased hepatic function.
5. Identify treatment goals for a patient with complications of cirrhosis.
6. Recommend a specific treatment regimen for a patient with cirrhosis that includes lifestyle changes, nonpharmacologic measures, and pharmacologic therapy.

INTRODUCTION

Cirrhosis involves replacement of normal hepatic architecture with fibrous scar tissue. Scarring is accompanied by the loss of viable hepatocytes (the functional cells of the liver) and alterations in hepatic blood flow. Cirrhosis is characterized by progressive damage and deterioration of liver function, but even with extensive scarring, some patients remain asymptomatic. **KEY CONCEPT** Advanced cirrhosis is irreversible and leads to portal hypertension, which in turn is responsible for the complications that define decompensated cirrhosis. Complications of cirrhosis include ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE), hepatorenal syndrome (HRS), and variceal bleeding.[1] These complications carry high mortality rates and indicate disease progression. The only cure for cirrhosis is liver transplantation.

EPIDEMIOLOGY AND ETIOLOGY

Overall, cirrhosis is the 11th leading cause of death in the United States. Rates vary by age, gender, race, and ethnicity, but cirrhosis places an enormous burden on society from hospitalizations, lost wages, decreased productivity, and emotional strain on patients and their families.

Cirrhosis results from long-term insult to the liver, but damage usually doesn't become clinically evident until the fourth decade of life. Infection with one or more strains of viral hepatitis causes acute, potentially reversible hepatic inflammation, whereas chronic infection with hepatitis B (HBV) or C (HCV) often leads to cirrhosis. Globally, viral hepatitis and alcoholic and nonalcoholic liver disease are the most common causes of cirrhosis. Alcohol and HCV are the most common causes of cirrhosis in the United States, whereas HBV accounts for the majority of cases worldwide.[2] Newer HCV therapies provide sustained virologic response (SVR) and are expected to dramatically decrease new cases of HCV cirrhosis. Even patients who have already developed HCV cirrhosis benefit from antiviral therapy, and recent guidelines recommend treatment for nearly all patients (see Chapter 25, Viral Hepatitis, for more details).[3]

Nonalcoholic fatty liver disease (NAFLD) begins with asymptomatic fatty liver but can progress to cirrhosis; it is the leading cause of chronic liver disease worldwide. NAFLD is a diagnosis of exclusion; viral, genetic, and environmental causes must be ruled out. NAFLD is so closely associated with diabetes mellitus, dyslipidemia, obesity, insulin resistance, and other conditions associated with increased hepatic fat that an international consensus recently recommended a change in nomenclature to metabolic dysfunction–associated fatty liver disease (MAFLD).[4]

Alcoholic cirrhosis usually develops after decades of heavy drinking. It develops more quickly in women than men, even after taking body weight into account. Estimates vary, but alcoholic cirrhosis can develop after as few as two to three daily drinks in women and three to four drinks in men, although five to eight daily drinks is more typical.[5] Differences in metabolism may account for the gender disparity; women metabolize less alcohol in the gastrointestinal (GI) tract, allowing delivery of more ethanol (which is directly hepatotoxic) to the liver.[6] Genetic factors also play a role in disease progression; some patients develop cirrhosis with much less cumulative alcohol intake than is typical (either fewer drinks per day or faster disease onset), while others with much larger intake may never develop cirrhosis.

Alcoholic Liver Disease

Alcoholic liver disease stimulates changes in metabolism that result in the deposition of fat in the liver, hypertriglyceridemia, and acidemia. The disease progresses through several distinct phases—fatty liver followed by alcoholic hepatitis (inflammation) and finally cirrhosis. Early stages (fatty liver, hepatitis) are often reversible with cessation of alcohol intake, and although the scarring of cirrhosis is permanent, stopping drinking can decrease complications and slow progression to end-stage liver disease.[7]

Ethanol metabolism to acetaldehyde begins in the gastric mucosa even prior to absorption. Because it is highly lipid soluble, the remaining alcohol is rapidly absorbed from the GI tract and transported to the liver. **KEY CONCEPT** Alcohol dehydrogenase oxidizes ethanol to acetaldehyde, which causes inflammation and fibrosis.[7] Acetaldehyde exerts direct toxic effects on the liver by damaging hepatocytes, inducing fibrosis, and directly coupling to proteins, interfering with their intended function. When ethanol saturates the alcohol dehydrogenase enzyme system, an inducible form of the cytochrome P450 (CYP450) enzyme system (CYP2E1) takes over the detoxification process. Metabolism via CYP2E1, like alcohol dehydrogenase, produces acetaldehyde as its end product and further adds to inflammation by producing reactive oxygen species (ROS).[8]

Less Common Causes of Cirrhosis

Genetics and metabolic risk factors mediate other less common causes of cirrhosis. These diseases vary widely in prevalence, disease progression, and treatment options.

Primary biliary cholangitis (PBC) is characterized by progressive inflammatory destruction of the bile ducts. Immune-mediated inflammation of the intrahepatic bile ducts causes remodeling and scarring, resulting in the retention of bile in the liver and hepatocellular damage, which can lead to cirrhosis. PBC is uncommon, and patients are frequently diagnosed incidentally during routine healthcare visits.

Hereditary hemochromatosis is an autosomal recessive disease that causes increased intestinal iron absorption and subsequent deposition in hepatic, cardiac, and pancreatic tissue. Hepatic iron overload can cause fibrosis, hepatic scarring, cirrhosis, and hepatocellular carcinoma. Repeated blood transfusions can also cause hemochromatosis, but transfusions alone rarely lead to cirrhosis.

In Wilson disease (an autosomal recessive disease), the protein responsible for facilitating copper excretion in the bile is faulty, and copper accumulates in hepatic tissue. High copper levels are toxic to hepatocytes, and fibrosis leading to cirrhosis can develop in untreated patients. Patients with Wilson disease usually present with symptoms of liver and/or neurologic disease while still in their teens.

A third genetic disease that can cause cirrhosis is α_1-antitrypsin deficiency (AATD). Abnormalities in the α_1-antitrypsin protein cause it to accumulate in the liver. AATD can cause cirrhosis in children and adults; adults usually have concomitant pulmonary disease.

PATHOPHYSIOLOGY

Cirrhosis and Portal Hypertension

Progressive destruction of hepatocytes combined with an increase in fibroblasts and connective tissue culminates in cirrhosis. Fibrotic scar tissue nodules modify the basic architecture of the liver, disrupting hepatic blood flow and overall liver function.

Reduced hepatic blood flow significantly alters normal metabolic processes and interferes with protein synthesis as well as alterations in carbohydrate and lipid metabolism. Hepatic drug metabolism is also disrupted. These changes can result in higher systemic drug concentrations and toxicity by extending half-life of drugs normally eliminated by the liver (especially drugs with high first-pass metabolism). Decreased hepatic metabolism can also reduce or delay prodrug activation causing therapeutic failure. A healthy liver processes metabolic waste products for excretion; in cirrhosis, bilirubin (from the enzymatic breakdown of heme) can accumulate causing jaundice (yellowing of the skin), scleral icterus (yellowing of the sclera), and tea-colored urine (urinary bilirubin excreted as urobilinogen).

Changes in steroid hormone production, conversion, and handling are prominent features of cirrhosis. In men, the relative increase in estrogens manifests as decreased libido, gynecomastia (development of breast tissue), testicular atrophy, and feminization. Another effect of changes in sex hormone metabolism is the development of palmar erythema and spider angioma (nevi). Spider angioma are vascular lesions found mainly on the trunk that have a central arteriole (body) surrounded by radiating "legs." When blanched, the lesions fill from the center body outward toward the legs. Spider angioma are not specific to cirrhosis, but the number and size do correlate with disease severity, and their presence relates to the risk of variceal hemorrhage.[9]

Portal hypertension describes increased blood pressure in the portal vein and is a consequence of increased resistance to hepatic blood flow.[9] Portal hypertension can develop from prehepatic, intrahepatic (sinusoidal), or posthepatic damage that obstructs blood flow to the liver.

Hepatic sinusoids are porous vessels within the liver that surround radiating rows of hepatocytes (Figure 23–1). Sinusoids transport systemic blood to the hepatocytes where ingested substances (eg, nutrients, drugs, toxins) and waste products are processed for immediate use, storage, or detoxification.

The superior mesenteric and the splenic veins join to form the portal vein that is the primary blood vessel leading to the liver. The portal vein carries deoxygenated venous blood from the splanchnic bed (intestines, stomach, pancreas, and spleen) at a rate of 1 to 1.5 L/min (Figure 23–2). Portal flow accounts for approximately 75% of blood delivered to the liver; the hepatic artery provides the remaining 25% in the form of oxygenated blood from the abdominal aorta.

Intrahepatic resistance to portal blood flow increases pressure on the entire splanchnic bed; an enlarged liver (hepatomegaly) and enlarged spleen (splenomegaly) are common findings in cirrhotic patients.

Portal hypertension causes systemic and splanchnic arterial vasodilation by triggering production of nitric oxide and other vasodilators in an attempt to balance the pressure gradient. The fall in systemic arterial pressure activates the sympathetic nervous system, increases antidiuretic hormone (ADH, vasopressin) release, and activates the renin–angiotensin–aldosterone system (RAAS). This attempt to restore arterial pressure results in avid sodium and water retention.[10]

As a result of the increased pressure, the umbilical vein (which is usually eradicated in infancy) may become patent and cause prominent dilated veins that are visible on the surface of the abdomen. This phenomenon is called *caput medusae* because it resembles the head of the mythical Gorgon Medusa.

Ascites

Ascites is the accumulation of fluid in the peritoneal space. It is the most common condition associated with decompensated cirrhosis and indicates a poor prognosis.[7]

The pathophysiology of ascites, portal hypertension, and volume overload are interrelated (Figure 23–3). Cirrhotic changes and subsequent decreases in synthetic function lead to decreased albumin production (hypoalbuminemia). Because albumin is the primary intravascular protein responsible for maintaining vascular oncotic pressure, low serum albumin levels, elevated hydrostatic pressure, persistent splanchnic vasodilation, and increased capillary permeability allow fluid to leak from the vascular space

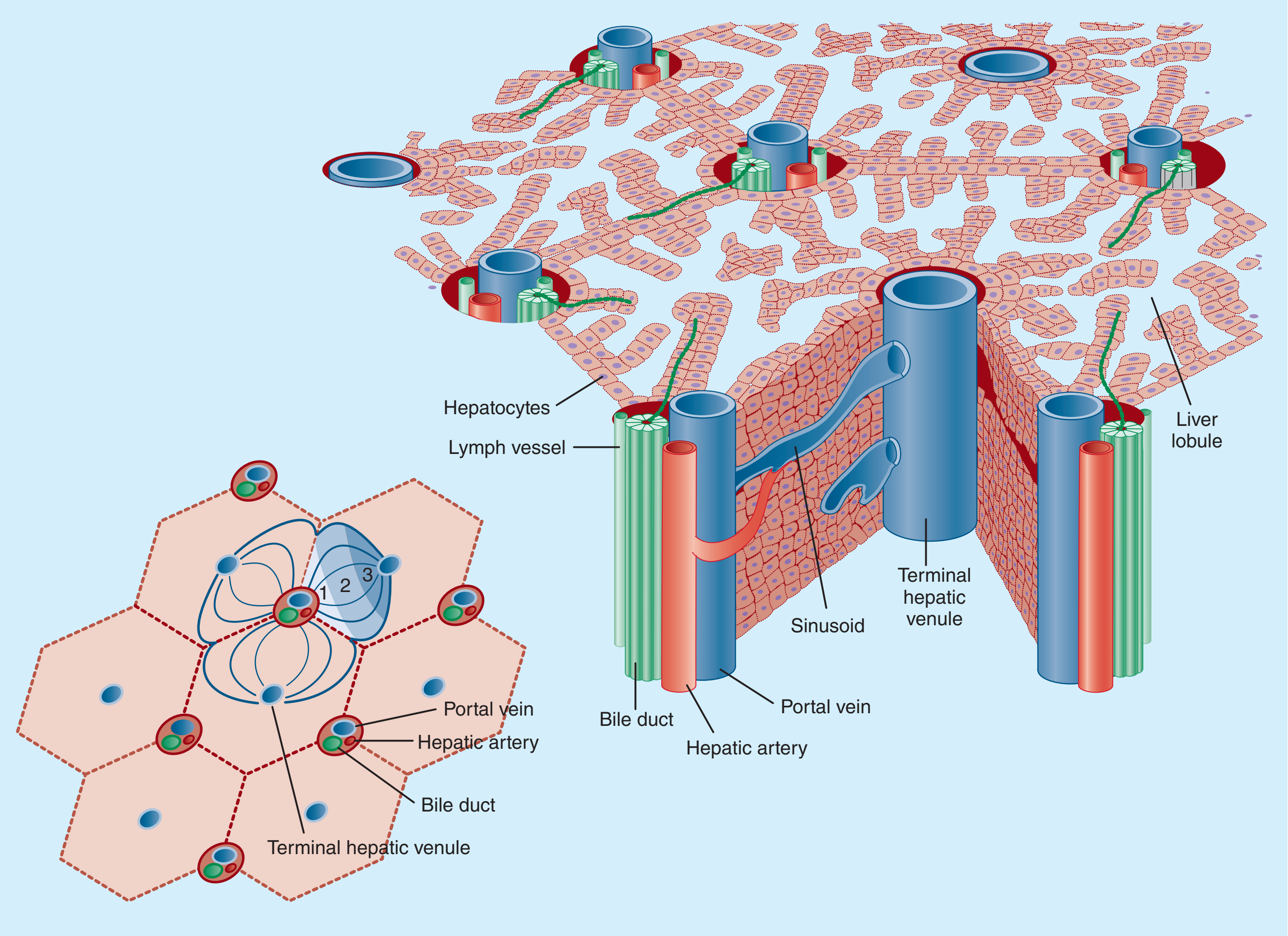

FIGURE 23–1. Relationship of sinusoids to hepatocytes and the venous system. (From Sease JM, Clements JN. Portal hypertension and cirrhosis. In: DiPiro JT, Yee GC, Posey LM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill, 2020. www.accesspharmacy.com, with permission.)

into body tissues. The result is ascites, peripheral edema, and fluid in the pulmonary system. Obstruction of hepatic sinusoids and hepatic lymph nodes also allows fluid to seep into the peritoneal cavity, further contributing to ascitic fluid formation.

Fluid redistribution results in decreased effective intravascular volume, which decreases renal perfusion. Decreased renal perfusion increases RAAS activity, increasing plasma renin levels, aldosterone production, and sodium retention. The subsequent increase in the intravascular volume furthers the imbalance of intravascular oncotic pressure, allowing even more fluid to escape to the extravascular spaces, increasing ascitic fluid volume and peripheral edema. Unchecked, these combined effects enable the cycle of portal pressure and ascites to continue, creating a self-perpetuating loop of ascites formation.

Patients with ascites avidly retain both sodium and water through multiple mechanisms. Elevated aldosterone concentrations (from a combination of increased production and decreased hepatic clearance), increases in ADH, and sympathetic nervous system activation all impair free water excretion, and patients often become hyponatremic. This is not the result of too little sodium; it is a dilutional effect. Hyponatremia also serves as a marker of disease severity. Untreated, this combination of factors can lead to a decrease in renal function and HRS.[4,10]

Hepatorenal Syndrome

HRS is a decline in renal function in the setting of cirrhosis that is not reversible with volume repletion. The deterioration is not caused by intrinsic renal disease but by ineffective arterial pressure resulting from the cumulative effects of portal hypertension.

Type 1 HRS is characterized by rapid deterioration of renal function (acute kidney injury [AKI]). Untreated, it is rapidly fatal with a 50% mortality rate at 14 days. Renal artery vasoconstriction (stimulated by the sympathetic nervous system and RAAS) and decreased mean arterial pressure (mediated by nitric oxide) decrease renal perfusion and precipitate renal failure. Production of renin stimulates a cascade that causes fluid retention and peripheral vasoconstriction to increase arterial pressure. Prostaglandin E_2 and prostacyclin production increase to stimulate renal vasodilation and maintain renal blood flow. HRS develops when these mechanisms are overwhelmed, and renal perfusion drops acutely. SBP is a common trigger for HRS, as are nonsteroidal anti-inflammatory drugs (NSAIDs), which precipitate HRS by inhibiting prostaglandin production. Type 2 HRS has similar pathophysiology to type 1 HRS but is characterized by a less acute decline in renal function.

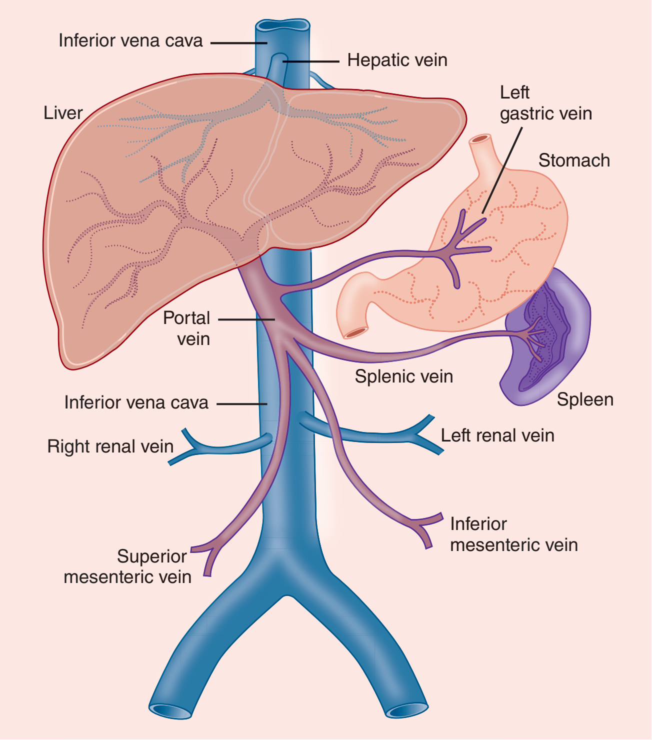
Inferior vena cava
Hepatic vein
Liver
Left gastric vein
Stomach
Portal vein
Splenic vein
Spleen
Inferior vena cava
Right renal vein
Left renal vein
Inferior mesenteric vein
Superior mesenteric vein

FIGURE 23–2. The portal venous system. (From Sease JM, Wilder AG. Portal hypertension and cirrhosis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill, 2017. www.accesspharmacy.com, with permission.)

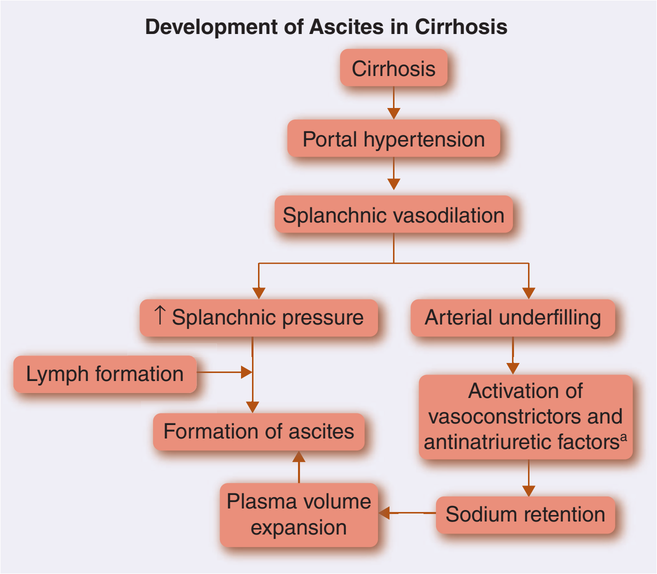
Development of Ascites in Cirrhosis
Cirrhosis
Portal hypertension
Splanchnic vasodilation
↑ Splanchnic pressure
Arterial underfilling
Lymph formation
Activation of vasoconstrictors and antinatriuretic factors[a]
Formation of ascites
Plasma volume expansion
Sodium retention

FIGURE 23–3. Development of ascites in cirrhosis. This flow diagram illustrates the importance of portal hypertension with splanchnic vasodilation in the development of ascites. [a]Antinatriuretic factors include the renin–angiotensin–aldosterone system and the sympathetic nervous system. (From Bacon BR. Cirrhosis and its complications. In: Kasper DL, Hauser SL, Jameson JL, et al., eds. Harrison's Principles of Internal Medicine, 19th ed. New York, NY: McGraw-Hill, 2015. www.accesspharmacy.com, with permission.)

The traditional laboratory parameters used to monitor renal function (serum creatinine, blood urea nitrogen [BUN]) tend to be deceptively low in cirrhotic patients because of reduced muscle mass and decreased hepatic urea production, respectively. Because of this, small changes in laboratory values can represent a significant decline in renal function, so even minor changes should be monitored closely.

Varices

The splanchnic system drains venous blood from the GI tract to the liver. Because portal hypertension increases resistance to drainage from the originating organ, collateral vessels (varices) develop in the esophagus, stomach, and rectum to compensate for the increase in pressure and blood volume. Varices divert blood meant for hepatic circulation back to the systemic circulation. This diversion decreases clearance of drugs and potential toxins through the loss of first-pass (presystemic) metabolism. Varices are weak superficial vessels; any additional increase in pressure can cause them to rupture and bleed.[9]

Spontaneous Bacterial Peritonitis (SBP)

SBP is an acute bacterial infection of peritoneal (ascitic) fluid in the absence of intra-abdominal infection or intestinal perforation; up to 30% of patients with ascites develop SBP.[11] The peritoneal cavity is usually a sterile space. One proposed mechanism of bacterial contamination is the translocation of intestinal bacteria to mesenteric lymph nodes, which then seed the ascitic fluid.[12] Bacterial translocation correlates with the delay in intestinal transit time and increased intestinal wall permeability observed in cirrhotic patients. Another possible mechanism of SBP is the hematogenous spread of bacteria into the peritoneal space.[12] Low-protein ascites (< 1 g/dL [10 g/L]) is associated with increased rates of SBP; low protein is presumably correlated to low antibacterial activity.

Enteric Gram-negative aerobes (*Escherichia coli*, *Klebsiella pneumoniae*) are the most common bacteria isolated from patients with SBP. *Streptococcus pneumoniae* is the most common Gram-positive pathogen.[7]

Hepatic Encephalopathy

Numerous factors, many of them poorly understood, are involved in the development of HE. In severe hepatic disease, systemic circulation bypasses the liver; substances that are normally metabolized by the liver accumulate in the systemic circulation. These by-products, especially nitrogenous waste, are neurotoxic.[13]

Ammonia (NH$_3$) is just one of the toxins implicated in HE. It is a metabolic by-product of protein catabolism and is also generated by gut bacteria. In a normally functioning liver, hepatocytes degrade ammonia to form urea, which is renally excreted; in cirrhosis, conversion to urea is reduced, and ammonia accumulates and contributes to encephalopathy. Patients with HE commonly have elevated serum ammonia concentrations, but ammonia levels do not correlate with the degree of CNS impairment.[13]

High levels of "false neurotransmitters" (aromatic amino acids, γ-aminobutyric acid, endogenous benzodiazepines) have also been implicated in HE. These substances bind to both the γ-aminobutyric acid and benzodiazepine receptors and act as agonists at the active receptor sites.[13]

HE is a clinical diagnosis; decreased cognition, confusion, and changes in behavior combined with physical signs such as asterixis (characteristic flapping of hands upon extension of arms with wrist flexion) indicate HE. A precipitating event associated with increased production and/or decreased elimination of nitrogenous waste products or toxins can often be identified in patients with previously stable cirrhosis who develop acute encephalopathy. Infections, variceal hemorrhage, renal insufficiency, electrolyte abnormalities, and increased dietary protein have all been associated with acute HE. Acute HE is often readily reversible, but changes of a more chronic, insidious nature are more difficult to treat; patients rarely recover fully from chronic HE.

Clinical Presentation of Cirrhosis and Complications of Portal Hypertension

General

- Many signs and symptoms are specific to the complication the patient is experiencing at presentation.

Symptoms

- Patients with cirrhosis may be asymptomatic until acute complications develop.
- Nonspecific symptoms include anorexia, fatigue, weakness, changes in libido, and disturbances in sleep patterns. Patients may also bruise easily or bleed from minor injuries.
- Patients with ascites describe feelings of abdominal fullness and pain, nausea, shortness of breath, and early satiety.
- Hemorrhage from esophageal or gastric varices often presents as nausea, vomiting, and **hematemesis** and may be associated with melena, pallor, fatigue, and weakness from blood loss. Bleeding from rectal varices may present as **hematochezia**.
- In patients with bleeding varices, digestion of swallowed blood can cause nausea and precipitate symptoms of HE.
- Neurologic changes from HE can be overwhelming or so subtle that they are not apparent except during a targeted clinical evaluation.
- Patients with HE may complain of disruption of sleep patterns; patients have delayed bedtime and wake times, which may progress to complete inversion of the normal diurnal cycle.
- SBP should be suspected in patients with symptoms of infection such as fever, chills, abdominal pain, and mental status changes.

Signs

- Nonspecific signs of liver disease include jaundice, scleral icterus, tea-colored urine, bruising, hepatomegaly, splenomegaly, spider angioma, caput medusae, palmar erythema, gynecomastia, and testicular atrophy.
- Ascites can be detected by increased abdominal girth accompanied by shifting dullness and a fluid wave.
- Signs of variceal bleeding depend on the degree of blood loss and abruptness of onset. Rapid and massive blood loss is more likely to result in hemodynamic instability than slow, steady bleeding.
- Signs of acute bleeding may include pallor, hypotension, tachycardia, mental status changes, and hematemesis.
- Markers of hepatic encephalopathy (HE) include decreased cognition, confusion, somnolence, changes in behavior or personality, and asterixis.
- Patients with SBP may present with fever, painful tympanic abdomen, and changes in mental status.
- Decreases in clotting factors and thrombocytopenia may manifest as abnormal bruising and bleeding.
- Dupuytren contracture is a contraction of the palmar fascia that usually affects the fourth and fifth digits. It is not specific to cirrhosis and can also be seen in repetitive use injuries.

Laboratory Abnormalities

- Hepatocellular damage manifests as elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The degree of elevation does not correlate with the remaining functional metabolic capacity of the liver. An AST level twofold higher than ALT suggests ongoing alcoholic liver damage.
- Elevated alkaline phosphatase is nonspecific and may correlate with liver or bone disease; it tends to be elevated in biliary tract disease; γ-glutamyl transferase (GGT) is specific to the bile ducts, and in conjunction with an elevated alkaline phosphatase, suggests hepatic disease. Extremely elevated GGT levels further imply obstructive biliary disease.
- Increased total, direct, and indirect bilirubin concentrations indicate defects in transport, conjugation, or excretion of bilirubin.
- Lactate dehydrogenase (LDH) is a nonspecific marker of hepatocyte damage; a disproportionate elevation of LDH points to ischemic injury.
- Thrombocytopenia may occur because of decreased platelet production and splenic sequestration of platelets.
- Anemia (decreased hemoglobin and hematocrit) occurs as a result of variceal bleeding, decreased erythrocyte production, alcohol use, and hypersplenism.
- Loss of hepatic synthetic function can manifest as elevated prothrombin time (PT) and international normalized ratio (INR).
- Decreased serum albumin and total protein occur in chronic liver damage due to the loss of synthetic capacity within the liver.
- Portal hypertension causes serum albumin-to-ascites gradient of 1.1 g/dL (11 g/L) or greater.
- Increased blood ammonia concentration is characteristic of HE, but levels do not correlate with the degree of impairment.
- Increased serum creatinine and blood urea nitrogen (BUN) signal a decline in renal function and may indicate hepatorenal syndrome.
- Hyponatremia is a result of sodium/water imbalance and does not imply a need for sodium supplementation.
- Signs and symptoms of infection (eg, mental status changes, fever, abdominal pain) should prompt a diagnostic paracentesis in a patient with ascites (**Figure 23–4**). In SBP, there is decreased total serum protein, elevated white blood cell count (with left shift), and the ascitic fluid usually contains at least 250 cells/mm^3 (0.250×10^9/L) neutrophils. Bacterial culture of ascitic fluid may be positive, but lack of growth or negative results on Gram stain does not exclude the diagnosis.

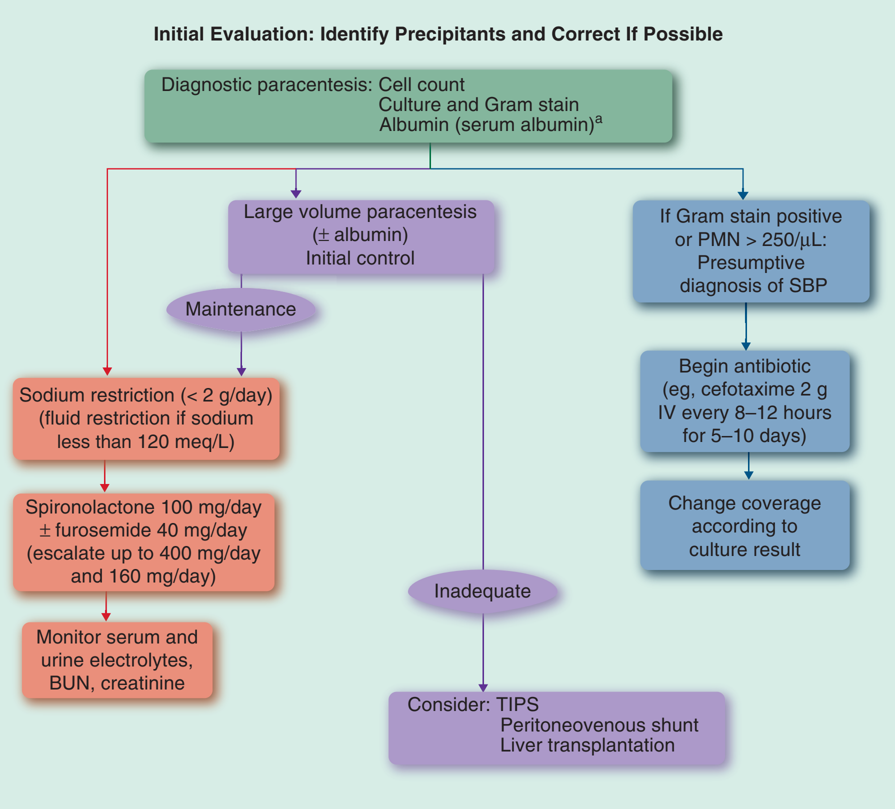
Initial Evaluation: Identify Precipitants and Correct If Possible
Diagnostic paracentesis: Cell count
Culture and Gram stain
Albumin (serum albumin)a
Large volume paracentesis
(± albumin)
Initial control
Maintenance
If Gram stain positive
or PMN > 250/μL:
Presumptive
diagnosis of SBP
Sodium restriction (< 2 g/day)
(fluid restriction if sodium
less than 120 meq/L)
Begin antibiotic
(eg, cefotaxime 2 g
IV every 8–12 hours
for 5–10 days)
Spironolactone 100 mg/day
± furosemide 40 mg/day
(escalate up to 400 mg/day
and 160 mg/day)
Change coverage
according to
culture result
Inadequate
Monitor serum and
urine electrolytes,
BUN, creatinine
Consider: TIPS
Peritoneovenous shunt
Liver transplantation

FIGURE 23–4. Approach to the patient with ascites and spontaneous bacterial peritonitis (SBP). [a]If PMN is greater than 250/μL (0.250 × 10^9/L) but culture is negative (culture-negative neutrocytic ascites), begin empiric antibiotics and retap after 48 hours. If culture is positive but PMN less than 250/μL (0.250 × 10^9/L), treat as if PMN greater than 250/μL (0.250 × 10^9/L) (presumed SBP). If polymicrobial infection exists, exclude SBP. (BUN, blood urea nitrogen; PMN, polymorphonuclear leukocyte; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt.) (Adapted from Chung RT, Podolsky DK. Cirrhosis and its complications. In: Kasper DL, Braunwald E, Fauci AS, et al., eds. Harrison's Principles of Internal Medicine, 17th ed. New York, NY: McGraw-Hill, 2005:1858–1869, with permission.)

Bleeding Diathesis and Synthetic Failure

Coagulopathies signal end-stage liver disease. The liver manufactures both procoagulant and anticoagulant factors essential for blood clotting and maintenance of blood homeostasis. In advanced disease, the liver is unable to synthesize these proteins, resulting in extended clotting times (increased prothrombin time and INR) and bleeding irregularities.[14] These patients were previously thought to be "autoanticoagulated," but better appreciation of the spectrum of coagulation abnormalities has led to the understanding that these patients are not only at increased risk of bleeding but are also at increased risk of venous thromboembolism because of decreased production of protective factors in addition to having prolonged clotting times.[14]

Thrombocytopenia is also very common in advanced liver disease. Patients with cirrhosis have a twofold reason for decreased platelet levels; decreased platelet production through the loss of hepatic thrombopoietin and splenic sequestration that prematurely removes formed platelets from circulation.

CLINICAL PRESENTATION AND DIAGNOSIS

Refer to accompanying clinical presentation box for symptoms, signs, and laboratory abnormalities associated with cirrhosis.

Diagnosis of Cirrhosis

Cirrhosis may be diagnosed incidentally before the patient develops symptoms or acute complications, but many patients have decompensated disease and complications such as ascites, SBP, variceal bleeding, or HE at initial presentation. Patients may have some, all, or none of the laboratory abnormalities and/or signs and symptoms of cirrhosis.[11]

Liver biopsy can definitively diagnose cirrhosis, but because of the invasive nature and elevated bleeding risk, biopsy is usually deferred in lieu of a presumptive diagnosis using a noninvasive technique such as ultrasound or computed tomography. A nodular liver with increased echogenicity is consistent with cirrhosis. The Model for End-Stage Liver Disease (MELD) score predicts 3-month mortality; it is used to classify disease severity and prioritize patients awaiting deceased-donor liver transplantation. The calculator is available at the Organ Procurement and Transplantation Network website (https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/).

Patients with ascites or known varices are presumed to have portal hypertension, but direct measurement is typically deferred because it requires invasive testing and increases the risk of bleeding.

Diagnosis of Ascites

Analysis of ascitic fluid obtained during paracentesis provides diagnostic clues to the etiology of peritoneal fluid accumulation. Evaluation includes cell count with differential, albumin, total protein, Gram stain, and bacterial cultures. In patients without an established diagnosis of liver disease, the serum ascites–albumin gradient (SAAG) is used to determine the cause of ascites.[7] SAAG compares serum albumin concentration to ascitic fluid albumin concentration:

$$\text{Alb}_{\text{serum}} - \text{Alb}_{\text{ascites}} = \text{SAAG}$$

A value of 1.1 g/dL (11 g/L) or greater identifies portal hypertension as the cause of the ascites with 97% sensitivity.[7] Low albumin in the peritoneal space balances the oncotic pressure gradient with the hydrostatic pressure gradient from portal hypertension. The differential diagnosis for SAAG values less than 1.1 g/dL (11 g/L) includes peritoneal carcinoma, peritoneal infection (tuberculosis, fungal, cytomegalovirus), and nephrotic syndrome. Serum albumin should be measured at the time of paracentesis for an accurate comparison.[7]

TREATMENT OF PORTAL HYPERTENSION, CIRRHOSIS, AND COMPLICATIONS

Desired Outcomes

Recognizing and treating the underlying cause of cirrhosis is paramount. **KEY CONCEPT** Until recently, cirrhosis was considered irreversible, but treating the underlying cause in its early stages may reverse the damage. Eradication of HCV decreases mortality even with advanced disease. In patients without a reversible cause, cirrhosis treatment is directed at limiting disease progression and minimizing complications.[11] Immediate treatment goals are to stabilize acute complications such as variceal bleeding and prevent SBP and HRS. Once life-threatening conditions have stabilized, the focus shifts to preventing complications and further liver damage. The sections that follow concentrate on therapy to prevent and treat cirrhotic complications.

Patient Encounter Part 1

A 47-year-old man was brought to the emergency department by ambulance after his family called for a wellness check when they had not heard from him for a week. On arrival, he is only oriented to name and became obtunded shortly after vomiting a large quantity of blood.

Chief Complaint: Found down at home by EMS

HPI: Unknown

PMH: Unknown; patient is obtunded

Drug Allergies: Unknown

PSH: Unknown

SH: Unknown, other than he lives alone

FH: Unknown

Meds (Outpatient): Unknown

ROS: Patient is obtunded

PE:

VS: BP 82/46 mm Hg, HR 110 beats/min, T 100.8°F (38.2°C), RR 18 breaths/min, oxygen saturation 99% (0.99) on room air, Ht 74″ (188 cm), Wt 79 kg, BMI 22.4 kg/m^2

General: Obtunded, pale man who appears older than stated age

HEENT: PERRL, EOMI, (+) scleral icterus, mildly jaundiced skin

CV: Tachycardic, no murmurs, rubs, or gallops

Chest: CTA bilaterally, spider angioma on upper chest and back

Abd: Soft, nondistended abdomen with decreased bowel sounds, hepatosplenomegaly, and small ascites

Ext: 3+ pedal pulses, 1+ pitting edema

What signs and symptoms are consistent with cirrhosis?

Based on the current information, what is the most likely cause of his hematemesis?

What risk factors does he have for cirrhosis?

Nonpharmacologic Therapy

Avoiding additional hepatic damage and preventing complications are critical for successful cirrhosis management. Lifestyle modifications can limit disease complications and slow further liver damage. The only proven treatment for alcoholic liver disease is immediate cessation of alcohol use, and because alcohol is hepatotoxic, all cirrhotic patients should abstain from alcohol to prevent further liver damage regardless of the etiology of their cirrhosis.

Patients with ascites require dietary sodium restriction. Intake should be limited to less than 800 mg sodium (2 g sodium chloride) per day. More stringent restriction may cause faster mobilization of ascitic fluid, but adherence to such strict limits is very difficult. Ascites usually responds well to sodium restriction accompanied by diuretic therapy.[7]

Drug therapies must be monitored carefully for potential adverse effects; hepatically, metabolized drugs can accumulate in patients with liver disease. Unfortunately, little guidance is available on drug dosing in hepatic impairment because these patients have historically been excluded from drug trials. Routine acetaminophen use should not exceed 2 g/day. Dietary supplements, herbal remedies, and nutraceuticals have not been well studied in hepatic impairment and cannot be recommended.

In patients with acute variceal bleeding, nasogastric (NG) suction reduces the risk of aspirating stomach contents; aspiration pneumonia is a major cause of death in patients with variceal bleeding. Because blood in the GI tract is very nauseating, NG suction during variceal bleeding can also decrease nausea and vomiting by removing blood from the GI tract.

Endoscopic band ligation (EBL) involves application of a stricture around the varix to stop acutely bleeding varices. EBL is the preferred endoscopic treatment and effective in up to 90% of patients.[15] EBL is also the standard of care for secondary prophylaxis of repeat bleeding in patients with a history of either esophageal or gastric variceal bleeding. Band ligation is best used in conjunction with pharmacologic treatment.[9]

During episodes of acute HE, temporary protein restriction to decrease ammonia production can be a useful adjuvant to pharmacologic therapy, but long-term protein restriction in cirrhotic patients is not recommended. Cirrhotic patients are already in a nutritionally deficient state, and prolonged protein restriction will exacerbate the problem.[13]

Vaccination against hepatitis A and B is recommended in all patients with cirrhosis to prevent additional liver damage from an acute viral infection.[16] Pneumococcal and influenza vaccination may also be appropriate and can reduce hospitalizations.

Shunts are long-term solutions to decrease elevated portal pressure. Shunts divert blood flow through or around the diseased liver, depending on the location and type of shunt employed. Transjugular intrahepatic portosystemic shunts (TIPS) create a communication pathway between the intrahepatic portal vein and the hepatic vein. TIPS procedures may be preferred over surgically inserted shunts because they are placed through the vascular system rather than more invasive surgical procedures, but they still carry a risk of bleeding and infection. TIPS placement can improve HRS but is associated with an increased incidence of HE.[13] The increased risk of HE results from the decreased detoxification of nitrogenous waste products because the shunt allows blood to evade metabolic processing.

Hemodialysis is usually used only as a bridge for HRS patients awaiting liver transplantation. It can contribute to hemodynamic instability and does not correct the underlying liver disease.

Pharmacologic Therapy

Drug therapy directed at reducing portal hypertension can alleviate symptoms and prevent complications but cannot reverse cirrhosis.

Patients with chronic hepatitis C infection and compensated cirrhosis should be considered for drug treatment (see Chapter 25) with a goal of achieving sustained virologic response (SVR).

▶ *Portal Hypertension*

KEY CONCEPT Nonselective β-blockers (NSBB) such as propranolol and nadolol are first-line treatments for portal hypertension. They reduce bleeding and decrease mortality in patients with known varices.

Only nonselective β-blockers (those that block both β_1 and β_2 receptors) reduce bleeding complications in patients with known varices. Blockade of β_1 receptors reduces cardiac output and splanchnic blood flow, while β_2-adrenergic blockade prevents β_2-receptor–mediated splanchnic vasodilation while allowing unopposed α-adrenergic effects; this enhances vasoconstriction of the systemic and splanchnic vascular beds. The combination of β_1 and β_2 blockade makes the NSBB preferable to cardioselective (β_1 selective) agents in treating portal hypertension.[1,9] Although cardioselective β-blockers do lose β_1 selectivity at higher doses, most patients with cirrhosis cannot tolerate the high doses.

Because β-blockers decrease blood pressure and heart rate, they should be started at low doses to increase tolerability; cirrhotic patients often already have low blood pressure and heart rate. Propranolol is hepatically metabolized, so initial drug concentration, half-life, and pharmacologic effects are all increased in cirrhosis. A reasonable starting dose of propranolol is 10 to 20 mg once or twice daily.

Doses should be titrated as tolerated with the goal of decreasing heart rate by 25% or to approximately 55 to 60 beats/min.[9] Heart rate reduction is not an accurate predictor of portal pressure reduction but is associated with maximally tolerated effect.

Carvedilol is a unique NSBB that also blocks α_1 receptors. The α_1 blockade induces intrahepatic vasodilation for a more potent decrease in portal pressure compared to other NSBB, but it also mediates greater decreases in mean arterial pressure.

The role of NSBB was called into question after observational trials suggested increased mortality in patients with a history of refractory ascites or SBP.[9] Later publications identified a complex dose–response relationship for NSBB in these patients; high doses (propranolol doses above 160 mg/day) are associated with increased mortality risk, while lower doses are associated with improved survival.[17,18] NSBB use should be carefully monitored in cirrhotic patients with tenuous blood pressure or other evidence of circulatory dysfunction, and discontinued in patients with acute decompensation (eg, variceal bleed, SBP, HRS). Carvedilol should be avoided in patients with refractory ascites to avoid additional vasodilation.[9]

Nitrates (such as isosorbide mononitrate) have been shown in clinical trials to reduce portal pressure when used alone or in combination with β-blockers. However, they cause systemic vasodilation and increase mortality when used alone, and because patients treated with combination therapy have significantly more adverse events compared to β-blocker monotherapy, nitrates are seldom used in cirrhotic patients.[9]

▶ *Ascites*

KEY CONCEPT The goals of treating ascites are to minimize acute discomfort, reequilibrate ascitic fluid, and prevent SBP. Treatment should modify underlying disease pathology; without directed therapy, fluid rapidly reaccumulates.

Acute discomfort from ascites may be ameliorated by therapeutic paracentesis. Often removing just 1 to 2 L of ascitic fluid provides relief from pain and fullness. Volume resuscitation should be provided for large volume paracentesis; 6 to 8 g of IV albumin should be given for each liter of fluid removed. Albumin 25% should be used because it has one-fifth the volume of the 5% product. Large-volume paracentesis without albumin administration can precipitate HRS through decreased perfusion. Albumin has not been shown to be beneficial in hemodynamically stable patients if less than 5 L of fluid is removed.[7]

Diuretics Diuretics are usually required in addition to sodium restriction (see Nonpharmacologic Therapy). **KEY CONCEPT** Spironolactone (an aldosterone antagonist) with or without furosemide forms the basis of pharmacologic therapy for ascites. Cirrhosis is a high aldosterone state; spironolactone counteracts the effects of RAAS activation. Not only is aldosterone production increased in patients with cirrhosis, but decreased hepatic metabolism prolongs aldosterone half-life.

A loop diuretic is typically added to spironolactone for more potent diuresis and to balance serum potassium levels. A ratio of

Patient Encounter Part 2

The patient's older brother arrives and states that he is not aware of any medical conditions that the patient has other than a history of illicit drug use (heroin) in his early 20s, a history of viral hepatitis (he does not know what type) and alcohol use. He cannot quantify alcohol intake but states that his brother drinks "socially."

Laboratory results for the patient showed the following:

Sodium 128 mEq/L (mmol/L)
Potassium 3.4 mEq/L (mmol/L)
Chloride 99 mEq/L (mmol/L)
Bicarbonate 21 mEq/L (mmol/L)
BUN 8 mg/dL (2.9 mmol/L)
SCr 0.9 mg/dL (80 μmol/L)
Glucose 76 mg/dL (4.2 mmol/L)
Hemoglobin 6.2 g/dL (62 g/L; 3.85 mmol/L)
Hematocrit 19% (0.19)
WBC 9.8 × $10^3/\text{mm}^3$ (9.8 × 10^9/L)
Platelets 68 × $10^3/\text{mm}^3$ (68 × 10^9/L)
Albumin 1.8 g/dL (18 g/L)
Total bilirubin 5.3 mg/dL (90.6 μmol/L)
Alk phos 152 IU/L (2.5 μkat/L)
AST 132 IU/L (2.2 μkat/L)
ALT 58 IU/L (0.97 μkat/L)
INR 2.8
PT 37 seconds
GGT 84 IU/L (1.4 μkat/L)
LDH 201 IU/L (3.35 μkat/L)
Serum NH_3 122 mcg/dL (72 μmol/L)

Which laboratory values support a diagnosis of cirrhosis?

What test(s), if any, should be done to further investigate the source of hematemesis?

What test(s), if any, should be done to further investigate and evaluate the source of hepatic dysfunction?

40 mg furosemide (the most common loop diuretic) to 100 mg spironolactone usually maintains serum potassium within the normal range.

Doses should be titrated upward every 3 to 5 days. Because spironolactone is being used specifically for its antialdosterone effects, high doses (up to 400 mg/day) are used. If intolerable side effects such as painful gynecomastia occur with spironolactone, other potassium-sparing diuretics may be used, but clinical trials have not shown equivalent efficacy.[7]

Because ascites equilibrates with vascular fluid at a much slower rate than does peripheral edema, aggressive diuresis is associated with intravascular volume depletion as opposed to better efficacy in removing peritoneal fluid and may lead to hemodynamic instability. The maximum amount of ascitic fluid that can be removed through diuresis is approximately 0.5 L/day.[7] Aggressive diuresis should be avoided unless patients have concomitant peripheral edema. These patients may require increasing furosemide doses until they are euvolemic, and IV diuretics are often necessary. Diuretic therapy is typically lifelong.

▶ *Varices*

Variceal bleeding is common in cirrhotic patients. **KEY CONCEPT** During acute variceal hemorrhage, it is crucial to control bleeding, prevent rebleeding, and avoid complications such as SBP. Mortality at 6 weeks is 15% to 25%.[9] A treatment algorithm for acute variceal bleeding is depicted in Figure 23–5.

Octreotide (a synthetic somatostatin analog) causes selective vasoconstriction of the splanchnic bed, decreasing portal venous pressure with few serious side effects. A common octreotide dose is a 50-mcg IV loading dose followed by a 50 mcg/hour continuous IV infusion. Therapy should continue for at least 24 to 72 hours after bleeding has stopped, but the optimal treatment duration has not been defined. Some clinicians continue octreotide for a full 5 days because this is the time frame associated with the highest risk of rebleeding. Octreotide combined with endoscopic therapy results in decreased rebleeding rates and transfusion needs when compared with endoscopic treatment alone.[9] Short-term IV proton pump inhibitor (PPI) therapy during an acute variceal bleed can reduce the risk of rebleeding. These patients are at high risk of developing SBP, and prophylactic antibiotics provide both a morbidity and mortality benefit in this situation. Choice of a specific agent should be based on the local susceptibility data, but ceftriaxone (1 g IV every 24 hours) for 5 to 7 days has been proven effective.[9]

Terlipressin (a vasopressin analog) is commonly used in Europe to treat variceal bleeding.

▶ *Spontaneous Bacterial Peritonitis*

Prophylactic antibiotic therapy is recommended during acute variceal bleeding to prevent SBP; this is typically initiated with a third-generation cephalosporin. Prophylactic antibiotic therapy reduces inhospital infections and mortality in patients hospitalized for variceal bleeding.[9]

If SBP is suspected, empiric antibiotic therapy should be initiated with a broad-spectrum anti-infective agent after ascitic fluid collection, pending cultures and susceptibilities (Figure 23–4). In the setting of presumed infection, delaying treatment while awaiting laboratory confirmation is inappropriate and may result in death. The preferred initial antibiotic should be an IV third-generation cephalosporin (eg, cefotaxime 2 g every 8 hours, ceftriaxone 2 g every 24 hours).[7,9] These agents cover the most common organisms implicated in SBP, but local resistance patterns must be taken into account when choosing empiric antibiotic therapy. Once a bacterial pathogen is identified, coverage should be narrowed to an agent that is highly active against that particular organism. SBP is rarely polymicrobial.

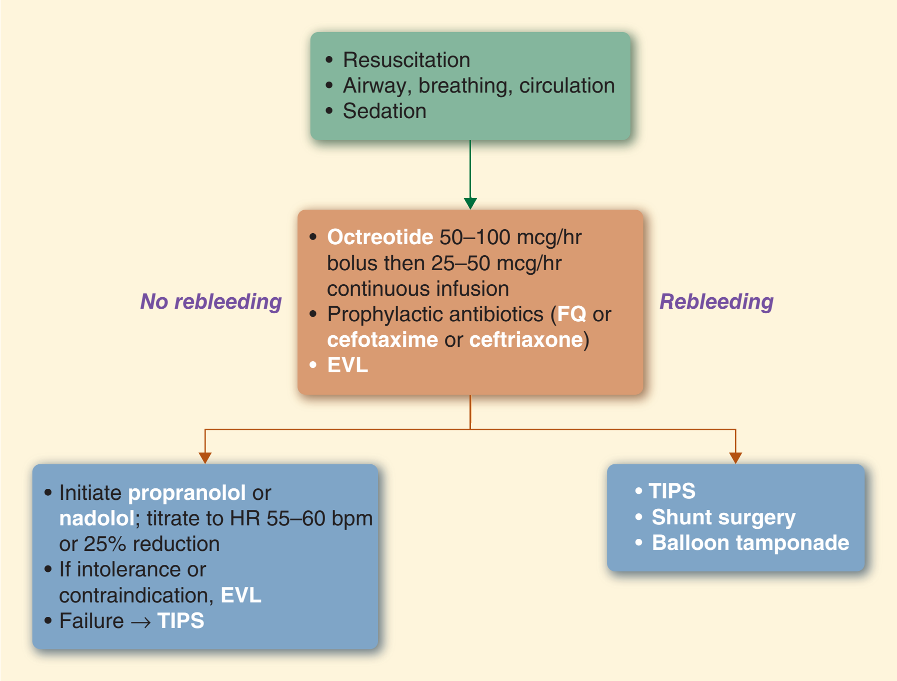
• Resuscitation
• Airway, breathing, circulation
• Sedation
No rebleeding
• Octreotide 50–100 mcg/hr bolus then 25–50 mcg/hr continuous infusion
• Prophylactic antibiotics (FQ or cefotaxime or ceftriaxone)
• EVL
Rebleeding
• Initiate propranolol or nadolol; titrate to HR 55–60 bpm or 25% reduction
• If intolerance or contraindication, EVL
• Failure → TIPS
• TIPS
• Shunt surgery
• Balloon tamponade

FIGURE 23–5. Treatment of acute variceal bleeding. (EVL, endoscopic variceal ligation; FQ, fluoroquinolone; HR, heart rate; TIPS, transjugular intrahepatic portosystemic shunt.) (From Ryan L, Attridge RL, Moote R, Miller ML. Chapter 9. Portal Hypertension and Cirrhosis. In: Attridge RL, Miller ML, Moote R, Ryan L, eds. Internal Medicine: A Guide to Clinical Therapeutics, New York, NY: McGraw-Hill; 2013, with permission.)

SBP is the primary cause of HRS. The risk of progression to HRS can be reduced with albumin therapy, 1.5 g/kg immediately (within 6 hours of diagnosis), followed by 1 g/kg on day 3 of SBP therapy for high-risk patients with SCr greater than 1 mg/dL (88 μmol/L), BUN above 30 mg/dL (10.7 mmol/L), or bilirubin higher than 4 mg/dL (68.4 μmol/L).[19]

KEY CONCEPT Long-term SBP prophylaxis decreases mortality and is recommended in a select group of patients—those with a history of SBP, and those with low-protein ascites (ascitic fluid albumin less than 1.5 g/dL [15 g/L]) plus one of the following: SCr 1.2 mg/dL (106 μmol/L) or greater, BUN 25 mg/dL (8.9 mmol/L) or greater, serum sodium 130 mEq/L (mmol/L) or less, or Child–Pugh score of at least 9 (Child–Pugh classification estimates mortality from cirrhosis), with bilirubin of at least 3 mg/dL (51.3 μmol/L). Oral options are one trimethoprim–sulfamethoxazole double-strength daily or ciprofloxacin 500 mg daily.[7]

▶ *Hepatorenal Syndrome*

HRS is a life-threatening complication of cirrhosis. Targeted treatment increases central venous system volume. Peripheral vasoconstriction redistributes fluid from the periphery to the venous system; fluid is retained in the vascular space by administering albumin (to increase oncotic pressure). The ultimate goal is to increase renal perfusion.

A common regimen involves giving albumin 1 g/kg on the day of diagnosis (day 1), followed by 20 to 40 g on subsequent treatment days. This regimen is used in combination with midodrine (an α-agonist) and octreotide. The initial midodrine dose is 7.5 mg orally three times daily; octreotide is usually administered subcutaneously (as opposed to IV during variceal bleeding) 100 mcg three times daily. Both drugs can be titrated as tolerated to achieve increases in mean arterial pressure of at least 15 mm Hg.

Terlipressin, a vasopressin analog, has been used successfully in patients with HRS in Europe and was recently approved for use in the United States.

▶ *Encephalopathy*

Lactulose **KEY CONCEPT** Lactulose is the foundation of pharmacologic therapy to prevent and treat HE. It is a nondigestible synthetic disaccharide laxative that is hydrolyzed in the gut to an osmotically active compound that draws water into the colon and stimulates defecation. Lactulose lowers colonic pH, which favors the conversion of ammonia (NH_3) to ammonium (NH_4^+), which cannot cross back from the gut into the systemic circulation because it is ionic. Lactulose is usually initiated at 15 to 30 mL two to three times per day and titrated to a therapeutic goal of two to three soft bowel movements daily.[13]

Antibiotic Therapy Rifaximin is a nonabsorbable antibiotic that decreases urease-producing gut bacteria, decreasing ammonia production. It is used extensively in Europe as first-line therapy for HE. Although rifaximin is both effective and well tolerated, its expense may prohibit long-term use. In the United States, it is reserved for use as add-on therapy after lactulose failure. The rifaximin dose is 550 mg twice daily to prevent HE recurrences and 400 mg three times a day for treatment.

Metronidazole and neomycin have also been used to treat HE but are not generally recommended because of toxicity; prolonged metronidazole use is associated with peripheral neuropathy, and although neomycin is classified as a nonabsorbable aminoglycoside antibiotic, patients with cirrhosis do have detectable plasma concentrations. This is thought to be a result of decreased intestinal mucosa integrity, and it may lead to nephrotoxicity. Neomycin should not be used if other options exist.[13]

Patient Encounter Part 3

Ultrasound results were consistent with a diagnosis of cirrhosis, and the emergency endoscopy revealed seven bleeding varices that were banded.

The viral panel was negative for HBV and HIV, but the HCV antibody test was reactive. The results of the nucleic acid test (NAT) for HCV RNA are pending.

The team was unable to perform a diagnostic paracentesis because the volume of fluid was too small.

What therapy (if any) should be initiated for variceal bleeding?

Should the patient receive vitamin K?

Should the patient receive antibiotics?

If antibiotics are initiated, what is the most appropriate regimen?

Should the patient receive a nonselective β-blocker?

What are potential sources of his altered mental status?

How should his confusion be treated?

Flumazenil Evidence for false transmitters as the cause of encephalopathy has been demonstrated by functional improvement after administering flumazenil (a benzodiazepine antagonist). Unfortunately, long-term benefit has not been demonstrated, and because flumazenil can only be administered parenterally, it is not an appropriate choice for clinical use; flumazenil use is limited to the research setting.

▶ *Coagulation Abnormalities*

Vitamin K is essential for hepatic synthesis of coagulation factors. The elevated clotting time that results from decreased protein synthesis is indistinguishable from coagulopathy that is a result of malnutrition or poor intestinal absorption. When vitamin K_1 (phytonadione) is given subcutaneously (10 mg for 3 days), it can replete stores and establish if coagulation abnormalities are due to

Patient Encounter Part 4

The next day, the patient's mental status has improved, and he is awake but still somnolent. He states that he is aware that he had contracted hepatitis C in the past but never sought treatment for it because he quit using IV drugs many years ago. He was not aware that he had liver disease and states that he only drinks two to three times a month and only has three drinks maximum each time. He does not take any prescription drugs but does use OTC NSAIDs, acetaminophen, antihistamines as needed, and "herbal" products for occasional insomnia.

What pharmacologic and nonpharmacologic treatments are appropriate to reduce the risk of future variceal bleeding and other complications of cirrhosis?

Does he require long-term prophylaxis to prevent recurrent SBP?

malabsorption alone. It is unusual to completely reverse clotting abnormalities, but INR decreases in most patients, conferring a decreased risk of bleeding. Because cirrhotic patients may have decreased bile production resulting in decreased absorption of fat-soluble vitamins, phytonadione should be given subcutaneously instead of orally to ensure absorption.

OUTCOME EVALUATION

- Reevaluate the pharmacotherapy regimen at each visit to assess adherence, effectiveness, adverse events, and need for drug titration.
- Ask the patient about adherence to lifestyle changes such as cessation of ethanol intake and avoidance of over-the-counter medications (particularly NSAIDs and acetaminophen) and dietary supplements that may exacerbate complications of cirrhosis.
- Assess dietary sodium intake by patient food recall. Measure dietary sodium adherence using spot urine sodium-to-potassium ratio to assess appropriate sodium excretion.
- Ask the patient specific, directed questions regarding adherence and adverse effects of β-blockers; inquire about symptoms of orthostatic hypotension (eg, lightheadedness, dizziness, fainting).
- Evaluate effectiveness of diuretic therapy with regard to ascitic fluid accumulation and development of peripheral edema. Ask the patient directed questions regarding abdominal girth, fullness, tenderness, and pain. Weigh the patient at each visit and ask the patient to keep a weight diary. Assess for peripheral edema at each visit.
- Obtain complete blood count (CBC) and PT/INR to assess for anemia, thrombocytopenia, and coagulopathy. Ask about bruising, bleeding, hematemesis, hematochezia, and melena to assess for bleeding.
- Review biopsy reports and laboratory data. Hepatic transaminases and blood ammonia levels do not correlate well with disease progression, but increased coagulation times and decreased serum albumin are markers of loss of synthetic function, and hyponatremia is a marker of worsening disease.
- Evaluate for signs and symptoms of HE. Mental status changes may be subtle; questioning family members or caregivers about confusion or personality changes may reveal mild HE even if the patient is unaware of deficits. Ask about sleep patterns to assess for the loss of circadian rhythm. In patients taking lactulose therapy, titrate the dose to achieve two to four soft bowel movements daily as tolerated.

Patient Care Process

Collect Information:

- Perform a medication history at each visit and ask specifically about prescription, nonprescription, herbal products, and nutraceuticals as well as illicit substances. Be especially mindful of NSAID pain relievers and herbal remedies that can be hepatotoxic or affect renal function. Ask the patient how each medication is taken; this can provide insight into adherence.
- Ask about dietary compliance with sodium restriction; a 24-hour diet recall can help identify high-sodium intake.
- Complete a comprehensive review of systems and physical examination to identify subtle changes. Pay particular attention to fluid status and any GI complaints.

Assess the Information:

- Determine if the patient is taking any drugs that could adversely affect their liver disease or renal function.
- Identify drugs that can precipitate altered mental status or cause confusion.
- Identify medications that may have better alternatives or are not crucial to continue.
- Identify any changes in health status that could signal decompensation: (a) changes in fluid status (peripheral edema or new or worsening ascites); (b) changes in GI habits that could signal hematochezia, melena, or hematemesis; and (c) changes in mentation such as confusion, changes in sleep patterns, or increased forgetfulness that could signal hepatic encephalopathy.
- Examine laboratory results for signs of worsening hepatic synthetic function or decompensation.

Develop a Care Plan:

- Identify methods to achieve and maintain lifestyle changes, including avoiding alcohol and illicit drugs and achieving a low-sodium diet.
- Choose drug therapies that do not worsen hepatic or renal function, and avoid drugs that may impair cognition or balance. A good resource for those (although targeted at the geriatric population) is the BEERS criteria medication list; a printable pocket card is available on the Internet.

Implement the Care Plan:

- Educate the patient (and family as applicable) about lifestyle changes and pharmacotherapy regimens; make sure they understand the purpose of each.
- Select medications that are expected to be well tolerated as well as affordable, and choose the least burdensome dosing regimen.
- Educate the patient on potential adverse effects of drug therapy, how to identify and potentially mitigate those affects, and when to seek medical care.

Follow-up: Monitor and Evaluate:

- Follow up at regular intervals to assess both drug therapy and disease progression.
- Review adherence to lifestyle changes and medication regimens.
- Complete review of systems, physical and laboratory examinations as appropriate to assess changes in patient status.

Abbreviations Introduced in This Chapter

ADH	Antidiuretic hormone
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CBC	Complete blood count
CYP450	Cytochrome P-450 isoenzyme
GGT	γ-Glutamyl transferase
GI	Gastrointestinal
HE	Hepatic encephalopathy
HRS	Hepatorenal syndrome
INR	International normalized ratio
LDH	Lactate dehydrogenase
MELD	Model for End-Stage Liver Disease
NAFLD	Nonalcoholic fatty liver disease
NG	Nasogastric
NH_3	Ammonia
NH_4^+	Ammonium
NSAID	Nonsteroidal anti-inflammatory drug
PT	Prothrombin time
RAAS	Renin–angiotensin–aldosterone system
SAAG	Serum ascites–albumin gradient
SBP	Spontaneous bacterial peritonitis
TIPS	Transjugular intrahepatic portosystemic shunt

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24 Pancreatitis

Lara M. Groetzinger

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the pathophysiology of acute pancreatitis and chronic pancreatitis.
2. Differentiate acute pancreatitis from chronic pancreatitis.
3. Formulate care plans for managing acute and chronic pancreatitis.
4. Choose appropriate pancreatic enzyme supplementation for patients with chronic pancreatitis.

INTRODUCTION

The pancreas is a glandular organ in the abdominal cavity lying below the liver and behind the stomach. It is primarily an exocrine gland but also has endocrine functions. The endocrine cells are the islets of Langerhans, which secrete regulatory hormones such as insulin and glucagon directly into the bloodstream.[1] The exocrine cells of the pancreas are called acinar cells that produce and secrete digestive enzymes that mix with a bicarbonate-rich solution released from ductular cells to produce pancreatic juice. This alkaline solution is released through the ampulla of Vater into the duodenum to aid in digestion and buffer acidic fluid released from the stomach (Figure 24–1).[2]

Pancreatic enzymes are responsible for breaking down proteins (protease), lipids (lipase), and carbohydrates (amylase) in the small intestine. Normally, these enzymes are produced and stored as inactive proenzymes within zymogen granules to prevent autolysis and digestion of the pancreas. Amylase and lipase are released from the zymogen granules in the active form, whereas the proteolytic enzymes are activated in the duodenum by enterokinase. Enterokinase triggers the conversion of trypsinogen to the active protease trypsin, which then activates the other proenzymes to their active enzymes. The pancreas contains a trypsin inhibitor to prevent autolysis. Pancreatitis is inflammation of the pancreas causing exocrine and endocrine dysfunction and can be acute or chronic in nature.

ACUTE PANCREATITIS

EPIDEMIOLOGY AND ETIOLOGY

Acute pancreatitis (AP) is one of the most common inpatient gastrointestinal (GI) diagnoses in the United States and places a significant burden on healthcare costs and resources.[3] **KEY CONCEPT** In the Western Hemisphere, AP is caused mainly by ethanol use/abuse and gallstones (cholelithiasis), accounting for 80% to 90% of cases in the United States.[4,5] Less common causes include hypertriglyceridemia, endoscopic retrograde cholangiopancreatography (ERCP), trauma, and autodigestion due to the early activation of pancreatic enzymes. Numerous medications have been implicated as causes of AP (Table 24–1), but other etiologies should be ruled out before diagnosing drug-induced pancreatitis.[3,6,7]

PATHOPHYSIOLOGY

The pancreas sustains an initial insult from alcohol, gallstones, or another etiology. This acute injury leads to the aberrant activation of zymogens within the acinar cell,[8] which is followed by neutrophil, lymphocyte, and macrophage invasion of the pancreas and further activation of enzymes within the pancreas. Trypsin triggers activation of multiple proenzymes, including chymotrypsin, elastase, and phospholipase, which in turn damage the pancreas and surrounding tissues (Figure 24–2). This eventually leads to autodigestion and a profound systemic inflammatory response syndrome (SIRS).[8]

Gallstones can obstruct the ampulla of Vater causing pancreatic enzymes or bile to move in a retrograde fashion into the pancreas. This retrograde movement may be responsible for premature pancreatic enzyme activation and pancreatic autolysis.[2] Ethanol abuse may cause precipitation of pancreatic enzymes in pancreatic ducts, leading to chronic inflammation and fibrosis resulting in the loss of exocrine function. Ethanol may also be directly toxic to pancreatic cells by increasing the synthesis of enzymes that produce toxic metabolites leading to further damage.[9,10] Drug-induced pancreatitis can be due to an immunologic reaction, accumulation of toxic metabolites, a direct toxic effect, intravascular thrombosis, or altered viscosity of pancreatic juice.[11] High serum triglycerides (> 1000 mg/dL [11.3 mmol/L]) release toxic concentrations of free fatty acids, which accumulate and lead to additional damage to acinar cells.[12]

AP can progress to peripancreatic fluid collections in or around the pancreas; they are sterile collections, usually require no intervention, and resolve spontaneously.[13,14] Pancreatic pseudocysts are mature walled-off fluid collections often outside the pancreas that form 4 weeks or longer after the onset of AP. Many pseudocysts resolve spontaneously, but some require surgical or percutaneous drainage. Rupture of a pancreatic pseudocyst is a serious complication and can lead to peritonitis and GI bleeding.[13]

Pancreatic enzyme damage may lead to pancreatic necrosis, which is diffuse inflammation of the pancreas containing both necrotic tissue and fluid. **KEY CONCEPT** Pancreatic necrosis occurs within the first 2 weeks in 10% to 20% of patients with AP and can be sterile or infected. Infected pancreatic necrosis is a late complication of necrotizing pancreatitis[8]; it occurs in 16% to 47% of

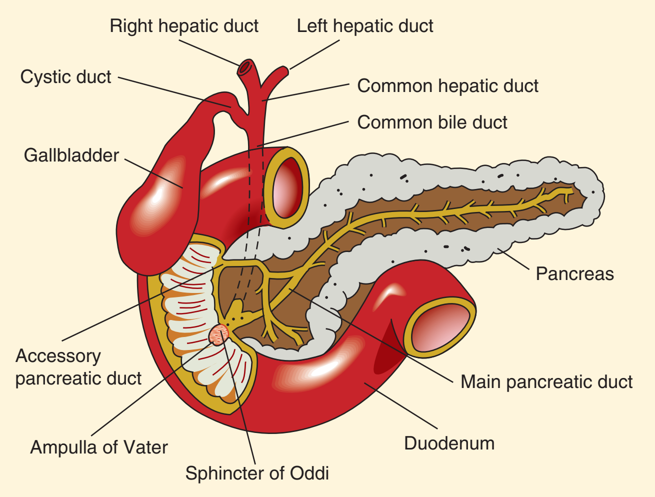

FIGURE 24–1. Anatomical structure of the pancreas and biliary tract. (From Bolesta S, Montgomery PA. Pancreatitis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020; Figure 56–1, with permission. www.accesspharmacy.com.)

patients, usually due to bacteria normally present in the GI tract (*Escherichia coli, Enterobacteriaceae, Enterococcal species, viridans group streptococci*, and anaerobes). Disseminated infection and subsequent serious complications may result from pancreatic necrosis.[13,15] Pancreatic abscess is pancreatic necrosis that is walled off by granulation tissue and occurs weeks after AP.

CLINICAL PRESENTATION AND DIAGNOSIS

AP presentation can range from mild, self-limiting disease to severe, life-threatening illness, including multiorgan failure and shock.[8] Multiorgan failure is a poor prognostic indicator. Disease severity can be predicted using the Ranson criteria, Glasgow severity scoring system, Acute Physiology and Chronic Health Evaluation II (APACHE II), and sequential organ failure assessment. Patients with APACHE II scores above 8 should be monitored and treated in an intensive care unit. Awareness of risk factors for severe disease, including age greater than 55 years, comorbid conditions, laboratory findings, and the presence of SIRS, may be more beneficial than scoring systems.[16]

Table 24–1

Selected Medications Associated with Acute Pancreatitis

Cardiovascular: Enalapril, lisinopril, ramipril, losartan, **furosemide**, **hydrochlorothiazide**, amiodarone, statins, ethacrynic acid
Anti-infectives: Metronidazole, **sulfonamides**, **tetracycline**, tigecycline, **pentamidine**, isoniazid, lamivudine, **didanosine**, nelfinavir, interferon/ribavirin, **erythromycin, rifampin, nitrofurantoin**
Gastrointestinal: Omeprazole, mesalamine, **cimetidine**, ranitidine, sulfadiazine
Neurologic: Valproic acid, clozapine
Hormonal: Conjugated **estrogens**, tamoxifen, **oral contraceptives**
Oncologic: Ifosfamide, cytarabine, bortezomib, capecitabine, cisplatin
Analgesics: Sulindac, salicylates, **acetaminophen**
Other: Propofol, **mercaptopurine**, **azathioprine**, **corticosteroids**, marijuana, **metformin**

Bold font= definite association.[8]

Clinical Presentation of Acute Pancreatitis

Signs and Symptoms

- Sudden upper abdominal pain is the most common symptom.
- Pain may radiate to the back, and ecchymosis may be present in the flank and periumbilical areas.
- Nausea and vomiting are common.
- Tachycardia, hypotension, fever, and abdominal distention may be present.

Laboratory Tests

- The serum amylase may be elevated to more than three times the upper limit of normal within the first 12 hours of the onset of AP. The degree of elevation does not correlate with disease severity, and levels may return to normal before the patient presents for care.
- Serum lipase rises within 4 to 8 hours of onset, peaks at 24 hours, and returns to normal within 8 to 14 days.
- Other laboratory abnormalities may include elevated white blood cell (WBC) count, hyperglycemia, hypocalcemia, hyperbilirubinemia, elevated serum lactate dehydrogenase (LDH), and hypertriglyceridemia.

DIAGNOSIS

Diagnosis of AP is based on patient history, signs and symptoms, and laboratory values. The history can identify risk factors, such as recent procedures, alcohol abuse, and medications. Abdominal pain is the hallmark presentation of AP.[8] It is epigastric and can radiate to the upper quadrants or back. Nausea and vomiting occur in 85% of patients.[7] Other findings with severe pancreatitis include fever, dyspnea, hypoxemia, and hypotension.[8] A serum lipase more than three times the normal limit supports the diagnosis. The serum lipase has greater sensitivity and specificity for AP than does the serum amylase due to its duration of elevation.[6,17] Elevated hepatic enzymes, alkaline phosphatase, and bilirubin may indicate gallstone pancreatitis,[8] and triglycerides should be checked to rule out hypertriglyceridemia as the cause.[6,16]

The diagnosis of AP requires at least two of the following: (a) upper abdominal pain, (b) serum lipase more than three times the upper limit of normal, or (c) evidence of AP on imaging such as computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound.[4,7] Abdominal ultrasound can identify gallstones and sludge in the common bile duct but has limited sensitivity. CT may be more useful in staging pancreatitis or identifying complications. ERCP should be used early when patients have concurrent acute infection of the biliary tract (cholangitis). MRI and magnetic resonance cholangiopancreatography (MRCP) are more costly options that can be used to evaluate severity and pancreatic abnormalities.[6,16]

TREATMENT

Desired Outcomes

The goals of treatment for AP include (a) resolution of nausea, vomiting, abdominal pain, and fever; (b) ability to tolerate oral intake; (c) normalization of serum amylase, lipase, and white blood cell count; and (d) resolution of abscess, pseudocyst, or fluid collection as measured by CT scan. **KEY CONCEPT** Therapy of AP is primarily supportive unless a specific etiology is identified (Figure 24–2). Supportive therapy involves fluid repletion, nutrition support, and analgesia.

Nonpharmacologic Therapy

Nonpharmacologic therapy consists of ERCP for removal of any biliary tract stones, other procedural interventions, and nutritional support.[7] Surgical or interventional procedures may be necessary if pancreatic necrosis or abscesses are present.

While it is common to discontinue oral feedings during AP, this does not prevent further damage because secretion of trypsin is already reduced.[15] In mild-to-moderate AP, a low-fat diet should be advanced based on resolution of nausea, vomiting, and pain. In severe AP enteral nutrition should be started as early as possible (ideally within 24 hours)[4] and may include nasogastric or nasojejunal feedings. Early use of enteral nutrition decreases surgical interventions and infectious complications.[18] Enteral feeding should ideally be delivered with an elemental or semielemental formula. Enteral nutrition has many advantages over total parenteral nutrition (TPN), including the ability to maintain gut integrity and therefore reduce bacterial gut translocation, decrease rate of ileus, fewer complications, and lower cost.[3] Additionally, randomized controlled trials have shown that TPN increases the risk of infected pancreatic necrosis, multiorgan failure, and need for surgical intervention.[4,19] For these reasons, enteral feeding is preferred. However, TPN may be necessary if enteral nutrition is not possible because of patient intolerance, failure to meet caloric goals, or other reasons.[7,15,20]

Pharmacologic Therapy

Pharmacologic therapy consists of fluid resuscitation, analgesics, and antibiotics.

▶ *Fluid resuscitation*

Early fluid therapy is one of the most important interventions but should be prescribed judiciously, especially when patients have concomitant cardiac, renal, or liver disease. Intravenous (IV) fluids are administered to maintain hydration and blood pressure. Crystalloids such as Lactated Ringer's solution or 0.9% sodium chloride (normal saline [NS]) are recommended. Lactated Ringer's solution may be preferred because it decreases systemic inflammation more than NS.[21] Additionally, NS may exacerbate acidosis, cause hyperchloremia, and potentially lead to renal failure when used as the resuscitative fluid in other disorders.[22,23] Aggressive fluid resuscitation at rates of 250 to 500 mL/hour has historically been recommended. However, there is limited evidence supporting this recommendation, and long-term aggressive fluid

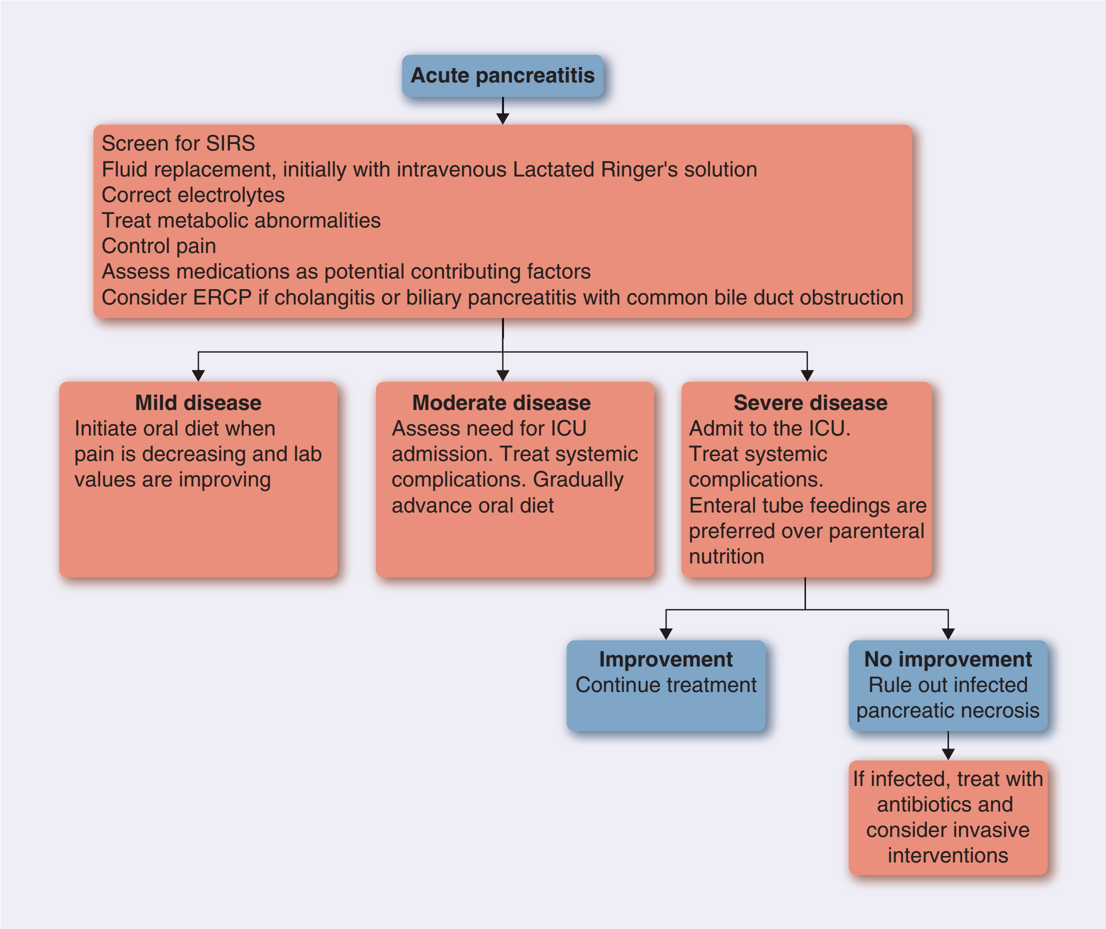
Acute pancreatitis
Screen for SIRS
Fluid replacement, initially with intravenous Lactated Ringer's solution
Correct electrolytes
Treat metabolic abnormalities
Control pain
Assess medications as potential contributing factors
Consider ERCP if cholangitis or biliary pancreatitis with common bile duct obstruction
Mild disease
Initiate oral diet when pain is decreasing and lab values are improving
Moderate disease
Assess need for ICU admission. Treat systemic complications. Gradually advance oral diet
Severe disease
Admit to the ICU. Treat systemic complications. Enteral tube feedings are preferred over parenteral nutrition
Improvement
Continue treatment
No improvement
Rule out infected pancreatic necrosis
If infected, treat with antibiotics and consider invasive interventions

FIGURE 24–2. Algorithm for evaluation and treatment of acute pancreatitis. (ERCP, endoscopic retrograde cholangiopancreatography; ICU, intensive care unit; SIRS, systemic inflammatory response syndrome.) (From Bolesta S, Montgomery PA. Pancreatitis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020; Figure 56–3, with permission. www.accesspharmacy.com.)

Patient Encounter 1, Part 1

A 48-year-old man presents to the emergency department with a 3-day history of nausea, vomiting, and persistent abdominal pain. He states that nothing makes the abdominal pain better, and it is exacerbated by eating. He has not eaten in the last 2 days. Upon examination, his abdomen is found to be distended.

What information about the patient presentation is consistent with acute pancreatitis?

What tests may be helpful in diagnosing acute pancreatitis?

therapy can be associated with harms in AP.[24–27] Alternatively, some guidelines recommend a goal-directed approach titrating IV fluids to specific clinical and biochemical perfusion targets, including heart rate, blood pressure, urine output, blood urea nitrogen, and hematocrit.[4] One approach for hemodynamically unstable patients is to give an initial bolus of 1 to 2 L followed by a continuous rate of 250 mL/hour and then reassess and titrate fluid requirements carefully and frequently based on clinical targets described previously. Electrolytes such as potassium and magnesium may be added to the infusions if necessary. Hyperglycemia can be managed with insulin-containing IV infusions.[16]

▸ *Analgesics*

No single opioid analgesic is superior to other opioids in treating pain associated with pancreatitis.[28] Opioids should be titrated to the lowest effective dose since they may promote ileus and subsequent failure of enteral nutrition. Consideration should also be given to nonopioid analgesic therapy based on current perioperative pain management strategies.[18] (See Chapter 35, Pain Management.)

▸ *Antibiotics*

Antibiotics do not prevent the formation of pancreatic abscess or necrosis when given early in the course of AP[6,16] and are not recommended prophylactically.[4] Empiric antibiotics are not indicated if the patient has a mild disease or a known noninfectious cause. In necrotizing pancreatitis, antibiotics may be appropriate for patients who deteriorate or fail to improve after 7 to 10 days.[16] A CT-guided fine needle aspiration for Gram stain and culture can confirm infected AP and guide antibiotic therapy, but it is no longer routinely used in many centers.[20] Stable patients with infected necrosis should be treated with antibiotics; surgical, radiologic, and/or endoscopic drainage would ideally be delayed by 4 weeks to allow for the area of necrosis to become walled-off.[15,16,18] Consideration should be given to discontinuing antibiotics if no source of infection is confirmed.

Infections are usually polymicrobial, so broad-spectrum antibiotics with activity against enteric Gram-negative bacilli (*E. coli, Proteus, Klebsiella*) and Gram-positive organisms (*Staphylococcus aureus, Streptococcus species, Enterococcus*) in addition to anaerobic bacteria are appropriate (Table 24–2).[20] Fluoroquinolones (eg, ciprofloxacin, levofloxacin) are not recommended due to high rates of resistance by common enteric pathogens.[20] Patients may receive long courses of broad-spectrum antibiotics and may develop superinfections with resistant bacteria. Routine use of antifungal agents (eg, fluconazole) is not recommended but may be considered if peritonitis or GI perforation develops due to the presence of fungi such as *Candida albicans* in the GI tract.[2,16]

Patient Encounter 1, Part 2

PMH: Hypertension, obesity

Allergies: None

FH: Father—gallstones, hypertension, obesity; mother—noncontributory

SH: History of heavy drinking; tobacco 1 ppd; no recreational drugs

Meds: Ibuprofen, hydrochlorothiazide

ROS: Positive for sharp RUQ abdominal pain that radiates to the right shoulder and back, nausea, and vomiting; negative for substernal chest pain

PE:

VS: BP 100/70 mm Hg, P 120 beats/min, RR 22 breaths/min, T 37.9°C (100.°F), pain score 10/10, Wt 120 kg (264 lb), Ht 6′1″ (185 cm)

CV: Tachycardic, regular rate and rhythm, no murmurs

Abd: Distended, (+) rebound tenderness, (+) bowel sounds, (+) guarding

Labs:

WBC 19.8 × 10^3/mm^3 (19.8 × 10^9/L)
Hgb 11.9 g/dL (119 g/L, 7.39 mmol/L)
Hct 30% (0.30)
Platelets 250 × 10^3/mm^3 (250 × 10^9/L)
BUN 19 mg/dL (6.8 mmol/L)
SCr 1.5 mg/dL (133 μmol/L)
Glucose 170 mg/dL (9.4 mmol/L)

Amylase 30 IU/L (0.5 μkat/L)
Lipase 1500 IU/L (25 μkat/L)
AST 520 IU/L (8.67 μkat/L)
ALT 420 IU/L (7.0 μkat/L)
Total bilirubin 3.2 mg/dL (54.7 μmol/L)
LDH 1050 IU/L (17.5 μkat/L)

Abdominal X-ray and ultrasound: Pending

What clinical signs are consistent with acute pancreatitis?

What treatment(s) would you initiate?

What are three possible etiologies of this patient's AP?

Table 24–2

Selected IV Antimicrobial Regimens for Pancreatic Necrosis

Drug	Usual Dose[a]	Notes
Meropenem	1–2 g every 8 hours	Risk of superinfection
Piperacillin/tazobactam	3.375–4.5 g every 6–8 hours	Avoid if allergic to penicillin
Cefepime + metronidazole	2 g every 8–12 hours + 500 mg every 8 hours	Will not cover enterococci
Aztreonam + vancomycin + metronidazole	1–2 g every 8 hours + 15 mg/kg every 8–12 hours + 500 mg every 8 hours	Option for penicillin-allergic patients

[a]Doses must be adjusted for the degree of renal impairment.

Patient Care Process for Acute Pancreatitis

Collect Information:

- Assess fluid and nutritional status and abdominal pain severity using a pain scale.
- Review laboratory data: lipase and/or amylase; triglycerides.
- Review imaging results to determine potential causes (eg, obstruction) and extent of pancreatic damage.

Assess the Information:

- Review laboratory data, imaging, and medication history for potential risk factors for pancreatitis (Table 24–1).

Develop a Care Plan:

- Determine the level of monitoring required based on the patient's location (eg, ICU, medical floor).
- Determine how to assess ongoing pain.

Implement the Care Plan:

- Provide fluid resuscitation until the patient shows signs of adequate perfusion (monitor blood pressure and urine output).
- Provide analgesia using multimodal therapy.
- Initiate enteral nutrition early; consider parenteral nutrition if enteral nutrition is not tolerated within 1 week.

Follow-up: Monitor and Evaluate:

- Assess vital signs and pain frequently.
- Provide ongoing monitoring for potential infection.

▶ *Ineffective Therapies*

KEY CONCEPT Therapies with no proven benefit on morbidity and mortality include reducing pancreatic secretion by administering somatostatin analogues or atropine, reducing gastric acidity and pancreatic secretion with histamine$_2$-receptor antagonists, probiotics, and immunomodulation.[29]

OUTCOME EVALUATION

- Monitor hydration and nutrition status closely; replace electrolytes as necessary.
- Provide analgesia and monitor pain severity using validated scales.
- Monitor patients with moderate-to-severe AP in an intensive care setting with frequent monitoring of vital signs.
- Continually assess patients for signs of infection, including fever, leukocytosis, and other signs of sepsis.

CHRONIC PANCREATITIS

EPIDEMIOLOGY AND ETIOLOGY

The incidence of chronic pancreatitis (CP) ranges from 5 to 12 per 100,000 persons and is higher in men than in women.[30] KEY CONCEPT The most common cause of CP in adults in Western countries is ethanol abuse. Other causes include genetic predisposition, obstructive disease (secondary to ductal strictures or pseudocysts), autoimmune pancreatitis, abnormal cystic fibrosis (CF) transmembrane conductance regulator (CFTR) function as seen in CF patients, tropical pancreatitis, and idiopathic pancreatitis.[9,31] Cigarette smoking is an independent risk factor for CP.[32] Smoking, older age at diagnosis, and alcohol intake are major predictors of mortality.[8]

PATHOPHYSIOLOGY

CP is an inflammatory process that occurs over time, leading to impaired endocrine (islet cells) and exocrine (acinar cells) function secondary to diffuse scarring and fibrosis. Unlike AP, the pathologic changes of CP are irreversible.[3,8] The pathogenesis of CP is not completely understood and varies depending on etiology. One theory is that the formation of protein-rich plugs causes ductal obstruction and inflammation, ultimately causing parenchymal fibrosis and ischemic injury to the acinar cells.[33] CP is characterized by scarring and shrinkage of the pancreas from acinus fibrosis and atrophy.[8]

KEY CONCEPT Long-term sequelae of CP include dietary malabsorption, osteoporosis, impaired glucose tolerance, cholangitis, and potential addiction to opioid analgesics. As pancreatic exocrine function diminishes, patients have decreased ability to absorb lipids and protein with normal dietary intake, leading to weight loss and malnutrition. Fat- or protein-containing stools are common; carbohydrate absorption is usually unaffected.[31] Patients with CP are at risk and should be screened for deficiencies of vitamin B_{12} and fat-soluble vitamins (A, D, E, and K).[34,35]

CLINICAL PRESENTATION AND DIAGNOSIS

The symptoms, signs, and laboratory abnormalities associated with CP are similar to AP (see Clinical Presentation box). In the early stages, CP presents as recurrent episodes of AP. Later stages present with pain, sclerosis, calcification, glucose intolerance, and steatorrhea.[36] Chronic pancreatitis is a clinical diagnosis because there is no "gold standard" diagnostic test.[37] Guidelines recommend starting with a CT scan or ultrasound.[38] CP can be difficult to diagnose in the early phases because the pancreas may appear relatively normal with preserved function.[37] Diagnosis of early chronic pancreatitis has relied on a combination of endoscopic

Patient Encounter 1, Part 3

The patient was discharged and presents again to the hospital 2 weeks later with similar pain and feeding intolerance. On this admission, his WBC count is more elevated at $21.2 \times 10^3/\text{mm}^3$ ($21.2 \times 10^9/\text{L}$), and he has a temperature of 38.7°C (101.6°F). After 2 liters of Lactated Ringer's solution in the ED, he is still hypotensive with a MAP of 59 mm Hg, and his HR is 130 beats/min. His RR is 28 breaths/min and SCr is 2.0 mg/dL (177 μmol/L). A CT scan demonstrates pancreatic necrosis. His APACHE II score is calculated to be 13. Blood cultures that were drawn in the ED just returned with Gram-negative rods and Gram-positive cocci in pairs and chains.

Should this patient be admitted to the ICU or general floor unit?

Does this patient meet criteria for antibiotics? If so, what agents should be considered?

Besides antibiotics, what other pharmacologic treatments may need to be optimized?

Clinical Presentation of Chronic Pancreatitis

General

- Presentation of CP can be similar to that of AP.

Symptoms

- Abdominal pain is the most common symptom, and it typically starts in the epigastrium and may radiate to the back or scapula. Pain can be sharp or dull, is not relieved by antacids, and can be provoked by ethanol ingestion or a fatty meal. Pain can be episodic with pain-free intervals, or prolonged and requiring hospitalization.
- Pain may be associated with nausea and vomiting, causing patients to avoid food.
- Weight loss can result from chronic fat and protein malabsorption.

Signs

- **Steatorrhea** (due to fat malabsorption), malnutrition, and glucose intolerance are often present in advanced CP.
- Chronic obstruction of the common bile duct by the inflamed pancreas can cause icterus (jaundice), cholangitis, and biliary cirrhosis.

Laboratory Tests

- Serum amylase and lipase concentrations may be normal to slightly elevated in CP and are not particularly useful in the diagnosis.
- Glucose intolerance may occur because of chronic destruction of pancreatic endocrine function.
- The serum bilirubin or alkaline phosphatase may be elevated due to inflammation near the common bile duct.
- Anemia due to malabsorption of vitamin B_{12} or iron may be present.
- Patients can also have hypocalcemia, hypophosphatemia, osteomalacia, osteopenia, and osteoporosis from vitamin D deficiency and the binding of dietary calcium to unabsorbed fatty acids in the gut.
- Erythrocyte sedimentation rate (ESR), IgG4, rheumatoid factor, antinuclear antibody (ANA), and antismooth muscle antibody titer may be elevated in autoimmune pancreatitis.

ultrasound (EUS), MRCP, and/or pancreatic function testing (PFT).[39]

Several genetic mutations have been associated with CP (*PRSS1*, *SPINK1*, and *CFTR* genes) and may be useful in the diagnostic workup of CP.[6] In clinical practice, steatorrhea and associated weight loss are the most common and noticeable signs of exocrine pancreatic insufficiency.[8] Malabsorption and steatorrhea can be diagnosed using quantitative estimations of stool fat, including a 72-hour stool collection or the less cumbersome fecal elastase test.[40]

TREATMENT

Desired Outcomes

Treatment of CP is mainly symptomatic.[8] Goals of pharmacotherapy for CP include (a) relief of acute and chronic abdominal pain, (b) correction of dietary malabsorption with exogenous pancreatic enzymes, and (c) treatment of endocrine insufficiency and associated diabetes.

▶ *Nonpharmacologic Therapy*

KEY CONCEPT Avoidance of ethanol, cigarette smoking, and fatty meals can decrease the pain associated with CP. Alcohol and cigarette abstainers may have slower disease progression and better response to pain therapy than nonabstainers.[9,31,32] Avoiding further exposure to these toxins can also reduce the risk of secondary pancreatic cancer and other nonpancreatic complications.[37] Patients should consume a diet consisting of frequent small low-fat meals (< 20 g fat/day) or one with medium-chain triglycerides where absorption requires only minimal amounts of pancreatic enzymes.[9,41] Surgical procedures for CP include drainage procedures, partial pancreatic resection, and total pancreatectomy. Indications for surgery include poorly controlled pain, ductal obstruction, and symptomatic pseudocysts.[33] Most surgical procedures to reduce inflammation or remove strictures have not been studied in clinical trials and carry a high risk of morbidity and mortality.[9,31]

Pharmacologic Therapy

▶ *Analgesics*

KEY CONCEPT Pain management is an important component of therapy and similar to that of AP. Nonopioid analgesics (eg, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs]) are preferred, but the severe and persistent nature of the pain often requires opioid therapy. Patients can require chronic doses of opioid analgesics, with resulting risk of addiction.[9,42] Patients should also be assessed for neuropathic pain and treated accordingly. Pregabalin (75 mg twice daily gradually titrated to 300 mg twice daily) has been shown to reduce pain in CP in a randomized, placebo-controlled trial.[43] Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs) may help patients with neuropathic pain and comorbid depression, but they have not been specifically studied for CP.[39,44] Refer to Chapter 35 (Pain Management) for guidance in selecting an analgesic dose.

▶ *Pancreatic Enzymes*

Pancreatic enzyme replacement therapy (PERT) is indicated in patients with maldigestion-related symptoms such as diarrhea, steatorrhea, weight loss, flatulence, abdominal distension, and nutritional deficiencies.[36] The goal is to deliver exogenous enzyme to the duodenum without causing further GI side effects, risking nonadherence due to the large number of dosage units required, or causing undue medication expense. **KEY CONCEPT** Supplementation with pancreatic enzymes may reduce pain and control fatty diarrhea associated with CP, restoring the absorption of fat to an acceptable level to cause weight gain.[3] Pancreatic enzymes contain lipase, protease, and amylase in varying proportions. The half-life of endogenous lipase is based on the presence of its substrates (ie, triglycerides), and therefore dietary fat restriction should be reconsidered when pancreatic enzyme replacement is used.[40,41]

PERT products approved by the US Food and Drug Administration are shown in Table 24–3.[45] These products are not interchangeable. Enteric-coated products are designed to release enzymes in the alkaline environment (pH > 5.5) of the duodenum, thus minimizing enzyme destruction in the stomach. However, in patients with delayed gastric emptying, the efficacy of the

Table 24–3

FDA-Approved Pancreatic Enzyme Supplements

	Enzyme Content (Units)[a]		
Product	**Lipase**	**Protease**	**Amylase**
Creon 3000	3000	9500	15,000
Creon 6000	6000	19,000	30,000
Creon 12,000	12,000	38,000	60,000
Creon 24,000	24,000	76,000	120,000
Creon 36,000	36,000	114,000	180,000
Pancreaze 2600	2600	6200	10,850
Pancreaze 4200	4200	14,200	24,600
Pancreaze 10,500	10,500	35,500	61,500
Pancreaze 16,800	16,800	56,800	98,400
Pancreaze 21,000	21,000	54,700	83,900
Pertyze[b]	4000	14,375	15,125
Pertyze[b]	8000	28,750	30,250
Pertyze[b]	16,000	57,500	60,500
Pertyze[b]	24,000	86,250	90,750
Viokace 10,440[c]	10,440	39,150	39,150
Viokace 20,880[c]	20,880	78,300	78,300
Zenpep 3000	3000	10,000	14,000
Zenpep 5000	5000	17,000	24,000
Zenpep 10,000	10,000	32,000	42,000
Zenpep 15,000	15,000	47,000	63,000
Zenpep 20,000	20,000	63,000	84,000
Zenpep 25,000	25,000	79,000	105,000
Zenpep 40,000	40,000	126,000	168,000

[a] All products are porcine derived.

[b] Bicarbonate-buffered enteric-coated microspheres.

[c] Nonenteric-coated immediate-release tablets; must be administered with a proton pump inhibitor.

enteric-coated PERT may be decreased due to the early activation of the lipase enzymes. Addition of an H_2-blocker or proton pump inhibitor will decrease stomach acidity, thereby enhancing delivery of the PERT to the site of action. The only nonenteric-coated PERT available is Viokace, which is deactivated immediately in an acidic environment and therefore must be administered with a proton pump inhibitor.[40,41]

PERT should be taken immediately prior to or portioned throughout meals and snacks to aid in the absorption and digestion of food. **KEY CONCEPT** Dosing is initiated on body weight and adjusted based on clinical symptoms and stool fat content. The usual starting dose is 500 units/kg/meal of lipase with half of the mealtime dose administered with snacks. If a patient does not have an evenly calculated dose, it should be rounded to the closest dose provided by the PERT product allowing the fewest number of pills per day. Because doses often need to be rounded, one approach is to round down initially and gradually titrate the dose up based on the patient response. Several days should be allowed between dose adjustments. Doses of lipase more than 10,000 U/kg/day should be used with caution because they may be associated with colonic stricture and fibrosis.[40,41]

▶ *Glucose Control*

Patients with CP can develop glucose intolerance, but it usually does not progress to overt diabetes mellitus until late in the disease. Pancreatogenic diabetes is referred to as type 3c diabetes mellitus (T3cDM).[39] Fasting blood glucose should be monitored annually, and ensuing diabetes should be treated with insulin. Patients with CP are at increased risk of hypoglycemia due to dysfunction of the pancreatic alpha cells that are responsible for glucagon secretion.[9,31,46]

Patient Encounter 2

A 59-year-old man presents to the ED complaining of a chronic dull pain with a burning/tingling sensation in his abdomen for several months that is no longer relieved with over-the-counter analgesics. He also has had light-colored liquid stools for the last month. Most of his meals consist of fast food, but he has noticed weight loss in the last few months because of decreased appetite due to nausea and vomiting, and worsening abdominal pain with meals.

PMH: Unknown, previous records show three prior ED admissions for recurrent acute pancreatitis, but the patient typically leaves the hospital prematurely against medical advice.

SH: Consumes a six-pack of beer per day and has a 45-pack-year history of cigarette smoking

Meds: Pantoprazole as needed for GERD symptoms

ROS: (+) for RUQ abdominal pain that radiates to his back, decreased appetite, 20-lb (9 kg) weight loss, and diarrhea for the last two months. (–) for chest pain or shortness of breath

PE:

VS: BP 160/90 mm Hg, HR 80 beats/min, RR 15 breaths/min, T 37.1°C (98.8°F), Wt 100 kg (220 lb), Ht 5′10″ (178 cm)

Pain assessment: Ranges from 6 to 8 out of 10 (numerical rating scale); currently 9/10 pain. Describes as dull aching pain and tingling, needle-like pain

CV: Regular rate and rhythm, no murmurs

Abd: Distended, (+) rebound tenderness, (+) bowel sounds

Labs:

Amylase 50 IU/L (0.83 μkat/L)	BUN 19 mg/dL (6.8 mmol/L)
Lipase 70 IU/L (1.17 μkat/L)	SCr 0.9 mg/dL (80 μmol/L)
AST 42 IU/L (0.7 μkat/L)	Glucose 260 mg/dL (14.4 mmol/L)
ALT 29 IU/L (0.48 μkat/L)	Triglycerides 180 mg/dL (2.03 mmol/L)

CT scan abdomen: Diffuse pancreatic scarring and calcifications

What signs and symptoms are consistent with chronic pancreatitis?

How can you determine if this is acute or chronic pancreatitis?

What lifestyle modifications would you recommend for this patient?

What treatment regimens would you initiate, and how would you monitor their effects?

▶ *Other Therapies*

In patients with autoimmune pancreatitis, prednisolone 30 to 40 mg/day tapered over a 3-month period may provide rapid relief of symptoms.[47] Antioxidants such as methionine, ascorbic acid, and selenium may reduce the number of painful days per month in patients with CP, but studies have showed conflicting results.[9,48–50]

Patient Care Process for Chronic Pancreatitis

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements.
- Review the medical history and physical assessment findings to identify signs/symptoms of abdominal pain, steatorrhea, decreased appetite secondary to abdominal pain, and/or signs of glucose intolerance.
- Speak with the patient and review lifestyle and dietary habits, specifically any significant alcohol or smoking history.
- Ask the patient to rate the pain, if any, and relate factors that exacerbate and relieve the pain.

Assess Information:

- Determine whether the patient is receiving any medication(s) that may cause or exacerbate pancreatitis.
- Using validated pain scales, determine whether the pain is currently controlled.
- Review relevant laboratory tests (eg, amylase, lipase, basic metabolic panel, liver panel, complete blood count, lipid panel, fasting glucose, fat-soluble vitamin levels) and imaging (eg, ultrasound, CT, MRI, MRCP).
- If the patient is already receiving pharmacotherapy, assess efficacy, safety, and patient adherence.
- Identify any significant adverse drug effects or interactions.

Develop a Care Plan:

- If the patient has signs of malnutrition or nutritional deficiencies, determine if PERT or supplemental vitamins are indicated.
- If the patient has elevated fasting blood glucose or A1C, consider starting insulin therapy (see Chapter 44, Diabetes Mellitus).
- Develop an analgesic plan to control and prevent pain (see Chapter 35, Pain Management).

Implement the Care Plan:

- Provide resources for alcohol and smoking abstinence, if applicable.
- Address any patient concerns about pancreatitis and its management.
- Initiate PERT in patients with steatorrhea.
- Discuss importance of diet, medication adherence, and lifestyle modifications to reduce complications of AP and/or CP.

Follow-up: Monitor and Evaluate:

- Adjust PERT dosage based on nutritional status and pain with meals on a monthly basis until adequate control is achieved. Once stable doses of PERT and analgesia are established, monitor the patient once or twice yearly.
- Evaluate the patient's vitamin A, D, E, K, and B_{12} levels, fasting blood glucose, and A1C at least annually.
- Reassess analgesia and adjust medication and dosages as indicated.

OUTCOME EVALUATION

- Encourage lifestyle modifications such as abstinence from ethanol and cigarettes.
- Monitor pain control and adjust analgesics accordingly.
- Counsel patients to monitor for weight gain or loss and fatty stool output as markers of malabsorption.
- Educate patients that adherence to PERT is the key to improved outcomes.

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Abbreviations Introduced in This Chapter

ANA	Antinuclear antibody
AP	Acute pancreatitis
APACHE II	Acute Physiology and Chronic Health Evaluation II
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CP	Chronic pancreatitis
CT	Computed tomography
ERCP	Endoscopic retrograde cholangiopancreatography
ESR	Erythrocyte sedimentation rate
GI	Gastrointestinal
LDH	Lactate dehydrogenase
MAP	Mean arterial pressure
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
PERT	Pancreatic enzyme replacement therapy
RUQ	Right upper quadrant
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment
WBC	White blood cell

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25

Viral Hepatitis

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Differentiate the five types of viral hepatitis by epidemiology, etiology, pathophysiology, clinical presentation, and natural history.
2. Identify modes of transmission and risk factors among the major types of viral hepatitis.
3. Evaluate hepatic serologies to understand how the type of hepatitis is diagnosed.
4. Create treatment goals for a patient infected with viral hepatitis.
5. Recommend appropriate pharmacotherapy for prevention of viral hepatitis.
6. Develop a care plan for treatment of chronic viral hepatitis.
7. Formulate a monitoring plan to assess adverse effects of pharmacotherapy for viral hepatitis.

INTRODUCTION

The most common types of viral hepatitis include hepatitis. Acute hepatitis may be associated with all five types of hepatitis and rarely exceeds 6 months in duration. Chronic hepatitis (disease lasting more than 6 months) is usually associated with hepatitis B, C, and D. **KEY CONCEPT** Chronic viral hepatitis may lead to the development of cirrhosis and may result in end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC). Complications of ESLD include ascites, edema, hepatic encephalopathy, infections (eg, spontaneous bacterial peritonitis), hepatorenal syndrome, and esophageal varices. *Therefore, prevention and treatment of viral hepatitis may prevent ESLD and HCC.*

Viral hepatitis may occur at any age and is one of the most common causes of liver disease in the world. The true prevalence and incidence may be underreported because most patients are asymptomatic. The epidemiology, etiology, and pathogenesis vary depending on the type of hepatitis and are considered separately below.

EPIDEMIOLOGY AND ETIOLOGY

Hepatitis A (HAV)

HAV affects 1.4 million people yearly worldwide.[1] The prevalence is highest in economically challenged and underdeveloped countries, including Central and South America, Africa, the Middle East, Asia, and the Western Pacific.[2] The numbers of acute HAV infections and hospitalizations have decreased since the introduction of the HAV vaccine in 1995.[2] However, there has been a recent resurgence of hepatitis A infections in the United States since 2017 affecting primarily the homeless and people who inject drugs (PWID). As of August 2020, more than 33,000 cases have been reported, up from 12,474 in 2018.[3,4]

HAV is primarily detected in contaminated feces and infects people via the fecal–oral route.[1,2] Outbreaks typically occur in areas of poor sanitation or consumption of food or water infected with the HAV.[1,3] About 40% of the cases reported have no identifiable risk factors; individuals at greatest risk of acquiring HAV are listed in Table 25–1.[4]

There are no documented cases of chronic hepatitis A infections.[2,4] Approximately 100 annual fatalities in the United States are associated with fulminant hepatitis, which occurs in less than 1% of cases.[4]

Hepatitis B (HBV)

Approximately 2 billion people worldwide have evidence of past or present HBV infection, and more than 250 million people have chronic hepatitis B (CHB).[5,6] Globally, approximately 887,000 deaths were associated with HBV in 2015.[6] Despite having an effective vaccine against HBV since 1982, it is estimated that there were 21,600 acute HBV infections in 2018 in the United States.[7] Fewer than 1% of individuals in North America and Western Europe are chronically infected, compared with greater than 5% in developing areas in parts of Africa, South America, East Asia, and Pacific Islands.[5]

The primary modes of transmission of HBV are by blood and body fluids through perinatal, sexual, or percutaneous exposure (Table 25–1).[5,8] Infants born to mothers who are infected with actively replicating HBV have a 90% risk of becoming infected.[8]

Hepatitis C (HCV)

It is estimated that 71 million people worldwide and 2.4 million Americans have chronic HCV. However, the true prevalence in the United States may be as high as 4.1 million because certain populations (eg, incarcerated, homeless, immigrants, active military personal, and nursing home residents) have not been fully evaluated.[9,10] The prevalence is highest in PWID, who account for more than 70% of newly diagnosed acute HCV infections.[11] High-risk factors for acquiring HCV are listed in Table 25–1.

HCV is categorized by genotypes, which are geographically specific. There are seven genotypes (numbered 1–7) and 67 subtypes (eg, genotypes 1a, 1b, 2a, and 3b).[12] Genotypes 1a, 1b, 2,

Table 25–1

Risk Factors for Acquiring Viral Hepatitis

Hepatitis A

High Risk

International travelers to endemic areas (eg, Africa, Asia, and parts of South America)
Men having sex with other men
Persons who use illegal drugs (injection or noninjection)
Workers involved with nonhuman primates
Persons with close contacts of international adoptees
Persons experiencing homelessness
Persons living in group settings with developmental disabilities
Persons incarcerated in jail or prison
Persons infected with HIV

Low Risk

Patients with clotting factor disorders
Persons who work in food service establishments
Food sources contaminated with HAV (eg, raw foods including seafood, shellfish, green onion, and fruit)
Child care centers and schools
Health care providers with direct or indirect patient contact
Workers exposed to sewage
Public water systems (eg, swimming pools, public drinking water)

Hepatitis B and D

Infants born to infected mothers
International travelers to endemic areas
Men having sex with other men
Individuals with multiple heterosexual partners
Persons who use illegal drugs (injection or noninjection)
Recipients of contaminated blood, blood products, or organ transplantation
Household contacts with acute hepatitis B (eg, sharing razor or toothbrush)
Health care providers and public safety workers in contact with infected blood
Residents and staff of facilities for developmentally disabled persons
Patients undergoing dialysis
Persons with HCV and/or HIV
Persons with diabetes

Hepatitis C

High Risk

Current or former injection drug users

Low Risk

Recipients of blood products (clotting factor concentrates made before 1987, blood transfusions or solid organ transplants before July 1992)
Health care providers in contact with infected blood
Chronic hemodialysis (eg, contaminated blood or dialysis equipment)
Individuals having multiple sexual partners, especially men having sex with other men
HIV infection
Unregulated body piercing and tattooing
Household contacts with hepatitis C (eg, sharing razor or toothbrush)

and 3 are the most common in the United States.[12] Genotype does not indicate disease severity but had been used during the non-pangenotypic HCV therapy era to determine duration of therapy and the likelihood of a therapeutic response.[13]

Hepatitis D (HDV)

Hepatitis D is estimated to affect 20 million people worldwide; however, new prevalence data suggest that the rate may be underreported by two- to three-fold.[14] Areas with the highest prevalence include the Middle East, parts of Africa, Northern and Southeast Asia, Eastern Europe, the Mediterranean basin, and parts of South America.[14]

HDV infection is unique because it can only occur in people who are also infected with the HBV.[14] The most likely modes of transmitting HDV are similar to those of HBV (Table 25–1), with PWID being the most common risk factor.[14]

Hepatitis E (HEV)

An estimated 20 million individuals worldwide are infected annually with HEV, and the disease was associated with about 44,000 deaths in 2015.[15] The highest prevalence is found in East and South Asia.[15] HEV infection primarily occurs in underdeveloped countries with poor sanitation. The HEV is transmitted mainly by the fecal–oral route (eg, contaminated drinking water).[15]

PATHOPHYSIOLOGY

Hepatitis A

Hepatitis A is a nonenveloped single-stranded RNA virus classified as the *Hepatovirus* genus under the Picornaviridae family.[2] The primary host for the HAV is humans, with hepatic cells as the main site for viral replication. As part of the viral degradation process, the HAV is released into the biliary system causing elevated HAV concentrations in the feces. Hepatitis A infections are usually self-limiting and do not lead to chronic disease; rarely, it may result in fulminant hepatitis.[2,3]

Hepatitis B

The HBV belongs to the Hepadnaviridae family.[8] It is a partially double-stranded DNA virus with a phospholipid layer containing hepatitis B surface antigen (HBsAg) that surrounds the nucleocapsid. The nucleocapsid contains the core protein that produces hepatitis B core antigen (HBcAg), which is undetectable in the serum. Hepatocellular injury from HBV is thought to be due to a cytotoxic immune reaction that occurs when HBcAg is expressed on the surface of hepatic cells. Fortunately, antibodies against hepatitis B core antigen (anti-HBc) are measurable in the blood, where anti-HBc to immunoglobulin M (IgM) indicates active infection, and anti-HBc to IgG indicates either chronic infection or possible immunity against HBV.

Viral replication usually occurs when the hepatitis B envelope antigen (HBeAg) is present and circulating in the blood. Serum HBV DNA concentration measures viral infectivity and quantifies viral replication. Once the HBV infection resolves, antibodies against the hepatitis B envelope (anti-HBe) and antibodies against hepatitis B surface antigen (anti-HBs) develop, and HBV DNA levels become undetectable. However, if antibodies do not develop, the likelihood of developing CHB increases. This depends primarily on the host's immune system at the time of infection. In immunocompetent individuals, the disease resolves spontaneously and does not lead to further complications. In immunocompromised persons, the HBV is less likely to be eradicated, thus causing persistent infection leading to hepatic cell damage and inflammation.[5,8]

Approximately 90% of adults infected with the HBV develop anti-HBs, which results in lifelong immunity. Unfortunately, about 90% of infants born to mothers with active HBV infection will develop CHB.[5] About 50% of adults with acute HBV infections are asymptomatic, and those with symptoms may experience jaundice or fatigue.[8]

Patient Encounter Part 1

A 38-year-old woman who went to visit a friend in Los Angeles for a week and returned now presents to the primary care physician's office 2 days later for her yearly checkup. She states that her friend had acute hepatitis A and was not hospitalized. The patient states that she is feeling well with no complaints except for fatigue.

PMH: Diet-controlled hypertension, diet-controlled diabetes, HCV

PSH: Skin mole removed at age 25

FH: Father with HTN; mother with NASH and diabetes; married with a 22-year-old daughter

SH: Smoked tobacco 0.5 PPD in her 20s. Does not smoke now. One-time use of IV cocaine at age 18. Drinks red wine daily with meals for the last 3 years. Accountant at a law firm.

Meds: Multivitamin daily, calcium and vitamin D, docusate sodium, and influenza and pneumococcal vaccine given last year.

ROS: Constipation present. No blood in the stools. No nausea, vomiting, diarrhea, abdominal pain, or anorexia; never experienced an episode of jaundice, pale stools, or tea-colored urine.

PE:

VS: BP 130/85 mm Hg, P 82 beats/min, RR 20 breaths/min, T 37.0°C (98.6°F), Wt 76 kg (167 lb), Ht 5′10″ (178 cm)

Abd: Soft, nontender, normal liver span; no hepatosplenomegaly, no ascites

The remainder of the examination was within normal limits.

Labs (obtained 4 week ago):

Sodium 141 mEq/L (mmol/L)
Potassium 4.5 mEq/L (mmol/L)
Chloride 99 mEq/L (mmol/L)
CO_2 21 mEq/L (mmol/L)
BUN 20 mg/dL (7.1 mmol/L)
SCr 1.1 mg/dL (97 μmol/L)
ALT 90 IU/L (1.5 μkat/L)
AST 82 IU/L (1.37 μkat/L)
T. bilirubin 1.0 mg/dL (17.1 μmol/L)
Alk phos 164 IU/L (2.73 μkat/L)
Albumin 3.6 g/dL (36 g/L)
Glucose 122 mg/dL (6.8 mmol/L)
A1C 5.9% (0.059; 41 mmol/mol Hgb)
WBC $5.1 \times 10^3/\text{mm}^3$ (5.1×10^9/L)
Hgb 14.2 g/dL (142 g/L; 8.81 mmol/L)
Hct 42.1% (0.421)
Plt $199 \times 10^3/\text{mm}^3$ (199×10^9/L)
TSH 1.3 μIU/mL (mIU/L)
Anti-HAV IgM (–)
Anti-HAV IgG (+)
Anti-HCV (+), genotype 2b
HCV RNA 542,091 IU/mL (kIU/L)

FibroScan: Moderate fibrosis, F2 (7.8 kPa)

Limited abdominal sonogram of liver and spleen: Liver: Normal echogenicity. No intrahepatic biliary dilatation. No discrete hepatic mass. Simple hepatic cysts. Spleen: Normal size and echogenicity. Portal vein: normal color Doppler flow. Gallbladder: No gallstones, biliary sludge, wall thickening, or pericholecystic fluid. Negative sonographic Murphy's sign. Common duct: Measures up to 4 mm in diameter. Common bile duct: Obscured by overlying bowel gas. Other findings: No large ascites.

What information is suggestive of viral hepatitis?

What risk factors does she have for viral hepatitis?

What additional information do you need before creating a treatment plan for this patient?

Hepatitis C

Hepatitis is a blood-borne infection caused by a single-stranded RNA virus belonging to the Flaviviridae family and the *Hepacivirus* genus.[16] Antibodies against HCV (anti-HCV) in the blood indicate infection. Acute hepatitis C persists for less than 6 months, occurs in about 15% of the population, and resolves without further complications.[7] If the infection persists longer than 6 months and viral replication is confirmed by HCV RNA levels, the person has chronic hepatitis C (CHC), which occurs in about 55% to 85% of cases.[5,17] CHC may be due to an ineffective host immune system, with cytotoxic T lymphocytes unable to eradicate the HCV, thereby allowing persistent damage to hepatic cells. The most common risk factors for developing hepatic fibrosis include obesity, diabetes, heavy alcohol use, male sex, and coinfections with HIV or HBV.[13]

From 55% to 85% of CHC progress to mild, moderate, or severe hepatitis. Cirrhosis and its complications may take several decades to develop in 15% to 30% of patients infected with HCV. Once cirrhosis is confirmed, the risk of developing HCC is 2% to 4% per year.[5,17]

Hepatitis D

The HDV belongs to the genus *Delta virus* of the Deltaviridae family. The HDV is a defective single-stranded circular RNA virus that requires the presence of HBV for HDV viral replication, causing either coinfection (both hepatitis B and D infection occurring simultaneously) or superinfection (acquiring HDV after having long-standing HBV disease).[14] This occurs because the HDV antigen (HDVAg) is coated by the HBsAg.[14]

Hepatitis E

Hepatitis E is a nonenveloped single-stranded messenger RNA virus with at least eight different genotypes; several are found in humans and some in animals.[18] The HEV is transmitted via the fecal–oral route with the primary source being contaminated food and water.[15] Unfortunately, animals can acquire the HEV; thus, human consumption of these animals is considered a risk factor. HEV infections are usually self-limiting and rarely result in hepatic complications. Chronic infections occur rarely but may lead to cirrhosis; they are more common in immunocompromised individuals (eg, HIV infection, elderly) and organ transplant recipients.[15,18]

CLINICAL PRESENTATION AND DIAGNOSIS

See box for the clinical presentation of viral hepatitis.

Diagnosis of Viral Hepatitis

Diagnosing viral hepatitis may be difficult because most infected individuals are asymptomatic.[2,5,14,18] Because symptoms alone cannot identify the specific type of hepatitis, laboratory serologies must be obtained (Table 25–2). A liver biopsy may be obtained

Table 25–2

Interpretation of Viral Hepatitis Serology Panels

Type	Laboratory Test	Result	Interpretation of Panel
Hepatitis A	IgM anti-HAV	Negative	Susceptible to infection
	IgG anti-HAV	Negative	
	IgM anti-HAV	Positive	Acutely infected
	IgG anti-HAV	Positive	Immune due to either natural infection or HAV vaccine
Hepatitis B[a]	HBsAg	Negative	Susceptible to infection
	Anti-HBc	Negative	
	Anti-HBs	Negative	
	HBsAg	Negative	Immune due to natural infection
	Anti-HBc	Positive	
	Anti-HBs	Positive	
	HBsAg	Negative	Immune due to hepatitis B vaccination
	Anti-HBc	Negative	
	Anti-HBs	Positive	
	HBsAg	Positive	Acutely infected
	Anti-HBc	Positive	
	IgM anti-HBc	Positive	
	Anti-HBs	Negative	
	HBsAg	Positive	Chronically infected
	Anti-HBc	Positive	
	IgM anti-HBc	Negative	
	Anti-HBs	Negative	
	HBsAg	Negative	Four interpretations possible: (a) Resolved infection (most common); (b) false-positive anti-HBc, thus susceptible; (c) low-level chronic infection; (d) resolving acute infection
	Anti-HBc	Positive	
	Anti-HBs	Negative	
Hepatitis C	Anti-HCV	Negative	Susceptible to infection
	Anti-HCV	Positive	Acutely or chronically infected
Hepatitis D[b]	IgM anti-HDV	Positive	Acute HBV-HDV coinfection
	HDVAg	Positive	
	HBsAg	Positive	
	HBeAg	Positive	
	IgM anti-HBc	Positive	
Hepatitis E	IgM anti-HEV	Negative	Susceptible to infection
	IgG anti-HEV	Negative	
	IgM anti-HEV	Positive	Acutely infected
	IgG anti-HEV	Positive	Immune due to natural infection

[a] Centers for Disease Control and Prevention. Hepatology [Internet]. http://www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf.

[b] Hepatitis D should be suspected in those who have HBsAg positivity. Hepatitis D may present as either coinfection where both HDV and HBV serologies appear simultaneously, whereas for superinfection, HBV has been present for some time and later HDV develops.

anti-HAV, hepatitis A antibody; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; anti-HCV, hepatitis C antibody; anti-HDV, hepatitis D antibody; anti-HEV, hepatitis E antibody; HAV, hepatitis A virus; HBV, hepatitis B virus; HDV, hepatitis D virus; HDVAg, hepatitis D antigen; IgG, immunoglobulin G; IgM, immunoglobulin M.

Clinical Presentation of Viral Hepatitis

Symptoms

- Most patients infected with any type of viral hepatitis have no symptoms.
- Symptomatic patients may experience a flu-like syndrome, fevers, fatigue/malaise, anorexia, nausea, vomiting, diarrhea, dark urine, pale-appearing stools, pruritus, and abdominal pain.

Signs

- Jaundice may be evident in the whites of the eyes (scleral icterus) or skin.
- An enlarged liver (hepatomegaly) and spleen (splenomegaly) may be present.
- In fulminant hepatitis with hepatic encephalopathy, patients may have **asterixis** and coma.
- In rare instances, extrahepatic symptoms may develop (arthritis, postcervical lymphadenopathy, palmar erythema, cryoglobulinemia, and vasculitis).

Laboratory Tests

- See Table 25–2.

to determine the severity of the liver disease, but this is an invasive test that may be associated with complications such as severe pain, bleeding, and death.[19] Therefore, several patented blood tests (FibroTest, HepaScore) have been developed that use a panel of serum biomarkers (e.g., ALT, AST, and platelet count) along with the age and sex of the patient to determine the degree of hepatic fibrosis. A noninvasive imaging test that uses ultrasound vibration-controlled transient elastography (VCTE) is now recommended to assess the severity of liver disease.[19] These invasive and noninvasive tests are imperfect and are usually only able to identify mild and severe disease. Therefore, it is important to monitor laboratory values over time to assess the severity of liver fibrosis (eg, AST, ALT, serum albumin, platelet counts, and prothrombin time/INR).

▶ *Hepatitis A*

Hepatitis A is diagnosed by detecting immunoglobulin antibodies to the capsid proteins of the HAV. Detectable IgM anti-HAV in the serum indicates acute infection and usually appears about 3 weeks after exposure and becomes undetectable within 6 months. In contrast, IgG anti-HAV appears in the serum at approximately the same time that IgM anti-HAV develops but indicates protection and lifelong immunity against the HAV.[2]

▶ *Hepatitis B*

Hepatitis B is diagnosed when HBsAg is detectable in the serum, but it does not distinguish between acute and chronic HBV. The presence of IgM antibodies to HBcAg indicates active infection. IgG anti-HBc indicates either chronic infection or possible immunity against HBV.[8]

In most cases, detectable HBeAg indicates active viral replication. Measurement of HBV DNA determines viral infectivity and quantifies viral replication. Once HBV viral replication ceases, anti-HBe is detected in the serum. However, a minority of patients may develop anti-HBe and still have elevated HBV DNA levels because of a mutation in the HBV.[20] Therefore, CHB infections may be differentiated as either HBeAg-positive or HBeAg-negative.[20]

▶ *Hepatitis C*

Chronic hepatitis C (CHC) is diagnosed by testing for anti-HCV in the serum and confirmed by the presence of HCV RNA. HCV RNA levels quantify viral replication and are used to determine if treatment is effective. Undetectable HCV RNA levels indicate past infection or that the infection is resolved. The HCV genotype should be determined if a nonpangenotypic regimen will be prescribed.

▶ *Hepatitis D*

Hepatitis D infection requires the presence of HBV for HDV viral replication. Measuring HDV RNA levels confirms hepatitis D infection and is the most accurate diagnostic test. The presence of IgM anti-HD indicates active disease, and IgG anti-HD also becomes detectable if the infection does not resolve spontaneously. HDV antibodies do not confer immunity.[21]

▶ *Hepatitis E*

Diagnosis of acute hepatitis E is based on the presence of IgM anti-HEV. IgG anti-HEV emerges when the HEV infection resolves.[15,18] HEV RNA levels can be obtained from either blood or stool and are usually tested if chronic HEV infection is suspected.[18]

PREVENTION AND TREATMENT OF VIRAL HEPATITIS

Desired Outcomes

Treatment outcomes for viral hepatitis are to: (a) prevent the spread of infection, (b) prevent and treat symptoms, (c) suppress viral replication, (d) normalize hepatic aminotransferases, (e) improve liver histology, and (f) decrease morbidity and mortality by preventing cirrhosis, HCC, and ESLD.

For hepatitis B, additional treatment goals include seroconversion or loss of HBeAg, and ultimately seroconversion or loss of HBsAg.[20] The primary goal of treating chronic HCV is to achieve undetectable HCV RNA for at least 12 weeks after completing hepatitis C therapy, known as achieving a sustained virologic response (SVR).[13]

General Approach

Managing viral hepatitis involves both prevention and treatment. Prevention of hepatitis A and B (and indirectly for hepatitis D) can be achieved with immune globulin (IG) or vaccines. **KEY CONCEPT** Acute viral hepatitis is primarily managed with supportive care. Mild-to-moderate symptoms rarely require hospitalization, but hospital admission is recommended in individuals experiencing significant nausea, vomiting, diarrhea, and encephalopathy. Liver transplantation may be required rarely if fulminant hepatitis develops. Treatment is available for CHB, CHC, and chronic HDV.

Hepatitis A Prevention

KEY CONCEPT Good personal hygiene and proper disposal of sanitary waste are required to prevent HAV fecal–oral transmission.[2,3] This includes frequent handwashing with soap and water after using the bathroom and prior to eating meals. Drinking bottled water and avoiding fruits, vegetables, and raw shellfish harvested from sewage-contaminated water may minimize the risk of becoming infected with the HAV. Individuals at risk of acquiring HAV (Table 25–1) should receive serum IG and/or the hepatitis A vaccine.[2,3]

▶ *Immune Globulin (IG)*

IG (GamaSTAN) is the only FDA-approved agent containing antibodies from sterilized pooled human plasma that provides short-term passive immunization against HAV.[3] IG is available as an intramuscular (IGIM) formulation and should not be administered intravenously because it may cause renal dysfunction or failure, hemolysis, or transfusion-related acute lung injury.[3,22] Recommended doses are given in Table 25–3. Even though the risk of acquiring severe infections (including Creutzfeldt–Jakob disease) is low and no cases have been documented, patients should be informed that the risk exists because IG is obtained from human plasma.[22]

IGIM does not affect the immune response of inactivated or live-virus vaccines; however, administrating live vaccines concomitantly may decrease the immune response significantly.[22]

IGIM administration is indicated for individuals: (a) at high risk of acquiring the HAV infection (Table 25–1, hepatitis A section), (b) who elect not to receive the hepatitis A vaccine, or (c) who cannot receive the hepatitis A vaccine (eg, because of allergic reaction). Preexposure and postexposure prophylaxis dosing is based on patient's age, indication, and health status (Table 25–4). When IGIM and another vaccination (eg, hepatitis A vaccine) are to be given at the same time, it is recommended that the two

Table 25–3

Recommended Intramuscular Doses of Immune Globulin (GamaSTAN) for Hepatitis A

Indication	Duration of Exposure/Travel	Dose (mL/kg)[a,b]	Instruction for Administration[c]
Preexposure	≤ 1 month travel	0.1	Before departure to endemic area(s)
	≤ 2 months travel	0.2	Before departure to endemic area(s)
	> 2 months travel	0.2	Before departure and repeat every 2 months
Postexposure	Exposed < 2 weeks	0.1	Within 2 weeks of exposure

[a] Dose is based on weight for all ages, there is no maximum dose for protection for hepatitis A prophylaxis.

[b] Patients with prolonged immobilization, indwelling central vascular catheter, hypercoagulable disorders, using estrogen products, history of thrombosis or cardiovascular risk factors are at risk of thrombosis with IG. Do not administer doses higher than what is recommended.

[c] Live vaccines (eg, measles, mumps, and rubella) should not be administered for at least 2 weeks before and 6 weeks after administering immune globulin.

From Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of Hepatitis A Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices, 2020. MMWR Recomm Rep. 2020 Jul 3;69(5):1-38. doi: 10.15585/mmwr.rr6905a1. PMID: 32614811.

immunizations be administered at different anatomical sites/limbs.[3]

▶ *Hepatitis A Vaccine*

Persons at risk of acquiring HAV should receive the hepatitis A vaccine to provide pre- and postexposure prophylaxis (Table 25–1). Children aged 12 to 23 months should receive the hepatitis A vaccine. Persons who did not receive the vaccine during the first 2 years of life should receive a catch-up HAV vaccination.[3] Two inactivated hepatitis A vaccines are available in the United States: HAVRIX and VAQTA. The recommended regimen is to administer two injections 6 months apart (at months 0 and 6).[3] These vaccines are considered interchangeable, and doses depend on age (Table 25–5).[3]

Efficacy is defined by measuring anti-HAV levels when they are greater than 10 mIU/mL (IU/L).[3] Within 4 weeks of administering the first vaccine dose, more than 95% of adults and 97% of children and adolescents develop protective antibody concentrations. All recipients receiving the second dose in clinical trials had 100% antibody coverage; therefore, postvaccination measurement of antibody response is not required.[2]

The hepatitis A vaccine may provide immunity for about 20 years in children more than 2 years of age and adults who completed the two-dose hepatitis A vaccination series.[3] The most common and often self-limiting adverse effects in adults include injection-site reactions (eg, tenderness, pain, and warmth), headaches, fatigue, and flu-like symptoms. Infants and children may have feeding disturbances. Local reactions may be minimized by using an age-appropriate needle length and injecting into the deltoid muscle. Data with hepatitis A vaccine given during pregnancy are limited; the risk of adverse events was not increased; however, infants may be smaller for their gestational age.[3]

Hepatitis B Prevention

KEY CONCEPT The risk of acquiring the HBV may be minimized by avoiding contaminated blood products and high-risk behavior (Table 25–1) and by receiving the hepatitis B vaccine.[23]

Screening pregnant women for HBV and providing universal hepatitis B vaccinations to all newborns is effective in preventing hepatitis B infections.[23] In some cases, postexposure prophylaxis with hepatitis B immune globulin (HBIG) may be recommended to prevent the development of acute infection and CHB.

Table 25–4

Preexposure and Postexposure Hepatitis A vaccine and Immune Globulin (GamaSTAN) dosing recommendations

Indication	Age of Patient	Risk Category/Health Status	HAV Vaccine	IGIM[a]
Postexposure[b,c]	< 12 months	Healthy	No	Yes
	12 months to 40 years old	Healthy	Yes	No
	> 40 years old	Healthy	Yes	Yes
	≥ 12 months	Immunocompromised, have chronic liver disease	Yes	Yes
	≥ 12 months	Contraindication to HAV vaccine	No	Yes
Preexposure	< 6 months	Healthy	No	Yes
	6–11 months	Healthy	Yes	No
	12 months to 40 years old	Healthy	Yes	No
	> 40 years old	Healthy	Yes	Yes
	> 6 months	Immunocompromised, have chronic liver disease	Yes	Yes
	> 6 months	Contraindicated to HAV vaccine or don't want vaccine	No	Yes

[a] See Table 25–3.

[b] Twinrix should not be used for postexposure prophylaxis since it contains half of the single -antigen hepatitis A vaccine adult dose.

[c] At least 1 dose of hepatitis A vaccine is recommended for persons exposed in a hepatitis A outbreak; completion of hepatitis A vaccine series is not required to achieve disease control but is recommended for long-term HAV protection.

Adapted from Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of Hepatitis A Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices, 2020. MMWR Recomm Rep. 2020 Jul 3;69(5):1-38. doi: 10.15585/mmwr.rr6905a1. PMID: 32614811.

Table 25–5

Recommended Intramuscular Doses of Hepatitis A Vaccines

Product	Recipient Age (years)	Dose (Units)	Volume (mL)	No. of Doses	Schedule (months)
VAQTA	1–18	25	0.5	2	0, 6–18
	≥ 19	50	1	2	0, 6–18
HAVRIX	1–18	720 ELISA	0.5	2	0, 6–12
	≥ 19	1440 ELISA	1	2	0, 6–12

ELISA, enzyme-linked immunosorbent assay.

Adapted from Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of Hepatitis A Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices, 2020. MMWR Recomm Rep. 2020 Jul 3;69(5):1-38. doi: 10.15585/mmwr.rr6905a1. PMID: 32614811.

Table 25–7

Recommendations for Nonoccupational Postexposure Prophylaxis to the Hepatitis B Virus

	Treatment to Administer If Serology Test of Source Person Is:	
Exposed Person's Vaccination Status	HBsAg-Positive	Unknown HBsAg Status
Unvaccinated	HBIG and initiate HB vaccine series	Initiate HB vaccine series
Previously vaccinated	Administer HB vaccine booster dose	No treatment

HB, hepatitis B; HBsAg, hepatitis B surface antigen; HBIG, hepatitis B immune globulin.

▶ *Hepatitis B Immune Globulin (HBIG)*

Nabi-HB and HepaGam B are the only two FDA-approved HBIG products containing antibodies prepared from pooled human plasma that provide short-term passive immunization to prevent CHB infections in persons who had sexual, perinatal, or acute exposure to an HBsAg-positive person[24,25] (Tables 25–6 and 25–7).

The efficacy, side effect profile, and warnings of HBIG are similar to IG when used for immunization against HAV.[3,23–27]

▶ *Hepatitis B Vaccine*

The first hepatitis B vaccines in the United States were Recombivax HB and Engerix-B, which are given at months 0, 1, and 6 and approved to be administered intramuscularly at birth (Table 25–6). Heplisav-B is a newer HBV vaccine indicated for persons aged 18 or older and administered intramuscularly at months 0 and 1. Heplisav-B has a unique adjuvant that stimulates direct immune response to the HBsAg, which has higher seroprotective antibody protection (greater than 90%) compared to Engerix-B of 70% to 90%.[26] Therefore, the advantage of Heplisav-B is an improved dosing regimen and immunogenicity, which may be beneficial in certain populations (eg, diabetics, smokers, and patients older than 40 years).[27] **KEY CONCEPT** Persons at high risk of acquiring the HBV (Table 25–1) should be vaccinated.

The hepatitis B vaccine is also indicated for postexposure prophylaxis to prevent CHB. All individuals exposed to HBV should receive the hepatitis B vaccine with or without HBIG, preferably within 24 hours of exposure based on the source of exposure and the vaccination status of the exposed person. Recommendations are divided into nonoccupational (Table 25–7) and occupational, where the latter refers the reader to the CDC guidelines for the most up-to-date recommendations.[23] Postexposure prophylaxis for perinatal exposure depends on several factors, including maternal HBsAg status and the newborn's weight (Table 25–8).[23]

The hepatitis B vaccine is effective when antibody concentrations are greater than 10 mIU/mL (IU/L). Postvaccination

Table 25–6

Recommended Intramuscular Dosing Regimens for Single-Antigen Hepatitis B Vaccines

Product	Patient Categories	Dose (mcg)	Volume (mL)	No. of Doses	Schedule (months)
Recombivax HB	0–19 years of age	5	0.5	3	0, 1, 6
	11–15 years of age[a]	10	1	2	0, 4–6
	≥ 20 years of age	10	1	3	0, 1, 6
	Hemodialysis[b] < 20 years of age	5	0.5	3	0, 1, 6
	Hemodialysis ≥ 20 years of age	40	1	3	0, 1, 6
Engerix-B	0–19 years of age	10	0.5	3	0, 1, 6
	≥ 20 years of age	20	1	3	0, 1, 6
	Hemodialysis[b] < 20 years of age	10	0.5	3	0, 1, 6
	Hemodialysis ≥ 20 years of age	40[c]	2	4	0, 1, 2, 6
Heplisav-B	≥ 18 years of age	20 mcg HBsAg and 3000 mcg CpG 1018 adjuvant	0.5	2	0, 1

[a] Adolescents 11 through 15 years of age may receive either the 5-mcg three-dose pediatric formulation or a 10-mcg two-dose regimen using the adult formulation, administered as a two-dose schedule.

[b] Higher doses might be more immunogenic, but no specific recommendations have been made.

[c] Two 1.0-mL doses administered at one site.

Centers for Disease Control and Prevention. Hepatitis B FAQs for Health Professionals [Internet]. http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#vaccFAQ

Table 25–8

Recommendations for Hepatitis B Prophylaxis to Prevent Perinatal Transmission with Single-Antigen Hepatitis B Vaccine

		Mother's HBsAg Status		
Infant Birthweight	Hepatitis B[a]	Positive	Negative	Unknown
≥ 2000 g	Dose 1	Within 12 hours of birth with HBIG[b]	Within 24 hours of birth	Within 12 hours of birth. +/– HBIG[b,d]
	Dose 2	Month 1–2	Month 1–2	Month 1–2
	Dose 3	Month 6[c]	Month 6–18[c]	Month 6[c]
< 2000 g	Dose 1	Within 12 hours of birth with HBIG[b]	Hospital discharge or age 1 month	Within 12 hours of birth with HBIG[b]
	Dose 2	Month 1	Month 2	Month 1
	Dose 3	Month 2–3	Month 6–18[c]	Month 2–3
	Dose 4	Month 6[c]		At month 6[c]

[a] See Table 25–6 for appropriate hepatitis B vaccine dose.

[b] 0.5 mL intramuscularly in a different site from vaccine.

[c] The final dose should not be administered before age 24 weeks (164 days).

[d] Test mother's HBsAg as soon as possible after admission for delivery. If positive, give HBIG as soon as possible and prior to age 7 days; if negative, give no HBIG.

From Schillie S, Vellozzi C, Reingold A, et al. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep. 2018 Jan 12;67(1):1-31. doi: 10.15585/mmwr.rr6701a1. PMID: 29939980; PMCID: PMC5837403.

antibody testing is not routinely recommended because most people completing the vaccination series obtain adequate antibody levels. However, it is recommended to determine if immunity has been achieved in infants born to HBsAg-positive mothers, health care and public safety workers with continued exposure to percutaneous and/or mucosal-infected body fluids, sex partners with CHB, and immunocompromised persons (eg, chronic dialysis, HIV, and organ transplant recipients).[23,28]

Effective immunity may last for more than 30 years in healthy individuals. However, patients with poor immune systems may have an anamnestic response that requires titers to be checked periodically with booster doses given.[23,28]

The most frequent adverse effects are local injection-site reactions, flu-like symptoms, nausea, dizziness, fever, and headaches.[23] Heplisav-B had more cardiovascular events than Engerix-B (0.27% vs 0.14%), but this difference is not statistically significant.[29] Recombivax HB and Engerix-B are not contraindicated during pregnancy and should be safe to the fetus because they are inactivated vaccines.[23] There are no data on Heplisav-B in pregnant women.[23]

▸ *Hepatitis A and B Combination Vaccine*

KEY CONCEPT Twinrix combines both inactivated HAV and HBV and is approved for individuals 18 years of age or older who are at risk for HAV and HBV infections.[3,23] A 1-mL dose of Twinrix may be administered at either months 0, 1, and 6 or in an accelerated schedule on days 0, 7, between 21 and 30, and with a fourth dose at month 12.[3,23] The accelerated schedule is intended for patients who start the vaccination series but are unable to complete the standard three-dose schedule in time to develop adequate immunity before embarking on travel that will put them at risk of exposure to hepatitis A and B.[27] The efficacy and side effect profile of Twinrix is similar to giving each vaccine separately.[3,28]

Chronic Hepatitis B Treatment

The American Association for the Study of Liver Diseases (AASLD) recommends treatment for HBeAg-positive patients with persistently elevated ALT (more than two times the upper limit of normal) or significant histological disease and elevated HBV DNA levels greater than 20,000 IU/mL (kIU/L) to delay progression to cirrhosis and prevent the development of ESLD.[20] Similar treatment criteria apply to patients infected with HBeAg-negative CHB except that therapy should be initiated when HBV DNA levels exceed 2000 IU/mL (kIU/L).[20]

The primary treatment endpoint is to suppress HBV replication to achieve undetectable serum levels. The ideal treatment should induce a biochemical response (normalize ALT levels), histological response (decrease liver inflammation documented by liver biopsy scores), and serological seroconversion (detectable antiHBe, antiHBs, and HBsAg loss).[20]

KEY CONCEPT The drug of choice for CHB depends on the patient's past medical history, ALT, HBV DNA level, HBeAg status, severity of liver disease, and history of previous HBV therapy. All HBV therapies are effective with no agent showing superiority to others in reducing the risk of developing HBV complications.[20]

Entecavir, tenofovir, and pegylated (peg) IFN-α_{2a} are recommended first-line therapies due to profound HBV DNA suppression; the latter agent should be considered in patients with compensated liver disease because of its finite treatment duration and lack of drug resistance.[20]

Adefovir and lamivudine are not recommended due to high rates of resistance.[20] Patients responding to therapy should continue them, but adding or switching to a more potent HBV agent should be considered if there is inadequate virologic response or drug resistance develops.

The side effect profiles for all oral HBV agents are mild; the most common complaints are nausea, headaches, dizziness, and fatigue. Patients should be monitored for lactic acidosis and severe hepatomegaly because some cases have been fatal. Hepatic function tests should be monitored if treatment is to be discontinued; severe acute hepatitis exacerbations have been reported. Dosage adjustments are required in patients with renal dysfunction. With all oral HBV agents, HIV resistance may develop if given as monotherapy; therefore, test for HIV prior to starting a single anti-HBV agent. Patients coinfected with HIV and HBV should receive concomitant highly active antiretroviral therapy (HAART) with an HBV agent. Each HBV agent is described in

Table 25–9

Antiviral Agents for Treatment of Chronic Hepatitis B

Generic Name	Brand Name	Recommended Dosing Regimen[a]	Notes
Pegylated interferon-α_{2a}	Pegasys	180 mcg SQ weekly for 48 weeks	Refer to Table 25–10 for adverse effects
Entecavir	Baraclude[b]	0.5 mg daily for treatment naïve 1 mg daily for resistance to lamivudine or telbivudine or decompensated liver disease	Give on empty stomach (at least 2 hours before or after a meal)
Tenofovir disoproxil fumarate	Viread	300 mg daily for patients weighing > 35 kg	Give on empty stomach
Tenofovir alafenamide	Vemlidy	25 mg daily	Take with food
Adefovir disoproxil	Hepsera[b]	10 mg daily	Take with or without food
Lamivudine	Epivir-HBV[b]	100 mg daily for adults 3 mg/kg, up to 100 mg for 2–17 years old	Take with or without food

[a] May need to treat longer per guidelines: Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Clin Liver Dis (Hoboken*)*. 2018;12(1):33–34. Published 2018 Aug 22. doi:10.1002/cld.728.

[b] Generic available.

(SQ, subcutaneous)

the sections that in the following sections with recommended dosing regimens in Table 25–9.

▶ *Interferon and Pegylated Interferon*

PegIFN-α_{2a} (Pegasys) is the only IFN therapy approved for HBV that is effective in suppressing, and in some cases ceasing, viral replication without inducing resistance.[20] Approximately one-third of HBeAg-positive patients achieve HBeAg seroconversion after 48 weeks of pegIFN therapy.[20] HBeAg-negative hepatitis B may require more than 48 weeks of treatment to attain undetectable HBV DNA levels.[20] Factors associated with a greater chance of HBeAg seroconversion include low baseline HBV DNA concentrations and high pretreatment ALT levels.[20]

Although pegIFN lacks resistance and possible HBsAg loss or seroconversion (development of anti-HBs), its disadvantages include the need for subcutaneous injections and a pronounced adverse-effect profile that may require dosage reductions or treatment discontinuation (see Table 25–10). PegIFN is contraindicated in patients with autoimmune disorders, uncontrolled psychiatric diseases (eg, suicidal thoughts, major depression), uncontrolled seizures, and decompensated cirrhosis.[20]

▶ *Entecavir*

Entecavir (Baraclude) is a guanosine nucleoside analog approved for patients over 2 years of age with either HBeAg-positive or HBeAg-negative CHB.[20] Resistance rates are low (1%–2%) in lamivudine-naive patients treated with entecavir for up to 5 years.[30] For patients previously treated with lamivudine and switched to entecavir, the resistance rate is approximately 28% at 1 year and up to 51% at 5 years.[31] Therefore, the dose of entecavir is 0.5 mg for patients 16 years or older with compensated liver disease and naïve to lamivudine therapy and 1 mg for lamivudine or telbivudine resistance or decompensated liver disease.

▶ *Tenofovir Disoproxil Fumarate and Tenofovir Alafenamide*

Tenofovir disoproxil fumarate (TDF; Viread) is an acyclic adenine nucleotide reverse transcriptase inhibitor similar in structure to adefovir disoproxil that inhibits HIV and HBV replication. It is indicated for HBV patients older than 2 years of age, weighing at least 10 kg with either HBeAg-positive or HBeAg-negative CHB and/or HIV when prescribed with other HAART therapies.

TDF has high efficacy with almost no development of resistance and is generally well tolerated.[20,30] However, rare but significant adverse effects include nephrotoxicity and Fanconi syndrome, decreased bone mineral density, and osteomalacia.[20,30] TDF is a prodrug that is converted to tenofovir in the plasma and then phosphorylated to tenofovir diphosphate. High concentrations of the diphosphate compound in cells increase risk of kidney and bone toxicity. Creatinine clearance (CrCl), serum phosphate, liver function tests, and bone mineral density should be monitored prior

Table 25–10

Adverse Effects of Pegylated Interferon and Ribavirin

Pegylated interferon

Adverse Effect	Therapeutic Intervention
Flu-like symptoms (eg, fevers, chills, rigors, myalgias)	Premedicate with acetaminophen or nonsteroidal anti-inflammatory drugs. Administer at bedtime.
Psychiatric abnormalities (eg, irritability, depression, and rarely, suicidal, or homicidal ideations)	Seek mental health specialist, antidepressants, and anxiolytics. If symptoms are severe, discontinue treatment.
Neutropenia	Obtain a complete blood count with differential and monitor ANC. Consider reducing dose if less than 1.0×10^9/L (1.0×10^3/mm^3)
Thrombocytopenia	Obtain a complete blood count and monitor platelet count. Consider reducing dose if platelet count is significantly low.
Elevated ALTs	Obtain LFTs and monitor. Only use pegylated interferon in patients with compensated liver disease.
Ribavirin	
Dermatological (rash, itching, dry skin)	Recommend creams, lotions, and oral antihistamines
Hemolytic anemia	Monitor hemoglobin, shortness of breath, chest pain. Reduce dose if hemoglobin less than 10 g/dL (100 g/L; 6.21 mmol/L) or significant symptoms

to initiating treatment and during therapy. The TDF dose must be reduced with CrCl less than 50 mL/min (0.83 mL/s).

Tenofovir alafenamide (TAF; Vemlidy) was subsequently approved for compensated CHB. TAF offers antiviral activity similar to TDF but with a safer side effect profile. TAF delivers the prodrug tenofovir directly to hepatic cells intracellularly, resulting in lower concentrations in the kidneys and bone.[20] TAF may be administered at full doses until the CrCl is less than 15 mL/min (0.25 mL/s).

▶ *Adefovir Dipivoxil*

Adefovir dipivoxil (Hepsera) is a prodrug of adefovir, an adenosine nucleotide analog that inhibits DNA polymerase; it is indicated for CHB in patients older than 12 years of age. Resistance to adefovir is minimal for the first few years of treatment but increases to approximately 30% after 5 years of therapy.[30]

Similar to TDF, rare but significant adverse effects include nephrotoxicity when doses are greater than 30 mg/day and Fanconi syndrome. Renal function should be monitored during treatment in all patients, especially those with preexisting or risk factors for renal impairment.

▶ *Lamivudine*

Lamivudine (Epivir-HBV) is an oral synthetic cytosine nucleoside analog that is effective in suppressing HBV replication, normalizing ALT levels, and improving liver histology. Patients may have a similar or a superior response in achieving these endpoints when compared with pegIFN. Prolonged lamivudine therapy (up to 5 years) may be needed to sustain seroconversion but may lead to resistance rates as high as 70% at 5 years.[20,30] Due to the high rate of resistance, lamivudine is no longer recommended as first-line therapy for CHB.[20]

Hepatitis C Prevention

There are currently no vaccines to prevent HCV, but several are under development.[12] Avoiding high-risk behaviors such as sharing needles among PWID is the primary means of acquiring HCV. More than 75% of individuals infected with the HCV were born during the "baby boomer" generation.[32] Additionally, from 2009 to 2017, similar HCV rates were found in people between the ages of 20 and 39. Because this population contains women of childbearing age, the number of live neonates infected with HCV has increased.[17,32] Therefore, the CDC recommends that all adults over the age of 18 be tested for HCV at least once in their lifetime.[17] Also, women should be tested for HCV during each pregnancy. Individuals with elevated ALT levels and those with HCV risk factors listed in Table 25–1 should be tested for HCV at least once in their lifetime. PWID or share intravenous drug paraphernalia or patients receiving hemodialysis should be tested yearly.[17]

Chronic Hepatitis C Treatment

Treatment for HCV has been revolutionized over the past decade, with efficacy rates well above 90% compared to 50% to 80% before 2011.[33] The primary goal of HCV treatment is to achieve a sustained virologic response (SVR), defined as undetectable HCV RNA levels at 12 weeks or longer after treatment completion. Normalization of liver function tests and improvement of histology are additional treatment outcomes, but the primary goal is to prevent progression and development of cirrhosis, HCC, and ESLD.[13] Patients who achieve SVR do not cure the existing liver disease; those with advanced disease and cirrhosis continue to have liver disease progression; thus, cirrhotic surveillance must be performed (eg, ultrasound to evaluate for HCC). Initiating HCV treatment early before development of advanced liver disease may slow the progression of cirrhosis and the complications associated with ESLD. Therefore, the World Health Organization (WHO) and National Academies of Sciences, Engineering, and Medicine (NASEM) recommend treating *all* patients infected with the HCV, in hopes of eliminating viral hepatitis in the world by 2030.[10,34]

Patient Encounter Part 2: Creating a Care Plan

Based on the information presented, create a care plan for this patient's hepatitis. Your plan should include:

(a) a statement of the drug-related needs and/or problems;

(b) the goals of therapy;

(c) a patient-specific detailed therapeutic plan;

(d) a follow-up plan to determine whether the goals have been achieved; and

(e) a follow-up plan to identify potential adverse effects of therapy.

▶ *Interferon/Pegylated Interferon and Ribavirin*

IFN and pegIFN are no longer recommended for chronic HCV because SVR rates (about 50%) are suboptimal along with a number of untoward events (Table 25–10). The addition of ribavirin, a synthetic guanosine analog that inhibits viral polymerase, had increased SVR rates with pegIFN (50%–80%) and continues to be prescribed with direct-acting antivirals (DAA) for certain patient populations to enhance SVR rates.[13] Ribavirin causes a dose-related hemolytic anemia that may require dosage reductions or discontinuation.[13] Dermatological effects (eg, rash, pruritus, and dry skin) occur commonly with ribavirin. Because ribavirin can be teratogenic and embryocidal, all women of childbearing age and men who are able to father a child must use two forms of contraception during HCV therapy containing ribavirin and for 6 months after completion of treatment. Patients with renal insufficiency require dosage adjustments with ribavirin.

▶ *Direct-Acting Antiviral Agents*

The two first-generation DAAs (boceprevir and telaprevir) and several second-generation DAAs (eg, simeprevir) are no longer available because newer agents have superior response rates, fewer adverse effects, reduced pill burden, simplified dosing regimens, fewer drug interactions, and lower rates of viral resistance.[13]

Third-generation DAAs (Table 25–11) have SVR rates well above 90%, once daily dosing, fewer adverse effects, safety for all stages of renal dysfunction, shorter treatment durations with less complex regimens, and several agents that are pangenotypic (treat all HCV genotypes). **KEY CONCEPT** Selection of a DAA is based on previous HCV treatment history, severity of liver disease, current medical conditions and medications, and the presence or absence of resistance-associated substitutions (RAS).[13] Selected DAAs require RAS testing before starting HCV therapy (Table 25–11). If RAS are present, the options are to choose a drug from a different DAA, add ribavirin, and/or treat for longer than 12 weeks.

Prior to having FDA-approved HCV pangenotypic HCV treatments, obtaining HCV genotypes was standard of care because it determines the likelihood of response and the duration of treatment. At present, genotyping is no longer recommended in naïve and noncirrhotic patients since several DAAs treat all genotypes; assuming a pangenotypic HCV regimen is prescribed. However, if patients have failed previous HCV therapy, have cirrhosis, or a nonpangenotypic DAA is selected, then the genotype should be

Table 25–11

Direct-Acting Antiviral Agents for Treatment of Hepatitis C

Brand Name	Generic Name	Dosage (mg)	Regimen[e]	Drug Interactions	Resistance Testing Required
Sovaldi	Sofosbuvir[3]	400	1 daily with other DAA ± ribavirin[e]	P-gp[b]	
Harvoni[d]	Ledipasvir[2]/ sofosbuvir[3] FDC[c]	90/400	1 daily ± ribavirin[e]	P-gp[b] BCRP[h] Acid suppressing agents	NS5A RAS Genotype 1a, treatment experienced
Zepatier	Elbasvir[2]/grazoprevir[1] FDC[c]	50/100	1 daily ± ribavirin[e]	OATP1B1/3 CYP3A	NS5A RAS
Epclusa[d]	Sofosbuvir[3]/velpatasvir[2] FDC[c]	400/100	1 daily	P-gp[b] BCRP[h] OATP1B1/3 OATP2B1 CYP2B6 CYP2C8 CYP3A4 Acid suppressing agents	NS5A RAS, Genotype 3, naïve and cirrhotic
Vosevi	Sofosbuvir[3]/ velpatasvir[2]/ voxilaprevir[1] FDC[c]	400/100/100	1 daily	P-gp[b] BCRP[h] OATP1B1/3 OATP2B1 CYP1A2 CYP2B6 CYP2C8 CYP3A4 Acid suppressing agents	
Mavyret	Glecaprevir[1]/ pibrentasvir[2,c]	100/40	3 daily	P-gp BCRP[h] OATP1B1/3 CYP3A CYP1A2 UGT1A1[i]	

[a] Wholesale acquisition cost

[b] P-glycoprotein

[c] Fixed-dose combination tablet

[d] Generic available

[e] Refer to www.hcvguidelines.org for the most up-to-date HCV treatment regimen.

[f] All patients should be evaluated for HBV and be vaccinated if not yet immune. If HBV is positive, then treat before initiating HCV therapy with any DAA.

[g] If coadministered with ribavirin, then refer to the warnings and contraindications associated with ribavirin.

[h] Breast cancer resistance protein

[1] NS3/4A protease inhibitor

[2] NS5A polymerase inhibitor

[3] NS5B Nucleotide polymerase inhibitor

obtained prior to initiating therapy.[13] Prior to administering any DAA regimen, the presence of HBV should be excluded because cases of HBV reactivation have occurred, leading to fulminant hepatitis or death. Patients positive for HBV should be treated either prior to or concomitantly with the DAA. Patients not immune against HBV should receive the HBV vaccine.

Patients with decompensated Child-Pugh B and Child-Pugh C cirrhosis should not receive DAA regimens that include a protease inhibitor (eg, voxilaprevir, grazoprevir, and glecaprevir) because hepatic decompensation and/or failure, need for transplant, or death may occur.

All DAA have potential drug–drug interactions that may render treatments ineffective or toxic. The more notable interactions include proton pump inhibitors, statins, antimicrobials, antiepileptic agents, amiodarone, immunosuppressive agents, St John's wort, and HAART agents. Prior to prescribing a DAA regimen, it is imperative to obtain an updated medication list of over-the-counter and prescription medications and dietary supplements. Clinicians may use the University of Liverpool's Hepatitis Drug Interactions website, https://www.hep-druginteractions.org/checker, to assess for DDIs.

The approved DAAs for HCV are described below; however, refer to www.hcvguidelines.org for the most up-to-date treatment recommendations.[13]

Sofosbuvir (Sovaldi) is the first agent of the NS5B polymerase inhibitor class approved for treatment of HCV genotypes 1, 2, 3, and 4 in patients older than age 3; it also has efficacy in genotypes 5 and 6.[13] Sofosbuvir is commonly administered with other DAAs in a fixed-dose combination (FDC) to achieve SVR rates above 90%. Treatment durations range from 8 to 24 weeks with the most common being 12 weeks.[13]

Sofosbuvir and Ledipasvir (Harvoni) is the first FDA-approved all-oral FDC HCV regimen that does not require administration with pegIFN or ribavirin. Ledipasvir has a different mechanism of action than sofosbuvir; it inhibits the HCV NS5A protein, which is required for viral replication. This FDC is indicated for CHC genotype 1, 4, 5, and 6 infection in patients older than age 3. Sofosbuvir 400 mg/ledipasvir 90 mg is given daily for 12 or 24 weeks depending on prior HCV treatment history, cirrhosis status, genotype, and baseline viral load.[13] Noncirrhotic patients with genotype 1a, 1b, and 4 (not 4r) without HIV with a HCV RNA level less than 6 million IU/mL may be treated for 8 weeks.[13]

Elbasvir and Grazoprevir (Zepatier) is an FDC tablet approved for HCV genotype 1 or 4. Elbasvir is an NS5A inhibitor and grazoprevir is a NS3/4A protease inhibitor; these mechanisms inhibit different parts of the virus to halt viral replication. Patients with genotype 1a disease should be tested for the NS5A RAS; if NS5A polymorphism is absent, monotherapy for 12 weeks results in a SVR rate above 90%. If the polymorphism is present, ribavirin is added and treatment is extended to 16 weeks. Patients with genotype 1b and having mild fibrosis (defined as a transient elastography score ≤ 9.5 kPa) may be considered for 8 weeks of therapy.[13] This FDC is safe and well tolerated for patients with renal insufficiency including those on hemodialysis because the drugs are primarily eliminated via the feces.

Sofosbuvir and Velpatasvir (Epclusa) is the first FDC approved for all six HCV genotypes (known as a pangenotypic DAA) and is indicated for patients older than 6 years or weighing greater than 17 kg. Sofosbuvir (400 mg), an NS5B polymerase inhibitor, is combined with velpatasvir (100 mg), an NS5A inhibitor (also available in 200 mg/50 mg, respectively, for children weighing 17–30 kg) that achieves an SVR well above 90% for all patients without cirrhosis and those with compensated cirrhosis (except for genotype 3). Patients with compensated cirrhosis and genotype 3 should be tested for the NS5A RAS Y93H prior to initiating treatment. If the polymorphism is present, ribavirin is added (or select another DAA) and if absent, then monotherapy with Epclusa may be recommended.[13] Because this once-daily DAA regimen for 12 weeks is highly effective with minimal adverse effects, the AASLD included Epclusa as part of the simplified treatment recommendations.[13] Patients with decompensated Child-Pugh B or C cirrhosis should take Epclusa with weight-based ribavirin for 12 weeks, if tolerated, and those not able to take ribavirin may receive monotherapy for 24 weeks.[13]

Sofosbuvir, Velpatasvir, and Voxilaprevir (Vosevi) is a pangenotypic FDC tablet that contains drugs targeting three different sites to inhibit HCV viral replication. Similar to Epclusa, Vosevi also includes a NS3/4A protease inhibitor, voxilaprevir. The once-daily FDC tablet is taken daily with food for 12 weeks for adults with or without compensated cirrhosis (Child-Pugh A) who have been previously treated with an HCV regimen that included an NS5A inhibitor or sofosbuvir. This triple therapy has SVR rates above 95%, particularly in DAA-experienced patients. There are no dosage recommendations for patients with renal insufficiency or ESRD.

Glecaprevir and Pibrentasvir (Mavyret) is the first pangenotypic FDC tablet containing an NS3/4A protease inhibitor (glecaprevir 300 mg) and an NS5A inhibitor (pibrentasvir 120 mg). It is approved for patients 12 years and older weighing at least 45 kg with or without compensated cirrhosis (Child-Pugh A) or patients who are treatment experienced with either an HCV NS3/4A or NS5A inhibitor. It may be administered for 8, 12, or 16 weeks. The 8-week DAA treatment is effective for all HCV genotypes in: (a) noncirrhotic naïve-treated patients, (b) patients with compensated cirrhosis (Child-Pugh A), (c) patients coinfected with HIV, and (d) patients with renal insufficiency. Because this once-daily DAA regimen for eight weeks is highly effective with minimal adverse effects, the AASLD includes Mavyret as part of the simplified treatment recommendations for treatment-naïve patients with compensated (Child-Pugh A) or no cirrhosis.[13] For treatment-experienced patients, the duration of retreatment may be as short as 8 weeks or as long as 16 weeks.

▶ *Cost of HCV Treatment*

The new generation of HCV agents is associated with improved SVR rates and side effect profiles. However, their high cost may prevent some patients from receiving HCV treatment. Typically, 8 to 12 weeks of DAA therapy has a wholesale acquisition price of $27,000 to $95,000. The price has steadily declined as more DAA regimens became available generically. In an ideal world, all patients infected with HCV would be treated to decrease morbidity and mortality associated with cirrhosis and HCC. In an analysis performed by Chhatwal et al., it was projected that 1.85 million Americans would be treated between 2014 and 2030.[35] The unfortunate reality is that only 5 million had been treated worldwide by the end of 2017.[10] The high cost of HCV regimens and lack of linkage to care may explain the difficulty in treating everyone.

The AASLD recommends that all patients be treated regardless of severity of the liver disease, except those with short life expectancies.[32] With the simplified treatment recommendations, and now having generic DAAs available in the United States, it is hoped that all infected with hepatitis C will be treated with ultimately eradication of HCV worldwide.

Hepatitis D Prevention and Treatment

Hepatitis D infection is possible only if the patient is also infected with HBV; therefore, hepatitis B vaccination can indirectly prevent hepatitis D infections. The recommended treatment for HDV is pegIFN for 48 weeks with several adverse effects (Table 25–10).[20,30] For patients with mild liver disease (low HBV DNA levels, elevated ALT levels, and elevated HDV RNA levels), pegIFN for 48 weeks is recommended. Monotherapy with oral HBV antiviral agents should only be considered in patients with cirrhosis since there is minimal effect on HDV RNA concentrations. Coadministration of oral HBV agents (TDF, TAF, or entecavir) and pegIFN may be recommended in patients with elevated HBV DNA and HDV RNA levels.[20] HBV DNA and HDV RNA levels are not strong treatment endpoints, considering that 40% of patients may have viral suppression at the end of treatment but may rebound after several years.[20] A loss of HBsAg may be a better endpoint; however, only about 25% of patients achieve this with at least 5 years of pegIFN therapy.[20] Due to a lack of effective HDV regimens, several investigational therapies are being evaluated.[36]

Hepatitis E Prevention and Treatment

Because hepatitis E is transmitted via the fecal–oral route, good personal hygiene and proper disposal of sanitary waste are the most effective ways to prevent viral acquisition. There are no commercially available vaccines in the United States to prevent hepatitis E. However, a hepatitis E vaccine has been licensed in China since 2012 and may become available for countries with high HEV infection incidence rates.[15] In rare cases, HEV may lead

Patient Encounter Part 3

Sodium 138 mEq/L (mmol/L)
Potassium 4.4 mEq/L (mmol/L)
Chloride 98 mEq/L (mmol/L)
CO2 19 mEq/L (mmol/L)
BUN 20 mg/dL (7.1 mmol/L)
SCr 1.2 mg/dL (106 μmol/L)
Glucose 103 mg/dL (5.7 mmol/L)
T. bilirubin 1.2 mg/dL (20.5 μmol/L)
Albumin 3.7 g/dL (37 g/L)

Alk phos 168 IU/L (2.80 μkat/L)
AST 18 IU/L (0.30 μkat/L)
ALT 19 IU/L (0.32 μkat/L)
HCV RNA level: 43 IU/mL (kIU/L)
WBC 4.1 × 10^3/mm^3 (4.1 × 10^9/L)
Hgb 14 g/dL (140 g/L; 8.69 mmol/L)
Hct 39.9% (0.399)
Plt 201 × 10^3/mm^3 (201 × 10^9/L)

What questions should you ask the patient?

What action should you take based on the patient's week 4 HCV RNA level?

to chronic hepatitis. PegIFN treatment has been successful, primarily in the solid organ transplantation population. However, there are many adverse effects (Table 25–10), and it is considered a contraindication in several solid organ transplants (kidney, pancreas, heart, and lung) because it may induce rejection. Ribavirin monotherapy had been evaluated in organ transplant recipients with promising SVR rates of 78%.[37]

OUTCOME EVALUATION

Monitoring for efficacy in patients treated for chronic hepatitis B or C includes evaluating aminotransferase levels and hepatitis B or C viral levels and serologies.

Hepatitis B

- Obtain an ALT at baseline and then every 3 to 6 months during hepatitis B treatment.
- Monitor HBV DNA levels every 3 to 6 months to determine treatment response.
- Monitor HBeAg and anti-HBe every 6 months to determine if seroconversion to anti-HBe occurred or HBeAg was lost in HBeAg-positive CHB patients after achieving undetectable HBV DNA levels.[20]
- Monitor HBsAg every 6 to 12 months to determine if HBsAg was lost or anti-HBs developed in CHB HBeAg-negative patients with persistently undetectable serum HBV DNA levels.[20]
- Continue treatment in CHB HBeAg-positive patients until HBeAg seroconversion has been attained along with undetectable HBV DNA levels. Once anti-HBe appears, complete an additional 12 months of hepatitis B therapy.[20]
- Continue treatment in CHB HBeAg-negative patients. Medication discontinuation may be considered if HBsAg is lost, but the risk versus benefit must be weighed when doing so.[20]
- Monitor ALT, HBV DNA levels, seroconversion, and signs and symptoms of hepatic decompensation every 3 months for at least 1 year when discontinuing hepatitis B therapy.[20]
- For patients receiving TDF, TAF, or adefovir, monitor serum creatinine, phosphorus, urine glucose, and urinary protein for nephrotoxicity at baseline then yearly (more frequently in patients with baseline renal insufficiency).[20]
- Monitor WBC, absolute neutrophil count (ANC), and platelets either weekly or biweekly during the first month of therapy and monthly thereafter if stable while on pegIFN (Table 25–10).
- Monitor thyroid-stimulating hormone (TSH) and fasting lipid panel every 12 weeks while receiving pegIFN.

Patient Encounter Part 4

The patient has completed her HCV treatment and the HCV RNA level is detectable at 502,113 IU/mL (kIU/L) 12 weeks off of HCV medications.

What action should you take based on this HCV RNA level?

What other information should you counsel the patient about in addition to the side effects associated with the hepatitis C therapy?

Hepatitis C

- Evaluate the patient's HAV and HBV status. If not yet immune, then vaccinate. If positive for CHB, then have the hepatologist evaluate the patient for HBV treatment.
- Test for HIV before initiating HCV therapy. If positive, then refer to an infectious diseases specialist.
- Conduct a thorough medication reconciliation of prescription and over-the-counter medications and dietary supplements prior to and during HCV therapy for drug interactions.
- Evaluate for signs and symptoms of decompensated liver disease prior to initiating DAA therapies containing an HCV NS3 protease inhibitor. Patients with Child-Pugh B or C should not receive NS3 protease inhibitors (Table 25–11).
- Evaluate for the presence of RAS prior to initiating HCV therapy (Table 25–11).
- The ultimate goal of HCV therapy is to achieve SVR, defined as having undetectable HCV RNA levels for at least 3 months posttreatment; this indicates virological cure.[13] Ensure that a baseline HCV RNA level had been obtained any time prior to starting a DAA for comparison.

Patient Encounter Part 5

The patient's daughter visits the doctor today because she tested positive on a home pregnancy test last week. Labs were obtained a week ago and she returns for results.
SH: marijuana—started using at age 17.
All laboratory test results are normal except for the following:

AST 28 IU/L (0.47 mckat/L)
ALT 32 IU/L (0.53 μkat/L)
Anti-HAV IgM (–)
Anti-HAV IgG (–)
Anti-HBs (+)
Anti-HBc titer < 10

hCG 4316 mIU/mL (IU/L)
Anti-HBc IgG (–)
Anti-HBc IgM (–)
HBsAg (–)
Anti-HCV (–)

Based on the information presented:

(a) create a detailed care plan for the patient;

(b) create a detailed viral hepatitis vaccination care plan for the patient's newborn

- Obtain a CBC, INR, and complete metabolic panel at baseline within 6 months before initiating DAA therapy.
- Monitor ALT levels every 4 weeks. Biochemical response is defined as the normalization of ALT. If elevated, obtain an HCV RNA level.
- Monitor hemoglobin weekly or biweekly during the first month and monthly thereafter if stable while on ribavirin (Table 25–10).
- Monitor for fatigue, shortness of breath, chest pain, and dermatological complications while on ribavirin; discontinue treatment if complaints are significant.
- Monitor serum creatinine in patients receiving ribavirin to detect renal insufficiency that may result in ribavirin accumulation and toxicity (eg, hemolytic anemia).
- Monitor for pregnancy while on ribavirin therapy and 6 months after completing therapy.

Patient Care Process

Collect Information:

- Speak with the patient to identify risk factors for acquiring viral hepatitis (Table 25–1).
- Review social history to determine if any practices may contribute to or worsen the severity of liver disease (ie, alcohol, high-fat food intake).
- Review past medical history focusing on hepatic and renal disorders.
- Review physical assessment findings focusing on mental status changes, edema, and color of skin and eyes (ie, jaundice).
- Perform a medication history (prescription, over-the-counter drugs, dietary supplements) to identify drug interactions (may refer to hep-druginteraction.org) or drug-induced liver toxicity.
- Review the use of any drugs in the past for the treatment of hepatitis B or C.
- Obtain a vaccination history to determine which vaccines have been given.
- Review laboratory tests to determine severity of liver disease. Review hepatitis serologies to determine if vaccination is needed (Table 25–2).
- Speak with the patient and review insurance coverage records for medical and medication history.

Assess the Information:

- Determine if treatment is indicated by reviewing laboratory values, liver serologies, and liver biopsy report (if available) or imaging (CT, Fibroscan, ultrasound).
- If the patient does not qualify for hepatitis therapy, then schedule return visits every 3 to 6 months to monitor health condition and laboratory tests.
- If the patient qualifies for treatment, assess for uncontrolled medical conditions, and if present, treat or refer to an appropriate medical specialty for evaluation (eg, HIV, diabetes, renal disease, HBV).
- Determine which vaccines need to be administered.
- For patients with HCV, assess severity of liver disease to recommend appropriate anti-HCV regimen (Table 25–12).
- Document, trend, and review laboratory values to determine severity of liver disease (platelet counts, AST, ALT, INR, albumin).
- Assess the efficacy, safety, and patient adherence of current pharmacotherapy.
- Assess current medications before initiating hepatitis therapy to identify potential drug–drug interactions and ensure that doses are appropriate based on organ function.
- Assess laboratory values and medications with potential for drug interactions or adherence problems for patients currently on treatment.

Develop a Care Plan:

- Refer to AASLD HBV guidelines for CHB treatment recommendations.
- Refer to www.hcvguidelines.org for HCV treatment guidelines.
- Refer to https://www.hepatitisc.uw.edu/ for HCV treatment regimens.
- Obtain a pregnancy test in women of childbearing potential who are prescribed ribavirin-based therapies.

Implement the Care Plan:

- Educate the patient about the hepatitis drug regimen, potential side effects, and duration of therapy.
- Inform the patient about the importance of drug adherence to minimize the risk of developing resistance.
- Educate the patient to avoid alcohol and illicit drug use during treatment and after completion of therapy.
- Work with the local specialty pharmacy to ensure that medications are covered by insurance and continued without disruption in treatment.
- Educate all men and women who are of childbearing age and are receiving ribavirin to use two forms of birth control during treatment and for 6 months after treatment.
- Address any patient concerns about the liver disease and its management.
- Discuss the importance of lifestyle modification to reduce the progression of liver disease.

Follow-up: Monitor and Evaluate:

- At each clinic visit, review the medication list, assess for medication adverse effects and drug interactions, and review laboratory tests to assess efficacy and toxicity.
- Confirm adherence and number of missed doses to minimize drug resistance.
- Obtain laboratory test results every week to every 2 to 4 weeks until complete treatment if ribavirin is prescribed.
- Assess for decompensated liver disease while on HCV therapy (Table 25–12).
- Follow up with a hepatologist every 6 months for cirrhosis surveillance in patients with advanced liver disease.

- For patients taking medications for diabetes, monitor symptoms of hypoglycemia during and after treatment.
- For patients taking warfarin, monitor INR during and after treatment.

Abbreviations Introduced in This Chapter

ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
Anti-HAV	Hepatitis A virus antibody
Anti-HBc	Hepatitis B core antibody
Anti-HBe	Hepatitis B envelope antibody
Anti-HBs	Hepatitis B surface antibody
Anti-HCV	Hepatitis C antibody
Anti-HDV	Hepatitis D antibody
Anti-HEV	Hepatitis E antibody
AST	Aspartate aminotransferase
CHB	Chronic hepatitis B infection
CHC	Chronic hepatitis C infection
CrCl	Creatinine clearance
DAA	Direct-acting antiviral
ESLD	End-stage liver disease
ESRD	End-stage renal disease
FDC	Fixed-dose combination
HAART	Highly active antiretroviral therapy
HAV	Hepatitis A virus
HBcAg	Hepatitis B core antigen
HBeAg	Hepatitis B envelope antigen
HBIG	Hepatitis B immunoglobulin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBV DNA	Hepatitis B deoxyribonucleic acid
HCV	Hepatitis C virus
HCV RNA	Hepatitis C virus ribonucleic acid
HDV	Hepatitis D virus
HDVAg	Hepatitis D antigen
HDV RNA	Hepatitis D virus ribonucleic acid
HEV	Hepatitis E virus
IgG	Immunoglobulin G
IgG anti-HD	IgG antibodies to hepatitis D virus antigen
IgM	Immunoglobulin M
IgM anti-HD	IgM antibodies to hepatitis D virus antigen
IG	Immune globulin
IGIM	Immune globulin for intramuscular administration
pegIFN	Pegylated interferon
PWID	People who inject drugs
RAS	Resistance-associated substitutions
SVR	Sustained virologic response
WBC	White blood cell count

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26

Acute Kidney Injury

Mary K. Stamatakis

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Assess a patient's kidney function based on clinical presentation, laboratory results, and urinary indices.
2. Identify pharmacotherapeutic outcomes and endpoints of therapy in patients with acute kidney injury (AKI).
3. Apply knowledge of the pathophysiology of AKI to develop a treatment plan.
4. Develop strategies to minimize the occurrence of drug-induced AKI.
5. Monitor and evaluate the safety and effectiveness of the treatment plan.

INTRODUCTION

Acute kidney injury (AKI) is a potentially life-threatening syndrome that occurs primarily in hospitalized patients and frequently complicates the course of those who are critically ill. It is characterized by a rapid decrease in glomerular filtration rate (GFR) and the resultant accumulation of nitrogenous waste products (eg, creatinine), with or without a decrease in urine output. AKI often coexists with other clinical syndromes such as shock and sepsis.

KEY CONCEPT AKI is defined as an increase in serum creatinine (SCr) of at least 0.3 mg/dL (27 μmol/L) within 48 hours, a 50% increase in baseline SCr within 7 days, or a urine output of less than 0.5 mL/kg/h for at least 6 hours. Only one of the three criteria needs to be met for diagnosis of AKI.[1]

Kidney disease is being increasingly viewed as a continuum.[2] Once kidney disease persists longer than 90 days, patients have progressed to chronic kidney disease (CKD).[2]

EPIDEMIOLOGY

Approximately 7% to 18% of all hospitalized patients and more than half of critically ill patients develop AKI, and mortality increases with greater AKI severity.[2,3] Despite improvements in the medical care of individuals with AKI, in-hospital mortality is greater than 40% when AKI is not resolved.[4]

Community-acquired AKI occurs outside the hospital setting. Its incidence is 20 to 200 cases per 1 million population,[2] and it accounts for 1% to 4% of hospital admissions.[5]

ETIOLOGY AND PATHOPHYSIOLOGY

There are three categories of causes of AKI that share some pathophysiologic mechanisms: prerenal, intrinsic, and postrenal AKI. Specific syndromes within these categories have unique pathophysiologic features and treatment strategies.

Prerenal AKI

Prerenal AKI occurs in approximately 10% to 25% of patients with AKI. Renal hypoperfusion can occur secondary to systemic vasodilation or intravascular volume depletion due to conditions such as hemorrhage, dehydration, GI fluid losses, and fluid depletion related to major surgery. Early preventive measures, such as fluid resuscitation, can prevent progression and improve recovery because it can restore renal blood flow before structural kidney damage occurs.[4] Conditions of reduced cardiac output (eg, heart failure [HF], myocardial infarction) can decrease effective circulation or increase central venous pressure. Sepsis and liver disease can also reduce effective circulatory blood flow, resulting in decreased glomerular perfusion and prerenal AKI.[4]

Drugs may cause a functional AKI when they interfere with autoregulatory mechanisms in the glomerulus. This often occurs when the offending drugs are administered to patients dependent on autoregulation to maximize intraglomerular pressure (ie, dilation of afferent arterioles [arteries supplying blood to the glomerulus] or constriction of efferent arterioles [arteries removing blood from the glomerulus]). Nonsteroidal anti-inflammatory drugs (NSAIDs) interfere with prostaglandin-mediated dilation of afferent arterioles, resulting in decreased intraglomerular pressure.[6] Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) decrease intraglomerular pressure by inhibiting angiotensin II–mediated efferent arteriole vasoconstriction.[6] The calcineurin inhibitors cyclosporine and tacrolimus are potent renal vasoconstrictors, particularly in high doses. These drugs can reduce intraglomerular pressure in at-risk patients, with a resultant decrease in GFR. Prompt discontinuation of the offending drug can often return kidney function to normal.

Other causes of prerenal AKI are renovascular obstruction (eg, renal artery stenosis), hyperviscosity syndromes (eg, multiple myeloma), and systemic vasoconstriction (eg, hepatorenal syndrome).

Intrinsic AKI

Intrinsic renal failure is caused by diseases that can affect the nephron structure, such as the tubules, glomerulus, interstitium, or blood vessels. Acute tubular necrosis (ATN) is a term that is often used synonymously with intrinsic AKI but relates more specifically to necrosis of tubular epithelial cells resulting from nephrotoxins (eg, aminoglycosides, contrast agents, amphotericin B), sepsis, or ischemia. ATN accounts for 50% of all cases of AKI.[7] In addition, prerenal AKI can progress to intrinsic AKI if the underlying cause is not promptly corrected.

Glomerular, interstitial, and blood vessel diseases may also lead to intrinsic AKI but occur with a much lower incidence. Examples include glomerulonephritis, systemic lupus erythematosus, acute interstitial nephritis, and vasculitis.

Postrenal AKI

Postrenal AKI is due to obstruction of urinary outflow and increased intratubular pressure, impaired renal blood flow, and inflammation. Causes include benign prostatic hyperplasia, pelvic tumors, and precipitation of renal calculi.[7] Rapid resolution of postrenal AKI without structural kidney damage can occur depending on the severity of the obstruction and if the underlying obstruction is promptly corrected. Postrenal AKI accounts for less than 10% of AKI cases.

CLINICAL PRESENTATION AND DIAGNOSIS

The definition and categorization of AKI has evolved over the past decade. The most widely accepted AKI classification is from the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury (Table 26–1).[1] The KDIGO definition is based on either an increase in SCr or a decrease in urine output and includes 3 stages. Stage 1 includes either a 1.5 to 1.9 increase in SCr from baseline within 7 days or an absolute increase in SCr of 0.3 mg/dL (27 μmol/L) over 48 hours. Thus, even small increases in SCr indicate AKI, and this highlights the importance of early detection.

Decreased urine output may be a more sensitive marker than increased SCr in early AKI; however, urine output will not always be decreased. Oliguria and anuria are defined as daily urine outputs of less than 400 mL and 50 mL, respectively. Reduced urine output is associated with increased mortality and may represent a more severe form of AKI.

As kidney function declines, SCr and blood urea nitrogen (BUN) rise. Monitoring SCr and BUN and comparing them to baseline values can help determine if a patient's kidney function is worsening or improving. BUN is a less sensitive marker for evaluation of AKI than SCr. Urea is a product of amino acid metabolism; other conditions that can increase BUN are excessive protein intake and GI bleeding (because of blood breakdown to amino acids in the gut). Although urea is eliminated via glomerular filtration, it also undergoes significant reabsorption in the proximal tubules. Increased urea reabsorption occurs at lower urine flow rates, such as that which occurs in prerenal AKI, leading to increased BUN through enhanced reabsorption. In comparison, creatinine does not undergo reabsorption and is not affected by a low urine flow rate; thus, an increase in the ratio of BUN to Scr in the blood (> 20:1; when both are expressed in mg/dL) occurs in prerenal AKI because urea is preferentially reabsorbed compared to creatinine. A BUN:SCr ratio greater than 20 can assist in diagnosing prerenal AKI.

Some clinical and laboratory findings assist in the diagnosis of AKI, whereas others are used to differentiate between prerenal, intrinsic, and postrenal AKI. For example, patients with prerenal AKI typically demonstrate enhanced sodium reabsorption, which is reflected by a low urine sodium concentration and a low fractional excretion of sodium (FENa). The FENa is calculated by the following equation:

$$\text{Fractional excretion of sodium (FENa)} =$$

$$100 \times \frac{(\text{Urinary sodium concentration} \times \text{Plasma creatinine concentration})}{(\text{Plasma sodium concentration} \times \text{Urinary creatinine concentration})}$$

FENa is a measure of the percentage of sodium excreted by the kidney. Ordinarily, 1% to 2% of sodium intake is excreted by the kidneys. A FENa less than 1% may indicate prerenal AKI because it represents the response of the kidney to decreased renal perfusion by enhancing sodium reabsorption. Loop diuretics such as furosemide enhance sodium excretion and increase FENa and can limit the utility of this parameter in patients treated with loop diuretics.

Urine is typically more concentrated with prerenal AKI, and there is a higher urine osmolality and BUN-to-Scr ratio (> 20:1 for units of mg/dL) compared to intrinsic and postrenal AKI. Other factors, such as patient symptoms, laboratory test results, urinary indices, and results of diagnostic procedures, aid in the diagnosis and assessment of disease severity.

Early Detection of AKI

SCr lacks sensitivity in detecting AKI; thus, identifying novel biomarkers that identify stress and that are released within hours of injury would aid in early detection of AKI.[8] Nephrocheck is a commercially available point-of-care test for critically ill patients with cardiovascular or respiratory compromise that measures urine concentrations of insulin growth factor (IGF)-binding protein 7 and tissue inhibitor of metalloproteinase-2. The test identifies stress to the kidney and provides a positive risk score to indicate risk for moderate-to-severe kidney injury within 12 hours.[9] A positive score could trigger an early nephrology consult, avoidance of nephrotoxic medications, fluid resuscitation, and other therapies to prevent progression.

The furosemide stress test is being investigated to predict the development of Stage 3 AKI in early AKI. Initial studies have

Table 26–1

Staging System for AKI

Stage	Change in Serum Creatinine from Baseline		Urine Output	Need for Renal Replacement Therapy
1	0.3 mg/dL (27 μmol/L) or greater increase from baseline	150%–199% (1.5–1.9-fold)	Less than 0.5 mL/kg/hour for 6–12 hours	No
2	—	200%–299% (2–2.9-fold)	Less than 0.5 mL/kg/h for 12 hours or longer	No
3	Increase to 4 mg/dL (354 μmol/L) or greater	300% or greater (greater than 3-fold)	Less than 0.3 mL/kg/hour for 24 hours or anuria for > 12 hours	Initiation of renal replacement therapy indicates stage 3 regardless of serum creatinine or urine output

Based on the KDIGO staging system for AKI. Only one of the three criteria needs to be met to qualify for the higher stage.

found that a urine volume of less than 200 mL at 2 hours following a one-time furosemide dose of 1 mg/kg in furosemide-naïve patients or 1.5 mg/kg in patients with prior furosemide exposure is predictive of severe AKI.[10] Additional studies to validate the test, used alone and in combination with other biomarker tests, are needed to aid in the early detection of AKI.

Early alert systems in electronic health records that flag patients with an increase in SCr from baseline for nephrology consultation

Clinical Presentation and Diagnosis of AKI

Clinical presentation is variable depending on the etiology. A clinician must interpret kidney function in combination with the clinical picture. Listed below are symptoms and other findings that may occur in AKI. A clinical presentation that reflects volume depletion may occur with patients in prerenal AKI, while symptoms of volume overload may occur with intrinsic AKI.

Symptoms of AKI

Nonspecific

- Decreased urination
- Nausea, vomiting, diarrhea, anorexia
- Fatigue
- Pruritus

More specific

- Orange, concentrated urine (prerenal AKI)
- Weight loss (prerenal AKI)
- Brown urine (may indicate blood in the urine associated with acute glomerulonephritis)
- Weight gain (several pounds over a few days may indicate fluid retention)
- Shortness of breath (may indicate fluid retention)
- Anuria alternating with **polyuria** (postrenal AKI)
- Colicky abdominal pain radiating from flank to groin (postrenal AKI)

Physical Examination Findings

Nonspecific

- Change in mental status

More specific

- Hypotension or orthostatic hypotension (prerenal AKI)
- Rash (intrinsic AKI due to acute interstitial nephritis)
- Bladder distention (postrenal bladder outlet obstruction)
- Prostatic enlargement (postrenal AKI)

Findings suggesting fluid overload

- Increased blood pressure
- Peripheral edema
- Jugular venous distention (JVD)
- Pulmonary edema
- Crackles
- Asterixis
- Pericardial or pleural friction rub

Laboratory Tests

- Elevated SCr (reference range ~0.6–1.2 mg/dL [53–106 μmol/L])
- Elevated BUN (reference range ~8–25 mg/dL [2.9–8.9 mmol/L])
- BUN:SCr ratio greater than 20:1 for units of mg/dL (prerenal AKI); (100:1 for units of μmol/L)
- Hyperkalemia
- Metabolic acidosis

Urinalysis

- Sediment
- Scant or bland (prerenal or postrenal AKI)
- Brown, muddy granular casts (intrinsic ATN)
- Proteinuria (glomerulonephritis or allergic interstitial nephritis)
- Eosinophiluria (acute interstitial nephritis)
- Hematuria or red blood cell casts (glomerular disease or bleeding in urinary tract)
- WBCs or casts (acute interstitial nephritis or severe pyelonephritis)

Urinary Indices	Prerenal AKI	Intrinsic and Postrenal AKI
Urine osmolality (solute concentration in the urine in mOsm/kg or mmol/kg)	Greater than 500	Less than 350
Urine sodium concentration (mEq/L or mmol/L)	Less than 20	Greater than 40
Specific gravity	Greater than 1.020	Less than 1.015
Urine-to-plasma creatinine ratio	Greater than 40:1	Less than 20:1
Fractional excretion of sodium (FENa)	Less than 1%	Greater than 1%–2%

Diagnostic Procedures

- Urinary catheterization is performed to rule out urethral obstruction; increased urine output may occur if postrenal obstruction is present.
- Renal ultrasound can assist in differentiating AKI (normal-sized kidneys) from CKD (small kidneys). It can also show urinary tract obstruction and **hydronephrosis**, which indicates postrenal AKI.
- Computed tomography (CT) provides similar information as renal ultrasound but with greater spatial resolution. It assists in diagnosing masses, stones, and pyelonephritis.
- Magnetic resonance imaging (MRI) can be an alternative to CT scanning to avoid administering radiocontrast media.
- Renal angiography can be useful in identifying conditions such as renal artery stenosis and renal vein thrombosis.
- **Retrograde pyelography** is used to localize the site of urinary tract obstruction.
- Kidney biopsy may aid in the diagnosis of glomerular and interstitial diseases.

may also improve early detection of AKI and ultimately improve patient outcomes.[11]

TREATMENT

Desired Outcomes

A primary goal in caring for patients with AKI is ameliorating identifiable underlying causes of AKI such as hypovolemia, nephrotoxic drugs, or ureter obstruction. Prerenal and postrenal AKI can be reversed if the underlying problem is promptly identified and corrected, whereas treatment of intrinsic renal failure is primarily supportive until kidney function recovers. **KEY CONCEPT** There is no evidence that drug therapy hastens patient recovery, decreases length of hospitalization, or improves survival in intrinsic AKI.

Pharmacologic Therapy

▶ *Hydration in Patients with Hypovolemia*

Isotonic crystalloid solutions such as 0.9% normal saline and balanced crystalloid solutions (eg, Lactated Ringer's, Normosol-R, Plasma-Lyte A) are used to expand intravascular volume and return volume status to neutral fluid balance (euvolemia) in volume depleted patients.[12] Crystalloids are preferred over colloidal solutions (eg, albumin, hydroxyethyl starch) for fluid resuscitation.[12] Albumin is just as effective as crystalloids but is more costly. Hydroxyethyl starch has a risk for kidney injury, and the FDA issued a black box warning against its use in critically ill patients.

Crystalloid solutions vary in pH and chloride composition as indicated in Table 26–2.

The chloride concentration in normal saline is significantly higher than that of the plasma and can cause hyperchloremic metabolic acidosis. High chloride concentrations in the distal tubule may induce tubuloglomerular feedback, where the kidney interprets the distal tubule chloride load as an increase in GFR and responds by decreasing renal blood flow.

Normal saline may be associated with greater adverse effect on the kidney compared to the balanced crystalloid solutions. Normal saline was associated with a small, but significant, higher final SCr compared to a group that received balanced crystalloid solutions.[13] Although the cost of balanced crystalloid solutions is roughly double that of normal saline, evidence from these studies favor their use.

Caution must be taken with hydration because overzealous fluid resuscitation can result in pulmonary edema, increased postoperative complications, and ultimately, increased mortality.[14] Some evidence suggests that too much fluid can worsen AKI; thus, the goal of treatment is to return to a state of euvolemia or slightly negative fluid balance.[14] Blood transfusions may be indicated when there is acute blood loss.

In addition to fluids, vasopressors (ie, norepinephrine, dopamine, vasopressin) may be needed in patients with shock to restore adequate organ perfusion. There are no definitive data to support one agent as superior over another; however, more arrhythmic events have been reported with dopamine than with norepinephrine.[15]

Table 26–2

pH and Chloride Content of Various Replacement Fluids

Fluid	Chloride Content	pH
0.9% normal saline	154 mEq/L	5.5
Balanced electrolyte solution in water (eg, Plasma-Lyte A, Normosol-R)	98 mEq/L	7.4
Lactated Ringer's solution	109 mEq/L	6.5

▶ *Loop Diuretics in Patients with Volume Overload*

Most studies evaluating loop diuretics (eg, furosemide, bumetanide, torsemide, and ethacrynic acid) for preventing or treating AKI demonstrated improved urine output but no improvement in survival or need for dialysis.[16] There are some reports that loop diuretics may worsen kidney function and may be harmful if given for prevention of AKI. Thus, loop diuretics should be reserved for treating volume overload and should not be given to prevent AKI or hasten recovery of kidney function in euvolemic or hypovolemic individuals.[17]

Although bumetanide and torsemide are more potent than furosemide on a weight basis, all loop diuretics are equally effective in fluid removal when given in equipotent IV doses (40 mg furosemide = 10–20 mg torsemide = 1 mg bumetanide).

Patient Encounter Part 1

A 62-year-old man presents to the clinic with complaints of pain in the back of his left leg. In addition, he has increased dizziness and drowsiness and has "generally not been feeling well" over the past week. He has a past medical history of stage 2 chronic kidney disease (CKD) with proteinuria (baseline SCr 1.3 mg/dL [115 µmol/L]), hypertension, depression, and obesity. He reports that he has been trying to make lifestyle changes to better manage his medical problems, including dieting, vigorous walking to lose weight, and using a pill organizer to ensure he doesn't miss doses of his medications. He went to a walk-in urgent care medical clinic 1 week ago for left leg pain. He was diagnosed with Achilles tendonitis secondary to power walking. He received a boot to immobilize his left foot and was started on naproxen for pain and inflammation. Today, he states that his left foot feels better in the boot after wearing it for 7 days, but he has little energy, he has been going to the bathroom less often, and his urine is dark. His weight is usually 220 pounds (100 kg), and today he weighs 215 lb (97.5 kg). His blood pressure was 115/60 and heart rate was 118 beats per minute.

Current Medications:

Losartan 100 mg orally once daily
Furosemide 40 mg orally twice daily
Simvastatin 40 mg orally daily in the evening
Metformin 500 mg orally twice daily
Glyburide 5 mg orally daily
Metoprolol 25 mg orally twice daily
Paroxetine 20 mg orally daily
Naproxen 275 mg orally every 8 hours as needed for pain and inflammation

What information is suggestive of acute kidney injury (AKI)?

What risk factors does he have for developing AKI?

What additional laboratory information do you need to fully assess the patient?

What additional information would you elicit from him regarding his pharmacotherapy before creating a treatment plan?

Therefore, selection is based on the side-effect profile, cost, and pharmacokinetic differences. Ototoxicity is a well-established side effect of ethacrynic acid and limits its use; it occurs rarely with bumetanide and torsemide. The risk of ototoxicity with furosemide is significant when administered by the IV route at a rate exceeding 4 mg/min. Bioavailability is lower and more variable for furosemide compared to bumetanide and torsemide; therefore, the IV-to-oral ratio for furosemide is about 1:2.[18] Furosemide, bumetanide, and torsemide all contain a sulfa moiety; however, a previous sulfonamide antimicrobial allergy does not prohibit loop diuretic administration. In the rare instance of a sulfonamide-like allergic reaction to one of the commonly used loop diuretics, ethacrynic acid could be given because it does not contain a sulfa moiety.

Loop diuretics exert their effect from the luminal (urinary) side of the tubule. Decreased tubular secretion of loop diuretics occurs in kidney disease and reduces drug concentration at the active site in the tubule lumen. Therefore, large doses of loop diuretics are often necessary in kidney disease to ensure that adequate drug reaches the nephron lumen. Loop diuretics also have a ceiling effect where maximal **natriuresis** occurs.[19] Thus, very large doses of furosemide (eg, 1 g) are not necessary and may unnecessarily increase the risk of ototoxicity.

Several adaptive mechanisms by the kidney limit effectiveness of loop diuretic therapy. As the concentration of diuretic in the loop of Henle decreases, postdiuretic sodium retention can occur. This effect can be minimized by decreasing the dosage interval (ie, dosing more frequently) or by administering a continuous IV infusion.[18]

Prolonged administration of loop diuretics can lead to a second type of diuretic resistance. Hypertrophy of distal convoluted tubule cells can occur because of enhanced sodium delivery to the distal tubule.[19] Subsequently, increased sodium chloride absorption occurs in the distal tubule, which diminishes the effect of the loop diuretic on overall sodium excretion. Combining a distal convoluted tubule diuretic, such as metolazone or hydrochlorothiazide, with a loop diuretic can result in a synergistic increase in urine output. There are no data demonstrating greater efficacy of one distal convoluted tubule diuretic over another. It is common practice to administer these diuretics 30 to 60 minutes prior to the loop diuretic to inhibit sodium reabsorption at the distal convoluted tubule first. However, the effectiveness of this strategy has not been studied.

KEY CONCEPT Loop diuretics are the diuretics of choice for managing volume overload in AKI. The usual starting dose of IV furosemide for treatment of AKI ranges from 40 to 80 mg (Figure 26–1). Reasonable starting doses for bumetanide and torsemide are 1 and 20 mg, respectively.[19] Efficacy of diuretic administration can be determined by assessing a patient's hourly fluid balance. Other methods to minimize volume overload, such as fluid restriction and concentration of IV medications, should be initiated as needed. If urine output does not increase to about 1 mL/kg/hour, the diuretic dosage can be increased to a ceiling dose of 160 to 200 mg of furosemide or its equivalent (Figure 26–1). Dosing frequency is based on the patient's response, the ability to restrict sodium intake, and the duration of action of the diuretic. Methods to improve diuresis can be initiated sequentially, such as (a) shortening the dosing interval, (b) adding hydrochlorothiazide or metolazone, and (c) switching to a continuous infusion. Continuous infusion loop diuretics may be easier to titrate than bolus dosing, require less nursing administration time, and lead to fewer adverse reactions. The hemodynamic and fluid status of the patient should be monitored closely when loop diuretics are administered in high doses or with a continuous infusion, particularly in combination with distal convoluted tubule diuretics. Additionally, the electrolyte status of the patient should be monitored at least daily to prevent profound diuresis and electrolyte abnormalities, such as hypokalemia.

▶ *Other Agents*

Thiazide diuretics, when used as single agents, are generally not effective for fluid removal in patients with AKI. Mannitol is also not recommended for treating volume overload associated with AKI. In patients with renal dysfunction, mannitol excretion is decreased, resulting in expanded blood volume and hyperosmolality. Potassium-sparing diuretics, which inhibit sodium reabsorption in the distal nephron and collecting duct, are not sufficiently effective in removing fluid. In addition, they increase the risk of hyperkalemia in patients already at risk.

Low-dose dopamine, in doses ranging from 0.5 to 3 mcg/kg/min, predominantly stimulates dopamine-1 receptors, leading to renal vasodilation and increased renal blood flow. Although this effect has been substantiated in healthy euvolemic individuals with normal kidney function, there are no conclusive efficacy data in patients with AKI. Thus, it is not indicated for treatment of AKI. Fenoldopam, a selective dopamine-1 receptor agonist, lacks convincing data to support its use and it is not recommended for prevention or treatment of AKI.[1]

Nonpharmacologic Treatment

▶ *Renal Replacement Therapy*

RRT may be necessary in patients with established AKI to treat pulmonary edema and volume overload that is unresponsive to diuretics, minimize accumulation of nitrogenous waste products, and correct electrolyte and acid–base abnormalities (eg, hyperkalemia, metabolic acidosis) while renal function recovers. There is wide variation in practice on indications for RRT, timing of initiation and discontinuation of RRT, intensity of treatment, and optimal type of RRT. Common criteria include:

- Anuria or severe oliguria
- Potassium greater than 6.5 mEq/L (mmol/L)
- Metabolic acidosis with a pH less than 7.2
- Pronounced elevations in BUN and SCr
- Symptoms of uremia
- Diuretic-resistant fluid overload.[20]

Approximately 10% to 30% of patients with AKI treated with RRT will not have recovery of kidney function and will need to remain on long-term dialysis.[21]

Two types of RRT modalities are used in AKI: intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT). IHD is a higher efficiency form of dialysis that results in fluid removal by ultrafiltration and solute removal by diffusion that is provided for several hours a day at a variable frequency (usually daily or three to five times per week). CRRT is a form of dialysis that provides slow fluid and/or solute removal on a continuous (up to 24 hours) basis. The characteristics of the different types of CRRTs and their associated fluid and solute removal are described In Table 26–3.

The primary advantage of CRRT is hemodynamic stability and better volume control, particularly in patients who are unable to tolerate rapid fluid removal. The primary disadvantages of CRRT are continuous nursing requirements, the potential need for continuous anticoagulation, frequent clotting of the dialyzer, patient immobility, and increased cost. There is no conclusive evidence

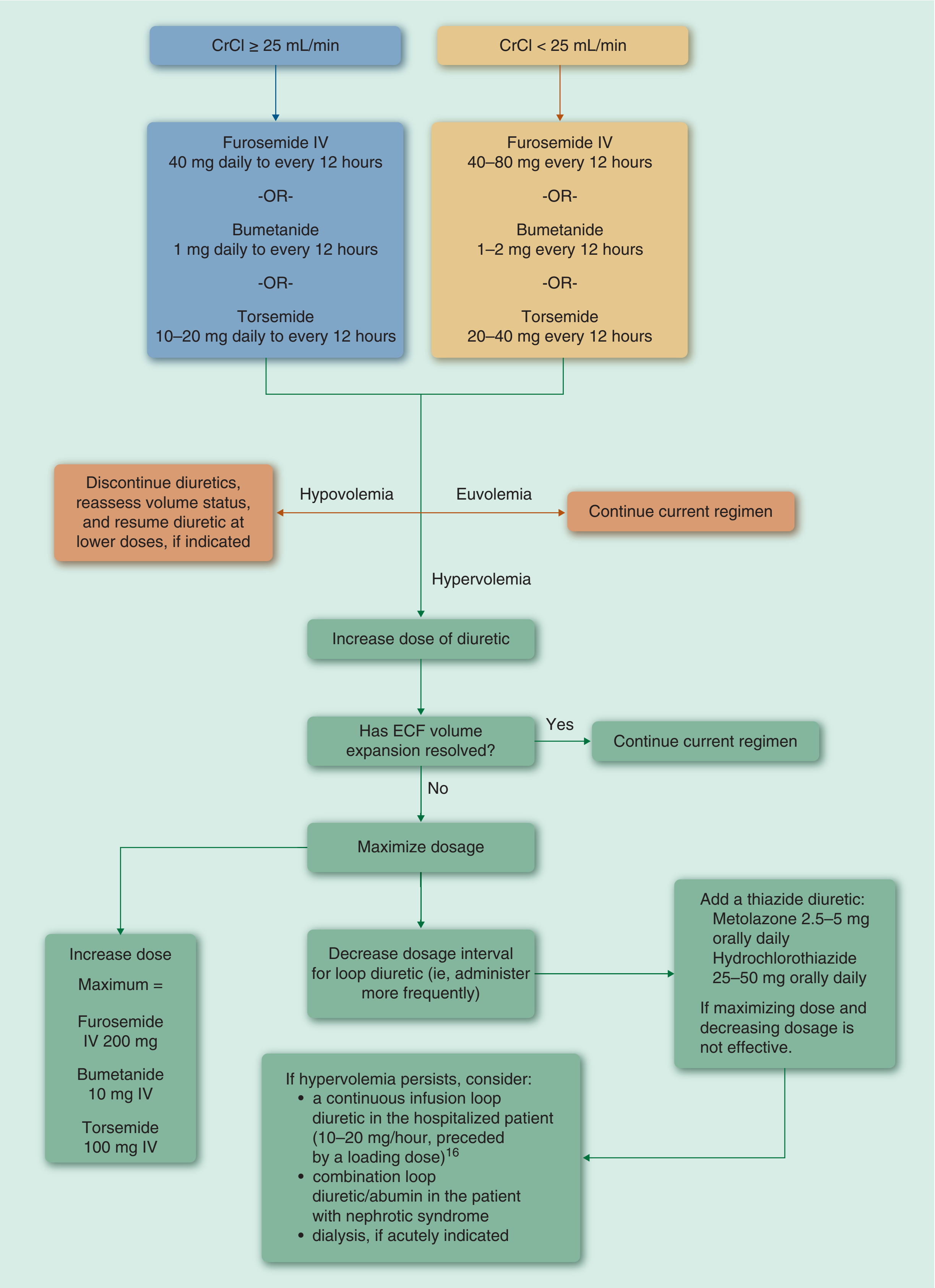
CrCl ≥ 25 mL/min
CrCl < 25 mL/min
Furosemide IV
40 mg daily to every 12 hours
-OR-
Bumetanide
1 mg daily to every 12 hours
-OR-
Torsemide
10–20 mg daily to every 12 hours
Furosemide IV
40–80 mg every 12 hours
-OR-
Bumetanide
1–2 mg every 12 hours
-OR-
Torsemide
20–40 mg every 12 hours
Discontinue diuretics, reassess volume status, and resume diuretic at lower doses, if indicated
Hypovolemia
Euvolemia
Continue current regimen
Hypervolemia
Increase dose of diuretic
Has ECF volume expansion resolved?
Yes
Continue current regimen
No
Maximize dosage
Increase dose
Maximum =
Furosemide IV 200 mg
Bumetanide 10 mg IV
Torsemide 100 mg IV
Decrease dosage interval for loop diuretic (ie, administer more frequently)
Add a thiazide diuretic:
Metolazone 2.5–5 mg orally daily
Hydrochlorothiazide 25–50 mg orally daily
If maximizing dose and decreasing dosage is not effective.
If hypervolemia persists, consider:
• a continuous infusion loop diuretic in the hospitalized patient (10–20 mg/hour, preceded by a loading dose)16
• combination loop diuretic/abumin in the patient with nephrotic syndrome
• dialysis, if acutely indicated

FIGURE 26–1. Algorithm for treatment of extracellular fluid expansion. (CrCl, creatinine clearance; ECF, extracellular fluid; HCTZ, hydrochlorothiazide; po, oral.)

Table 26–3

Modalities for Continuous Renal Replacement Therapy

		Technique		Process of Solute Removal		
Type of CRRT	Abbreviation	Filtration	Dialysis	Convection	Diffusion	Description
Slow **C**ontinuous **U**ltra**f**iltration	SCUF	√		√ (limited)		Low rate of fluid removal without significant solute removal.
Continuous **V**eno**v**enous **H**emofiltration	CVsH	√		√		Higher rate of fluid removal and solute removal (small and large molecule).
Continuous **V**eno**v**enous **H**emo**d**ialysis	CVsHD		√		√	Diffusive removal of solutes (small molecule) with limited fluid removal.
Continuous **V**eno**v**enous **H**emo**d**ia**f**iltration	CVsHDF	√	√	√	√	Fluid removal and removal of solutes (small and large molecule) via diffusion (dialysis).

that one type of dialysis is preferred over another in terms of mortality and recovery of renal function. Thus, selection of dialysis type is often governed by the critical illness of the patient and by the comfort level of the institution with one type of dialysis. KDIGO Clinical Practice Guidelines suggest CRRT in hemodynamically unstable patients.[1] Mortality in critically ill patients receiving CRRT is 44% to 65%.[22]

▶ *Supportive Therapy*

Supportive therapy in AKI includes adequate nutrition, correction of electrolyte and acid–base abnormalities (particularly hyperkalemia and metabolic acidosis), fluid management, and correction of any hematologic abnormalities. Because AKI can be associated with multiorgan failure, treatment may include medical management of infections, cardiovascular and GI conditions, and respiratory failure. See Table 26–4 for treatment of electrolyte abnormalities in AKI.

Historically, patients were often placed on a protein-restricted diet to avoid the production of uremic toxins and minimize the rise in BUN. However, adequate protein intake should be administered to maintain metabolic balance. Protein intake of 0.8 to 1 g/kg/day is recommended in patients with AKI who are not undergoing dialysis, and higher protein intake in patients undergoing RRT or who are hypercatabolic.[1] Some studies have shown

Patient Encounter Part 2: Medical History and Physical Examination

PMH: Type 2 diabetes mellitus for 15 years (labs from 3 months ago: A1C 7.7% [0.077; 61 mmol/mol Hb], SCr 1.3 mg/dL [115 μmol/L])

Dyslipidemia for 10 years

Hypertension for 20 years

Depression for 5 years

Obesity

FH: Father with history of type 2 diabetes and CKD; mother with history of hypertension

SH: No smoking, no alcohol use

PE:

VS: BP 115/60 mm Hg, pulse 118 bpm, RR 15/min, temperature 99.5°F (37.5°C), weight 97.5 kg (215 lb), ht 5′11″ (180 cm)

Chest: lungs clear to auscultation and percussion

CV: RRR, S_1 and S_2, normal

MS/Ext: Achilles tendon swollen and red 6 cm from its insertion on to the back of the heel bone

Urinalysis: Color, dark yellow; character, cloudy; glucose (–); ketones (–); specific gravity 1.022; pH 5; (+) protein; no bacteria; nitrite (–); blood (–); osmolality 525 mOsm/kg (mmol/kg); urinary sodium 15 mEq/L (mmol/L); creatinine 86 mg/dL (7602 μmol/L)

Laboratory values: Sodium 137 mEq/L (mmol/L), potassium 5.1 mEq/L (mmol/L), chloride 104 mEq/L (mmol/L), bicarbonate 21 mEq/L (mmol/L), BUN 47 mg/dL (16.8 mmol/L), SCr 1.9 mg/dL (168 μmol/L), magnesium 1.6 mg/dL (0.66 mmol/L), glucose 118 mg/dL (6.5 mmol/L), WBC 7.9 × 10^3/mm^3 (7.9 × 10^9/L), hemoglobin 14.3 g/dL (143 g/L; 8.88 mmol/L), hematocrit 41.5% (0.42).

Interview information: Patient takes all his medications as prescribed. He has been taking them for years, except for naproxen. He started taking it for Achilles tendonitis 8 days ago and has been taking it around the clock. He says it upsets his stomach, and he feels he has not been eating and drinking as much in the past week. He has also vomited on several occasions. He states he has been taking it on an empty stomach. He checks his fasting glucose each morning, and it ranges from 110 to 125 mg/dL (6.1–6.9 mmol/L). He also checks it in the afternoon, and it runs low 4 to 5 times per week (in the range of 60–70 mg/dL [3.3–3.9 mmol/L]). He checks his blood pressure several times a week and it is usually in the range of 140 to 150/80 to 90 mm Hg.

Given this additional information, what is your assessment of the patient's condition?

Identify your treatment goals for the patient.

Table 26–4

Treatment of Electrolyte Abnormalities in AKI

Hyperkalemia	• Restrict dietary potassium intake. • Discontinue potassium-sparing diuretics, ACE inhibitors, ARBs, NSAIDs. • Loop diuretics to promote urinary potassium loss. • Potassium binding ion-exchange resin (sodium polystyrene sulfonate, sodium zirconium cyclosilicate, patiromer) for non–life-threatening treatment. • Insulin (10 units regular) and glucose (50 mL of 50% dextrose) to promote entry of potassium intracellularly. • Inhaled beta-agonists therapy to promote entry of potassium intracellularly. • Calcium gluconate or calcium chloride (1 g) to stabilize the myocardium. • Renal replacement therapy.
Metabolic Acidosis	• Sodium bicarbonate (if pH < 7.2 to keep serum bicarbonate > 15 mEq/L [mmol/L]). • Renal replacement therapy.
Hyperphosphatemia	• Restrict dietary phosphate intake. • Phosphate binding agents (calcium acetate, sevelamer hydrochloride—taken with meals).
Hypocalcemia	• Calcium carbonate or calcium gluconate if symptomatic.
Hypermagnesemia	• Discontinue magnesium-containing antacids.

Adapted with permission Walker SS, Benventre JV. Acute kidney injury. In: Jameson JL, Fauci AS, Casper DL, et al., eds. Harrison's Principles of Internal Medicine, 20th ed. [Internet]. New York, NY: McGraw-Hill Medical; 2018 [cited 2020 Nov 17]. [about 1 p.]. Available from: https://accesspharmacy.mhmedical.com/ViewLarge.aspx?figid=196776812&gbosContainerID=0&gbosid=0&groupID=0&sectionId=186950567

a beneficial effect of tight glycemic control in decreasing the incidence and severity of AKI, whereas others have shown a higher incidence of hypoglycemia. Thus, glycemic control in the range of 110 to 149 mg/dL (6.1–8.3 mmol/L) is recommended.[1]

PREVENTION OF ACUTE KIDNEY INJURY

KEY CONCEPT It is critically important to identify patients at high risk for developing AKI and to implement preventive methods to decrease its occurrence or severity.

Avoidance of Nephrotoxic Medications

The best preventive measure for AKI, especially in high-risk individuals, is to avoid medications known to precipitate AKI. Drug therapy may contribute to AKI in about 20% of cases.[20] Nephrotoxicity is a significant side effect of aminoglycosides, ACE inhibitors, ARBs, amphotericin B, NSAIDs, calcineurin inhibitors, and radiographic contrast agents.[20] It is also reported with cisplatin, carboplatin, antiviral agents (acyclovir, foscarnet, tenofovir, indinavir), and vancomycin (particularly when combined with piperacillin-tazobactam).[6,23] Unfortunately, an effective, nonnephrotoxic alternative may not always be appropriate for a given patient, and the risks and benefits of selecting a drug with nephrotoxic potential must be considered. For example, serious gram-negative infections may require double antibiotic coverage, and an aminoglycoside may be necessary based on culture and sensitivity reports. Monitoring of serum aminoglycoside concentrations is warranted in these situations.

▶ *Drug-Induced AKI*

Aminoglycosides Aminoglycosides (gentamicin, tobramycin, and amikacin) cause nonoliguric intrinsic AKI in about 10% to 25% of treated patients.[6] Injury is due to binding of positively charged aminoglycoside molecules to negatively charged phospholipids in proximal tubular epithelial cells within the renal cortex, cellular uptake with formation of reactive oxygen species, and alterations in cell membrane transporters and cell death.[24] Gentamicin, tobramycin, and amikacin have comparable nephrotoxicity; thus, similar precautions should be used for all of the agents. Risk factors for aminoglycoside-induced AKI include high cumulative drug exposure, prolonged course of therapy (typically after 7–10 days), preexisting CKD, increased age, and concurrent administration of other nephrotoxic drugs. There is conflicting evidence as to whether the combination of vancomycin and an aminoglycoside increases the risk of AKI compared to aminoglycoside therapy alone.[23] Individualized pharmacokinetic monitoring to achieve specific serum concentrations or alternative antibiotics should be selected in individuals at high risk for developing AKI.

Traditional aminoglycoside dosing entails a loading dose followed by multiple daily doses (eg, gentamicin 1–2.5 mg/kg IV every 8 hours). Methods to minimize drug exposure with traditional dosing include maintaining trough concentrations less than 2 mcg/mL (mg/L; 4.2 µmol/L) for gentamicin and tobramycin and less than 10 mcg/mL (mg/L; 17.1 µmol/L) for amikacin, minimizing length of therapy, avoiding repeated courses of aminoglycosides, and minimizing concurrent exposure to other nephrotoxic medications. Renal recovery occurs in about half of patients.[25]

The principle behind extended-interval aminoglycoside administration (eg, gentamicin 5–7 mg/kg IV every 24 hours) is that large doses are given less frequently, which provides both high peak concentrations of drug that saturate proximal tubule uptake sites and a drug-free period. Once saturated, the remaining aminoglycoside molecules pass through the proximal tubule and are excreted in the urine. Thus, less drug is available for cellular uptake during a 24-hour period. Aminoglycosides also demonstrate concentration-dependent bactericidal activity, with optimal activity when the peak drug concentration is 8 to 10 times greater than the MIC.[26] Bacterial growth is also suppressed after concentrations decrease below the MIC due to its postantibiotic effect. Thus, extended-interval aminoglycoside dosing can maximize efficacy while minimizing nephrotoxicity. Extended-interval aminoglycoside dosing is as effective or superior to conventional dosing and is not more nephrotoxic; some studies have shown it to be less nephrotoxic. Extended-interval dosing is not recommended for patients with preexisting kidney disease (CrCl $<$ 20 mL/min [0.33 mL/s]), conditions where high concentrations are not needed (eg, urinary tract infections), hyperdynamic patients who may demonstrate increased drug clearance (eg, burn patients), gram-positive infections where aminoglycoside is used for synergy, suspected altered pharmacokinetics (eg, morbid obesity, significant liver disease, pregnancy), or increased risk of ototoxicity.

Amphotericin B The reported incidence of amphotericin B–induced AKI varies widely in the literature, ranging from 12% to 53% with the conventional desoxycholate formulation.[27] Nephrotoxicity is due to renal arterial vasoconstriction and renal tubule cell damage. Risk factors for development of AKI include high daily dosage, large cumulative dose ($>$ 2–3 g), preexisting kidney dysfunction, dehydration, and concomitant use of other nephrotoxic drugs. Tubular abnormalities manifesting as hypomagnesemia and hypokalemia often occur within the first 2 weeks of treatment, followed by overt development of AKI.

Three lipid-based formulations of amphotericin B have been developed in an attempt to improve efficacy and limit toxicity, particularly nephrotoxicity: (a) amphotericin B lipid complex, (b) liposomal amphotericin B, and (c) amphotericin B cholesteryl sulfate (no longer available in the United States). These formulations have a significantly lower incidence of nephrotoxicity compared to the conventional formulation.[27,28] The mechanism for decreased nephrotoxicity is thought to be due to preferential delivery of amphotericin B to the site of infection, with less affinity for cells in the kidney.[27] Costs for lipid-based formulations are significantly higher than for the conventional formulation; thus, lipid-based formulations are typically recommended for individuals with risk factors for AKI. Administration of IV normal saline (1 L during therapy) may also attenuate nephrotoxicity associated with amphotericin B.

It is unclear whether there are significant differences in nephrotoxicity among the lipid-based formulations. No differences in incidence of nephrotoxicity or other endpoints of therapy, such as new-onset dialysis, length of hospital stay, or mortality have been identified.[27,29] However, large prospective studies are needed to definitively ascertain differences in nephrotoxicity among liposomal formulations.

Radiocontrast Agents Radiocontrast agents are administered during radiologic studies and are associated with a risk of contrast-induced AKI (CI-AKI). Although definitions vary, CI-AKI is frequently defined as a rise in SCr of at least 0.5 mg/dL (44 μmol/L) or a 25% increase in SCr within 48 hours of contrast administration. More recent studies suggest that the incidence may be lower than earlier reports, and that the term "postcontrast AKI" may be more indicative when it is not clear that the nephropathy is due to the contrast agent.[30] Patient-related risk factors are CKD, diabetes, dehydration, older age, concomitant nephrotoxic drug administration, and high doses of contrast dye.[31]

Contrast agents are water-soluble, triiodinated, benzoic acid salts. Nephrotoxicity results from both ischemia and direct proximal tubule toxicity, with a resultant decrease in GFR and increased SCr within 24 to 48 hours of the damage.[32] The incidence of nephrotoxicity with ionic and nonionic agents is similar in patients at low risk for developing AKI; however, in high-risk patients, nephrotoxicity is significantly greater when high ionic, high osmolar contrast agents are used. The cost of nonionic agents is approximately 10-fold higher, and their use is usually limited to high risk patients.

Therapeutic measures to decrease the incidence of CI-AKI include extracellular volume expansion with isotonic solution, judicious use of contrast media, and use of nonionic contrast agents in high-risk patients. Treatment with oral acetylcysteine has produced mixed results. Theophylline, fenoldopam, furosemide, mannitol, dopamine, statins, vitamins C and E, and calcium antagonists have been studied but with no strong evidence that they prevent CI-AKI.[31,33]

KEY CONCEPT The most effective therapeutic maneuver to decrease the incidence of CI-AKI is extracellular volume expansion with an isotonic solution.[33] Hydration with normal saline or sodium bicarbonate is recommended.[34] Sodium bicarbonate may have the theoretical benefit of alkalinizing renal tubule fluid, which is thought to reduce the formation of oxygen free radicals. However, a large, multicenter trial found no benefit of sodium bicarbonate compared to sodium chloride, or a benefit of oral acetylcysteine over placebo at 90 days for a decrease in kidney function, need for dialysis, or death.[35] The KDIGO Clinical Practice Guidelines workgroup recommends either agent until more definitive data are available.[1] The infusion should begin from 3 to 12 hours before the procedure and continue for 6 to 12 hours afterward to achieve a urine flow rate of at least 150 mL/hour.[1] Fluid should be administered cautiously to patients with HF, left ventricular dysfunction, and significant renal dysfunction.

Because production of reactive oxygen species has been implicated in the pathophysiology of contrast-induced AKI, prophylactic administration of the antioxidant acetylcysteine has been investigated, usually in combination with hydration. Acetylcysteine doses in clinical studies ranged from 600 to 1200 mg orally every 12 hours for 2 days, with the first one or two doses administered prior to the contrast procedure. Many studies have evaluated the efficacy of oral acetylcysteine with mixed results.[36,37] The KDIGO Clinical Practice Guidelines suggest that oral acetylcysteine can be used in combination with IV fluids in patients at risk for CI-AKI due to its low risk of adverse effects and low cost.[1] However, other organizations, such as the American College of Cardiology, do not advocate its routine use.

Cyclosporine and Tacrolimus The calcineurin inhibitors cyclosporine and tacrolimus are administered as part of immunosuppressive regimens in solid organ and bone marrow transplant recipients. They are also used in autoimmune disorders such as psoriasis and multiple sclerosis. The pathophysiologic mechanism for AKI is renal afferent arteriole vasoconstriction and ATN.[38,39] AKI often occurs within the first 6 to 12 months of treatment and can be reversible with dose reduction or drug discontinuation.[38] Risk factors include high dose, elevated trough blood concentrations, increased age, and concomitant therapy with other nephrotoxic drugs.[39] Cyclosporine and tacrolimus are extensively metabolized by the liver through the cytochrome P450 3A pathway; drugs that inhibit their metabolism (eg, erythromycin, clarithromycin, fluconazole, ketoconazole, verapamil, diltiazem, nicardipine) can increase blood concentrations of cyclosporine and tacrolimus and precipitate AKI. Pharmacogenetic variability in drug absorption and metabolism can also alter blood concentrations.

Careful monitoring of cyclosporine or tacrolimus trough concentrations and maintaining them in the target range can reduce the occurrence of AKI; however, AKI can still occur with therapeutic or even low blood concentrations. Calcium channel blockers may have a renoprotective effect through dilation of afferent arterioles and are often used preferentially as antihypertensive agents in kidney transplant recipients.[40] However, the calcineurin inhibitor dose would need to be reduced to avoid high blood concentrations because of reduced metabolism.

It is often difficult to differentiate AKI from acute organ rejection in kidney transplant recipients, because the conditions may present with similar symptoms and physical examination findings. However, fever and graft tenderness are more likely to occur with rejection, whereas neurotoxicity is more likely to occur with cyclosporine or tacrolimus toxicity. Kidney biopsy is often needed to confirm the diagnosis of rejection.

ACE Inhibitors and ARBs In instances of decreased renal blood flow (eg, kidney disease, renal artery stenosis, HF, volume depletion), production of angiotensin II increases, causing efferent arteriole vasoconstriction and maintenance of glomerular capillary pressure and GFR. However, ACE inhibitors decrease angiotensin II synthesis, and ARBs block the action of angiotensin II at the receptor, which results in dilation of efferent arterioles, a reduction in glomerular capillary pressure, and decreased GFR.[6]

When initiating therapy with an ACE inhibitor or ARB for management of hypertension or prevention of CKD progression, a modest increase in SCr should be anticipated within the first week of starting therapy.[41] However, an increase of greater than 30% in patients with SCr concentrations greater than 1.4 mg/dL (124 μmol/L) and that does not plateau after several weeks of therapy suggests AKI, and the drug should be discontinued.[41] Risk factors for developing AKI are preexisting renal dysfunction, severe atherosclerotic renal artery stenosis, volume depletion, and severe HF. Discontinuation of the drug usually results in return to baseline kidney function. Initiating therapy with low doses of a short-acting agent such as captopril is recommended for patients at risk of developing AKI. If tolerated, patients can later be converted to a longer-acting agent.

Nonsteroidal Anti-inflammatory Drugs Traditional nonselective NSAIDs (eg, ibuprofen, naproxen, sulindac) and the cyclooxygenase-2 (COX-2) selective inhibitor celecoxib can cause prerenal AKI through inhibition of prostaglandin-mediated renal vasodilation.[6] Risk factors are similar to those for ACE inhibitors and ARBs. Concurrent use of NSAIDS in patients on diuretics and ACE inhibitors or ARBs results in increased risk of AKI, particularly within the first 30 days of coadministration.[42]

The onset of AKI is often within days of initiating therapy, and patients typically present with oliguria, which is usually reversible with drug discontinuation. COX-2 selective inhibitors and traditional nonselective NSAIDs pose similar risk for AKI.

Drug-induced Acute Interstitial Nephritis Unexplained AKI with a temporal relationship to new drug therapy may be due to acute interstitial nephritis. A variety of drugs have been implicated, most commonly penicillin and cephalosporin antibiotics, NSAIDs, and proton pump inhibitors. Less than 10% of patients will present with nonrenal symptoms such as rash, fever, and eosinophilia, making the diagnosis difficult.[43] A kidney biopsy may aid in the diagnosis. Primary treatment is discontinuation of the offending drug. In addition, limited evidence suggests that early treatment with corticosteroids may hasten recovery.[43] However, this is supported primarily with case reports and nonrandomized studies. Potential benefits of corticosteroids must be weighed against risks, such as hyperglycemia in patients with diabetes or an increased risk of infection.

OUTCOME EVALUATION

Goals of therapy are to maintain a state of euvolemia with good urine output (at least 0.5–1 mL/kg/hour), to return SCr to baseline, and to correct electrolyte and acid-base abnormalities. Additional goals include appropriate drug dosages based on kidney function and avoidance of nephrotoxic drugs. Assess vital signs, weight, fluid intake, urine output, BUN, creatinine, and electrolytes daily in unstable patients.

Patient Encounter Part 3: Follow-Up

The patient is admitted to the hospital for treatment of AKI.

Based on the information available, create a care plan for this patient's AKI and provide overall recommendations for his drug therapy. The plan should include (a) a statement of the drug related needs and/or problems, (b) a patient-specific detailed therapeutic plan, and (c) monitoring parameters to assess efficacy and safety.

In patients with volume overload, monitoring includes body weight changes, fluid input compared to urine output, signs of pulmonary and peripheral edema, and blood pressure.

DRUG DOSING CONSIDERATIONS IN AKI

Assessment of Kidney Function

Appropriate drug dosing in kidney disease requires an accurate assessment of kidney function. The best index of overall kidney function is GFR. Defined as the volume of plasma filtered across the glomerulus per unit time, GFR correlates with the excretory, endocrine, and metabolic functions of the kidney. The CrCl is routinely used as a measure of kidney function for purposes of drug dosing; however, equations to estimate CrCl (eg, Cockcroft–Gault equation) are not accurate or reliable in AKI, particularly in critically ill patients because they tend to overestimate CrCl.[44,45] Use of such equations should be limited to instances when SCr is at steady state, with no more than a 10% to 15% change in SCr within 24 hours. Measurement of 24-hour urinary creatinine clearance may be more accurate and is calculated by the following formula:

$$\text{Measured CrCl (mL/min)} = \frac{[\text{Urine creatinine concentration (mg/dL)} \times \text{urine volume (mL)}]}{[\text{Plasma creatinine concentration (mg/dL)} \times \text{time (minutes)}]}$$

or

$$\text{Measured CrCl (mL/s)} = \frac{[\text{Urine creatinine concentration } (\mu\text{mol/dL}) \times \text{urine volume (mL)}]}{[\text{Plasma creatinine concentration } (\mu\text{mol/dL}) \times \text{time (seconds)}]}$$

As part of kidney function test results, many laboratories report an estimated GFR (eGFR), typically calculated from the Modification of Diet in Renal Disease Study (MDRD) equation. However, the equation has not been validated in AKI. This estimation is not accurate in AKI because non–steady-state conditions for SCr are present, leading to inaccurate estimates.

Factors Influencing Drug Dosing in AKI

Determining the optimal dose of drugs in AKI is challenging. A variety of factors influence drug dosing, such as (a) alterations in drug pharmacokinetics that occur during AKI, (b) difficulties in accurately quantifying kidney function in AKI, (c) the influence of intermittent or continuous RRT on drug clearance, and (d) challenges in interpreting information from the literature and applying it to a specific patient. See Table 26–5 for a more complete list of considerations when dosing medications in patients with AKI.

For drugs with a narrow therapeutic window, serum drug concentration monitoring may be available to guide drug dosing. If this is not available, dosing based on an eGFR is recommended, with frequent reassessment of kidney function and evaluation of the patient's status to assess efficacy and adverse effects of therapy. Selection of a drug with hepatic elimination rather than renal excretion is a reasonable alternative, if possible.

In critically ill septic patients, interpatient variability in pharmacokinetics renders dosing of antibiotics difficult. Underdosing a critically ill patient may be a greater risk than potential adverse effects attributed to higher plasma concentrations, particularly with antibiotics such as beta lactams, quinolones, and carbapenems, for which therapeutic drug monitoring is not available.[46] Thus, the risk of undertreatment of the infection needs to be balanced with the risk of adverse effects from the antimicrobial agent.

Table 26–5

Drug Dosing Considerations in AKI

Alteration in drug pharmacokinetics	• Increase in volume of distribution due to fluid retention may occur. • Reduction in excretion of both drugs and metabolites eliminated by the kidney. • Nonrenal clearance of some drugs may be reduced.
Difficulty in quantifying an accurate assessment of kidney function in AKI	• Cockcroft–Gault and MDRD equations are not meant for AKI population; equations are based on a single SCr. • SCr as a marker for kidney function is influenced by nonrenal factors (such as nutritional status and liver function). • Equations to estimate kidney function in cases of changing kidney function have not been well studied.
AKI patients undergoing dialysis	• Different types of dialysis modalities result in differences in drug removal (eg, IHD vs. CRRT). • Differences in intensity of dialysis dose may affect drug removal (eg, length of dialysis treatment, blood, and dialysate flow rate). • Populations studied in the literature are likely to be different than the specific patient being treated (eg, different types of dialysis, length of treatment).
Textbook dosing and literature recommendations	• Studies in patients with AKI are sparse. • Many drug information resource recommendations on dosing are based on the manufacturer's original pharmacokinetics information, often in patients with chronic kidney disease. • Most drug dosing guidelines were developed prior to standardization of SCr measurements between labs; thus, today's SCr measurements are 5% to 10% higher than those reported prior to 2010.[48] • There is growing support for incorporating the MDRD equation in future pharmacokinetic studies and to guide drug dosing, although use of this equation is limited to chronic kidney disease.

MDRD, Modification of Diet in Renal Disease equation; SCr, serum creatinine.

DRUG DOSING CONSIDERATIONS IN DIALYSIS

Several characteristics of a drug influence its removal during dialysis: percentage of drug eliminated by the kidney, volume of distribution, and protein binding. Drug elimination is greater when renal clearance accounts for 30% or more of total body clearance of the drug, volume of distribution is less than 1 L/kg, and protein binding is less than 50%.[47] Other factors that affect drug clearance include type of RRT (ie, IHD, CVVH, CVVHD); permeability of

The Patient Care Process

Collect Information:

- Perform a thorough and accurate drug history including use of nonprescription drugs that may affect kidney function, such as NSAIDs.

Assess the Information:

- Assess kidney function by evaluating a patient's signs and symptoms, physical exam findings, laboratory test results (eg, SCr, BUN, electrolytes), and urinary indices; CrCl, if possible.
- Assess whether current medications may be contributing to AKI. Consider not only drugs that can directly cause AKI (eg, aminoglycosides, amphotericin B, NSAIDs, cyclosporine, tacrolimus, ACE inhibitors, ARBs) but also drugs that can predispose a patient to nephrotoxicity or prerenal AKI (ie, diuretics and antihypertensive agents). The risk of AKI increases when potential nephrotoxic medications are not discontinued.[49]
- Based on physical exam and review of systems, determine whether the patient is experiencing hypervolemia or hypovolemia.

Develop a Care Plan:

- Determine if any drugs should be discontinued, or alternative drugs selected, to prevent worsening of kidney function based on kidney function assessment.
- Determine if any drugs undergo significant kidney elimination and require dosage reduction or specific monitoring during AKI.
- Determine if additional therapy is warranted. For example, determine if a patient should receive hydration (for volume depletion) or a loop diuretic (for volume overload).

Implement the Care Plan:

- Adjust drug dosages based on estimated kidney function or evidence of adverse drug reactions or interactions.
- Provide supportive therapy, including adequate nutrition, correction of electrolyte and acid–base abnormalities (particularly hyperkalemia and metabolic acidosis), fluid management, and correction of hematologic abnormalities.
- Implement preventative strategies to decrease the risk of AKI, such as administration of normal saline when contrast media are administered.
- Educate the patient and/or caregiver about changes in drug therapy, potential adverse effects related to new medications, and how to manage them if they occur.

Follow-up: Monitor and Evaluate:

- Monitor the patient's weight, urine output, electrolytes (such as potassium), and blood pressure to assess efficacy of the medication regimen.
- Monitor SCr to evaluate whether kidney function is worsening or improving.
- Review and encourage medication adherence.

the dialysis membrane; and blood, ultrafiltrate, and dialysate flow rates. Higher permeable filters result in greater drug elimination than lower permeable membranes, particularly for middle molecular weight drugs, such as vancomycin, that can pass through the pores of higher permeable filters.[48] Supplemental doses postdialysis may be indicated when significant drug is removed during dialysis.

CRRT procedures that rely on convection for solute removal (eg, CVVH, CVVHDF) result in greater solute removal than procedures utilizing diffusion (eg, CVVHD, IHD). In the case of antibiotics, residual renal function, the seriousness of the infection, the minimum inhibitory concentration (MIC) of the organism, and the clinical status of the patient must also be considered to avoid underdosing the patient.

Drug information references provide drug dosing recommendations in IHD and CRRT; however, they must be interpreted cautiously due to the variability in dialysis techniques used. Referring to more than one drug information resource is recommended due to variability in published recommendations.[48]

Abbreviations Introduced in This Chapter

ACE	angiotensin-converting enzyme
AKI	acute kidney injury
ARB	angiotensin II receptor blocker
ATN	acute tubular necrosis
BUN	blood urea nitrogen
CI-AKI	contrast-induced acute kidney injury
CKD	chronic kidney disease
CI-AKI	contrast-induced AKI
CrCl	creatinine clearance
CT	computed tomography
CRRT	continuous renal replacement therapy
CVVH	continuous venovenous hemofiltration
CVVHD	continuous venovenous hemodialysis
CVVHDF	continuous venovenous hemodiafiltration
FENa	fractional excretion of sodium
GFR	glomerular filtration rate
HF	heart failure
IHD	intermittent hemodialysis
JVD	jugular venous distention
KDIGO	Kidney Disease: Improving Global Outcomes
MDRD	Modification of Diet in Renal Disease Study
MRI	magnetic resonance imaging
NSAIDs	nonsteroidal anti-inflammatory drugs
RRT	renal replacement therapy
SCr	serum creatinine

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Chronic and End-Stage Kidney Disease

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. List the risk factors that increase susceptibility for chronic kidney disease (CKD).
2. Explain the mechanisms associated with progression of CKD.
3. Outline the desired outcomes for treatment of CKD.
4. Develop a therapeutic approach to slow progression of CKD including lifestyle modifications and pharmacologic therapies.
5. Identify specific consequences associated with CKD.
6. Design an appropriate therapeutic approach for specific consequences associated with CKD.
7. Recommend an appropriate monitoring plan to assess the effectiveness of pharmacotherapy for CKD and specific consequences.
8. Educate patients with CKD about the disease state, the specific consequences, lifestyle modifications, and pharmacologic therapies used for treatment of CKD.

INTRODUCTION

The kidney is made up of approximately 2 million **nephrons** that are responsible for filtering, reabsorbing, and excreting solutes and water. The kidney has three primary functions: excretory (excrete fluid, electrolytes, and solutes); metabolic (metabolize vitamin D and some drugs, such as insulin and some beta-lactams); and endocrine (produce **erythropoietin**). As the number of functioning nephrons declines, the primary functions of the kidney that are affected include:

- Production and secretion of erythropoietin (EPO)
- Activation of vitamin D
- Regulation of fluid and electrolyte balance
- Regulation of acid–base balance

Chronic kidney disease (CKD) is defined as abnormalities in the structure or function of the kidney, present for 3 months or more, with implications for health.[1] Markers of structural abnormalities include albuminuria (30 mg/24 hours or more or an albumin:**creatinine** ratio (ACR) of more than 30 mg/g [or 3.5 mg/mmol for female and 2.5 mg/mmol for male, but varies between different guidelines and location]); hematuria or casts in urine sediment; electrolyte and other abnormalities caused by renal tubular disorders; abnormalities detected by histology or imaging; or history of kidney transplantation. Functional abnormalities are indicated by a decline in **glomerular filtration rate (GFR)** less than 60 mL/min/1.73 m^2 (0.58 mL/s/m^2). Generally, CKD is a progressive decline in kidney function (number of functioning nephrons) that occurs over several months to years. A rapid decline in kidney function over days to weeks is known as acute kidney injury (AKI), which is discussed in Chapter 26. Because the decline in kidney function in CKD is often irreversible, treatment of CKD is aimed at slowing the progression to end-stage kidney disease (ESKD).

EPIDEMIOLOGY AND ETIOLOGY

The United States Renal Data System (USRDS), using data from the National Health and Nutrition Examination Survey (NHANES), estimates the prevalence of CKD in the United States in 2016 is 14.2%, corresponding to nearly 46 million people.[2] CKD is more common in people over age 60 years and African American patients.[3] Diabetes, hypertension, cardiovascular disease, and higher body mass index (≥ 30 kg/m^2) are associated with CKD.[3] Furthermore, mortality is three times higher in people with CKD compared to those without CKD.[3]

KEY CONCEPT The Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group developed a classification system for CKD.[1] The staging system defines the stages of CKD based on GFR and albuminuria categories (Tables 27–1 and 27–2). The estimated GFR (or eGFR) is calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study equation:[4]

$$\text{eGFR} = 175 \times (\text{SCr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \\ \times (1.21 \text{ if African American})$$

Alternatively, eGFR can be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI):[1]

$$\text{eGFR} = 141 \times \min\,(S_{Cr}/\kappa, 1)\alpha \times \max\,(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \\ \times 1.018\ [\text{if female}] \times 1.159\ [\text{if African American}],$$

where κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of S_{Cr}/κ or 1.

Note: serum creatinine expressed in units of μmol/L should be divided by 88.4 to express in units of mg/dL prior to calculation using either MDRD or CKD-EPI equations presented here.

KEY CONCEPT CKD is a progressive disease that eventually leads to ESKD. The prevalence of ESKD has increased every year since

Table 27–1

GFR Categories in CKD[1]

GFR Category	GFR		Terms
	(mL/min/1.73m^2)	(mL/s/m^2)	
G1[a]	≥ 90	≥ 0.87	Normal or high
G2[a]	60–89	0.58–0.86	Mildly decreased
G3a	45–59	0.43–0.57	Mildly-to-moderately decreased
G3b	30–44	0.29–0.42	Moderately-to-severely decreased
G4	15–29	0.14–0.28	Severely decreased
G5	<15	<0.14	Kidney failure

[a] Kidney damage must be present to meet criteria of CKD.

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3:1–50.

1980 to over 700,000 people in 2016 with over 124,000 new cases of ESKD diagnosed in 2016.[3] The prevalence of ESKD is related to ethnicity, affecting 9.5 times more American Indians/Alaska Natives, 3.7 times more African Americans, 1.3 times more Asians, and 1.4 more Hispanics as Whites.[3]

Risk Factors for CKD

Identifying risk factors for CKD is difficult because CKD progresses slowly and is often not diagnosed until late in the disease. Disease states and factors that can increase susceptibility to CKD are listed in Table 27–3. These factors can be used to identify targets for CKD screening programs. For example, older patients, those with low kidney mass or birth weight, or those with a family history of kidney disease should be routinely screened for CKD. Minority and low socioeconomic communities may be targets for more widespread CKD screening programs.

The three most common causes of CKD in the United States are diabetes mellitus (DM), hypertension, and glomerulonephritis. These are discussed in further detail below. Other causes of CKD include polycystic kidney disease, Wegener's granulomatosis, vascular diseases, human immunodeficiency virus (HIV) nephropathy, and AKI.

Table 27–2

Albumin Categories in CKD[1]

Category	AER (mg/24 hours)	ACR (approximate equivalent)		Terms
		(mg/mmol)	(mg/g)	
A1	< 30	< 3	< 30	Normal to mildly increased
A2	30–300	3–30	30–300	Moderately increased
A3	> 300	> 30	> 300	Severely increased

Abbreviations: CKD, chronic kidney disease; AER, albumin excretion ratio; ACR, albumin-to-creatinine ratio. From Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3:1–50.

Table 27–3

Risk Factors that Increase Susceptibility for CKD

- Diabetes mellitus
- Hypertension
- Autoimmune disease
- Polycystic kidney disease
- Human immunodeficiency virus (HIV)
- Drug toxicity
- Urinary tract abnormalities (infections, obstruction, stones)
- Advanced age
- Reduced kidney mass
- Low birth weight
- Racial/ethnic minority
- Family history of kidney disease
- Low income or education
- Systemic inflammation
- Dyslipidemia

▶ *Diabetes*

DM is the most common cause of CKD, causing 36% of all CKD.[3] The risk of developing diabetic kidney disease (DKD) associated with DM is closely linked to hyperglycemia and is similar for both type 1 (T1D) and type 2 (T2D). Structural changes appear in the glomerulus as early as 2 years after diagnosis of T1D. Changes in GFR can occur as early as 5 to 7 years after diagnosis.[5] Similar changes occur in T2D, but the timing of onset of T2D and presentation of kidney disease is more difficult to determine. Albuminuria develops in 40% of patients with T2D and GFR decreases below 30 mL/min/1.73 m^2 (0.29 mL/s/m^2) within 15 years of diagnosis of T2D.[5]

▶ *Hypertension*

The second most common cause of CKD is hypertension, accounting for 31% of cases of CKD.[3] It is more difficult to determine the true risk of developing CKD in patients with hypertension because the two are so closely linked, with CKD also being a cause of hypertension. The prevalence of hypertension is correlated with the degree of kidney dysfunction (decreased GFR) with 36% of patients with CKD G1, 48% of patients with CKD G2, and 85% of patients with CKD G3 presenting with hypertension.[6] The risk of developing ESKD increases with the degree of hypertension and is linked to both systolic and diastolic blood pressure.[6]

▶ *Glomerulonephritis*

The term *glomerulonephritis* includes many specific diseases that can affect glomerular function. These include such diseases as IgA nephropathy and glomerulonephritis associated with systemic lupus erythematosus and streptococcal disease, among many others. The etiologic and pathophysiologic features of glomerular diseases vary with the specific disease, making it difficult to extrapolate the risk for progression of CKD in patients affected by glomerular diseases. Certain glomerular diseases are known to rapidly progress to ESKD; others progress more slowly or may be reversible.

Risk Factors for Progression of CKD

Several factors increase the progression of CKD, or rate of decline in GFR. The most important risk factors for progression of CKD include proteinuria, elevated blood pressure, hyperglycemia, hyperlipidemia, and AKI. Smoking tobacco also plays a role in progression of CKD.

▶ *Proteinuria*

The presence of protein in the urine is a marker of structural damage to the glomerulus and some tubulointerstitial diseases. The degree of proteinuria correlates with the risk for progression of CKD.[7] Proteinuria causes more significant effects in patients with milder stages of CKD. Compared with patients with no proteinuria in the same GFR category, patients with CKD G3 who have proteinuria are 15 times more likely to double serum creatinine within 5 years; patients with CKD G4 who have proteinuria are 8 times more likely to double serum creatinine within the same timeframe.[7] The mechanisms by which proteinuria potentiates CKD are discussed later.

▶ *Elevated Blood Pressure*

Systemic blood pressure correlates with glomerular pressure, and elevations in both independently contribute to glomerular damage. The rate of GFR decline is related to elevated systolic blood pressure and mean arterial pressure. The decline in GFR is estimated to be 14 mL/min/year (0.23 mL/s/year) in patients with diabetes with a sustained systolic blood pressure of 180 mm Hg. Conversely, the decline in GFR decreases to 2 mL/min/year (0.03 mL/s/year) with a systolic blood pressure of 135 mm Hg.[8]

▶ *Elevated Blood Glucose*

The reaction between glucose and protein in the blood produces advanced glycation end products (AGEs), which are metabolized in the proximal tubules. Hyperglycemia increases the synthesis of AGEs, which affects glomerular, tubular, and vascular function in the kidney. AGEs are known to affect activity of podocytes, the epithelial cells responsible for filtering blood in the glomerulus, which contributes to proteinuria, and, in turn, damages tubules.[9]

▶ *Hyperlipidemia*

Dyslipidemia can promote kidney injury and subsequent progression of CKD.[10] The dyslipidemia in CKD is manifested primarily as elevated triglycerides and lipoprotein(a) levels and decreased high-density lipoprotein cholesterol (HDL-C) levels. Total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels generally remain within normal limits, but LDL-C particles are smaller, denser, and more atherogenic. Furthermore, kidney disease alters lipid metabolism, allowing lipoproteins to remain in blood circulation longer.[10] In contrast, patients with nephrotic syndrome, characterized by urine protein rates that exceed 3 g/24 hours, often have elevated total cholesterol and LDL-C.[10]

▶ *Acute Kidney Injury*

Nephron damage that results from AKI increases the risk of developing CKD, even if renal function recovers.[11] The most predictive risk factor of whether patients will develop CKD is the severity of AKI. Severe AKI is associated with a 28-fold increased risk of developing CKD, but even mild AKI is associated with a 2-fold increased risk. Older age also increases the risk of developing CKD after AKI. The cause of AKI may also affect the risk of CKD.[11]

PATHOPHYSIOLOGY

A number of factors can cause initial damage to the kidney. The resulting sequelae, however, follow a common pathway that promotes progression of CKD and results in irreversible damage leading to ESKD (Figure 27–1).

Regardless of the initial cause of kidney damage, the result is a decrease in the number of functioning nephrons. The remaining nephrons hypertrophy to increase glomerular filtration and

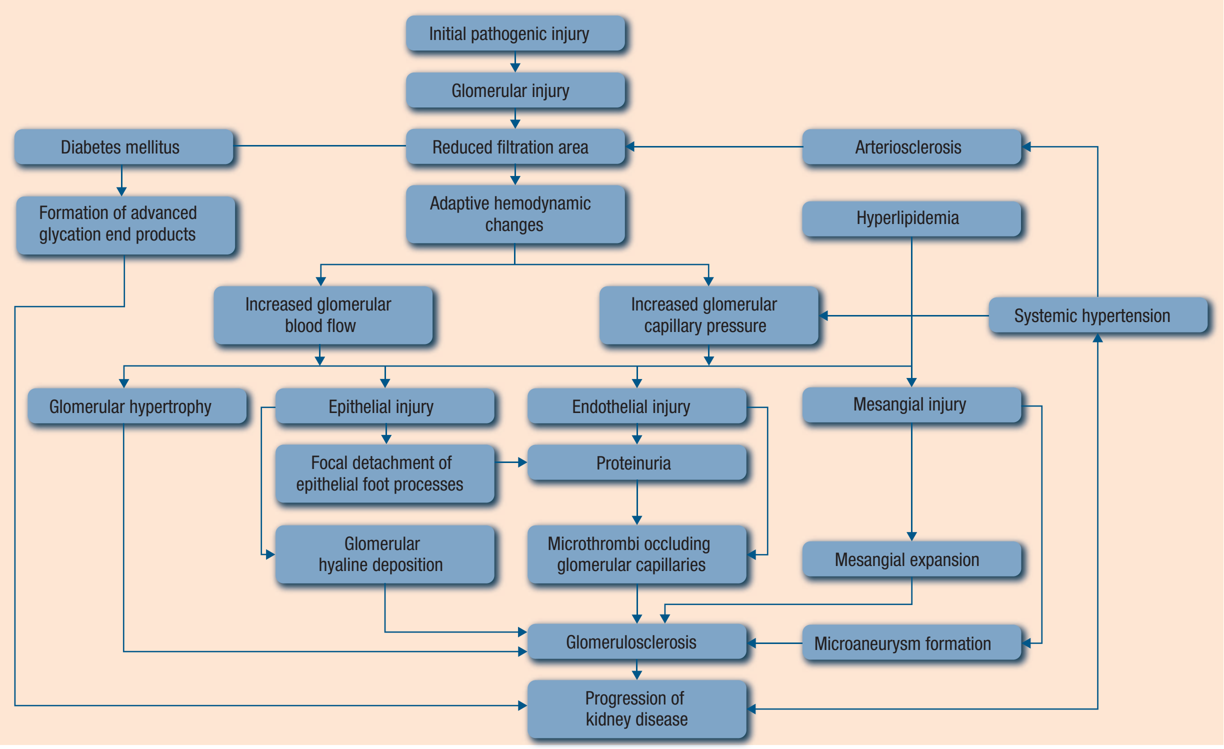

Initial pathogenic injury
Glomerular injury
Diabetes mellitus
Reduced filtration area
Arteriosclerosis
Formation of advanced glycation end products
Adaptive hemodynamic changes
Hyperlipidemia
Increased glomerular blood flow
Increased glomerular capillary pressure
Systemic hypertension
Glomerular hypertrophy
Epithelial injury
Endothelial injury
Mesangial injury
Focal detachment of epithelial foot processes
Proteinuria
Glomerular hyaline deposition
Microthrombi occluding glomerular capillaries
Mesangial expansion
Glomerulosclerosis
Microaneurysm formation
Progression of kidney disease

FIGURE 27–1. Proposed mechanisms for progression of kidney disease. (From Hudson JQ, Wazny LD, Komenda P. Chronic kidney disease. In: DiPiro JT, Yee GC, Posey M, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill Education; 2020, with permission.)

Clinical Presentation and Diagnosis of CKD

General

The development of CKD is usually subtle in onset, often with no noticeable symptoms.

Symptoms

CKD G1 and G2 are generally asymptomatic.

CKD G3a to 3b and G4 may be associated with minimal symptoms.

CKD G5 can be associated with pruritus, dysgeusia, nausea, vomiting, constipation, muscle pain, fatigue, and bleeding abnormalities.

Signs

Cardiovascular: Worsening hypertension, edema, dyslipidemia, left ventricular hypertrophy, electrocardiographic changes, and chronic heart failure.

Musculoskeletal: Cramping.

Neuropsychiatric: Depression, anxiety, impaired mental cognition.

Gastrointestinal (GI): Gastroesophageal reflux disease, GI bleeding, and abdominal distention.

Genitourinary: Changes in urine volume and consistency, "foaming" of urine (indicative of proteinuria), and sexual dysfunction.

Laboratory Tests

CKD G1 and G2: Blood urea nitrogen (BUN) and serum creatinine (SCr) are generally within normal limits, despite mildly decreased GFR.

CKD G3a to G3b, G4, and G5: Increased BUN and SCr; decreased GFR.

Advanced stages: Increased potassium, phosphorus, and magnesium; decreased bicarbonate (metabolic acidosis); calcium levels are generally low in earlier stages of CKD and may be elevated in CKD G5, secondary to the use of calcium-containing phosphate binders.

Decreased albumin, if inadequate nutrition intake in advanced stages.

Decreased red blood cell (RBC) count, hemoglobin (Hgb), and hematocrit (Hct); Decreased iron stores (decreased iron level, increased total iron binding capacity [TIBC], decreased serum ferritin level, and decreased transferrin saturation [TSat]). Erythropoietin levels are not routinely monitored and are generally normal to low. Urine positive for albumin or protein.

Increased parathyroid hormone (PTH) level; decreased vitamin D levels (CKD G4 or G5).

Stool may be Hemoccult-positive if GI bleeding occurs from uremia.

Other Diagnostic Tests

Structural abnormalities of kidney may be present on diagnostic examinations.

tubular function, both reabsorption and secretion, in an attempt to compensate for the loss of kidney function. Initially, these adaptive changes preserve many of the clinical parameters of kidney function, including **creatinine** and electrolyte excretion. However, as time progresses, angiotensin II is required to maintain the hyperfiltration state of the functioning nephrons. Angiotensin II is a potent vasoconstrictor of both the afferent and efferent arterioles but has a preferential effect to constrict the efferent arteriole, thereby increasing the pressure in the glomerular capillaries. Increased glomerular capillary pressure expands the pores in the glomerular basement membrane, altering the size-selective barrier and allowing proteins to be filtered through the glomerulus.[12]

Proteinuria increases nephron loss through various complex mechanisms. Filtered proteins are reabsorbed in the renal tubules, which activates the tubular cells to produce inflammatory and vasoactive cytokines and triggers complement activation. These cytokines cause interstitial damage and scarring in the renal tubules, leading to damage and loss of more nephrons. Ultimately, the process leads to progressive loss of nephrons to the point where the number of remaining functioning nephrons is too small to maintain clinical stability, and kidney function declines.

ASSESSMENT

Because CKD often presents without symptoms, assessment for CKD relies on appropriate screening strategies in all patients with risk factors for developing CKD. Evaluation for CKD and the subsequent treatment strategies depend on the diagnosis, comorbid conditions, severity and complications of disease, and risk factors for the progression of CKD. KEY CONCEPT Early treatment of CKD and the associated complications of CKD are the most important factors to decrease morbidity and mortality associated with CKD. Screening for CKD should be performed in all people with an increased risk for developing CKD including patients with DM, hypertension, genitourinary abnormalities, autoimmune disease, increased age, a family history of kidney disease, or following AKI. Assessment for CKD includes measurement of SCr, measurement of creatinine clearance (ie, 24-hour urine collection) or estimation of GFR (ie, MDRD or CKD-EPI), urinalysis, blood pressure, serum electrolytes, and/or imaging studies. It is important to note that SCr should be stable when estimating GFR or measuring creatinine clearance in patients with CKD. In patients with known CKD, the presence and assessment of CKD-related complications, including anemia and bone and mineral disorders, should be performed.

A key part of CKD assessment is analysis for proteinuria, which is the primary marker of structural kidney damage, even in patients with normal GFR. Protein excretion can be assessed by measuring urine ACR, urine protein-to-creatinine ratio, or urinalysis with a reagent strip test. A urinary protein excretion of 30 mg/day or more or an ACR of 30mg/g (or 3.5 mg/mmol for female and 2.5 mg/mmol for male, but varies between different guidelines and locations) or more on a random untimed urine sample is considered to be significant in the context of CKD. Albuminuria should be assessed with GFR at least annually in people with CKD, and more frequently as GFR declines.[1]

Complications

KEY CONCEPT The decline in kidney function is associated with a number of complications, which are discussed later in the chapter, including:

- Hypertension
- Fluid and electrolyte disorders
- Anemia
- Metabolic bone disease

TREATMENT

Desired Outcomes

The primary goal is to prevent and slow the progression of CKD to prevent a cardiovascular event, CKD complications, and the need for renal replacement therapy (RRT). This requires early identification of patients at risk for CKD to initiate interventions as early as possible in the course of the disease.

Nonpharmacologic Therapy

▶ *Nutritional Management*

In people with diabetic CKD G3-5 without dialysis, protein intake should be lowered to 0.8 g/kg/day in adults reduces the accumulation of by-products of protein catabolism in CKD and hyperfiltration associated with protein intake, which may delay the progression of CKD and the need for **dialysis**.[13] On the contrary, the recommended protein intake for people on dialysis is 1 to 1.2 g/kg/day to decrease the risk for nutritional abnormalities.[13] Malnutrition is common in patients with ESKD for various reasons, including decreased appetite, protein catabolism due to protein losses in the **dialysate**, and nutrient losses through dialysis. Overall caloric intake should be maintained at 25 to 35 kcal/kg/day (105–146 kJ/kg/day) for people at all stages of CKD.[13]

Limiting salt intake to less than 2 g (90 mmol) of sodium per day (equivalent to 5 g sodium chloride) will help to control blood pressure and reduce water retention in CKD. Patients with CKD should be encouraged to increase physical activity, with a goal of at least 30 minutes 5 times per week, to achieve a healthy weight, with a goal BMI of 20 to 25 kg/m^2.[1]

Pharmacologic Therapy

▶ *CKD with Diabetes*

The KDIGO guidelines recommend that the target hemoglobin A1c (HbA1c) should be less than 6.5% (0.065; 48 mmol/mol Hgb) to less than 8% (0.08; 64 mmol/mol Hgb) for patients with DM who are not receiving dialysis.[14] This generally involves intensive insulin therapy for T1D or insulin-dependent T2D or optimizing doses of oral hypoglycemic agents in patients with non–insulin-dependent T2D. The choice of oral hypoglycemic agents can impact CKD progression and cardiovascular outcomes in people with CKD. Sodium glucose cotransporter 2 (SGLT2) inhibitors have been demonstrated to decrease progression of CKD and cardiovascular disease. This effect is seen at all stages of CKD.[14] The KDIGO guidelines recommend using metformin or a sodium glucose cotransporter 2 (SGLT2) inhibitor with GFR 30 to 60 mL/min/1.73 m^2 (0.29–0.58 mL/s/m^2) as first-line agents for T2D.[14] Higher A1c targets should be considered for patients with limited life expectancy with late stages of DM and CKD to minimize the risk of hypoglycemia and associated complications.

▶ *Optimal Blood Pressure Control*

Reductions in blood pressure are associated with a decrease in proteinuria, leading to a decrease in the rate of progression of kidney disease. The 2017 High Blood Pressure Clinical Practice Guideline recommends targeting a goal blood pressure of less than 130/80 mm Hg for all patients with CKD without dialysis.[15]

KEY CONCEPT Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) are the antihypertensive agents of choice in patients with CKD with an albumin excretion ratio (AER) of 30 mg/day or more because of their greater effect on lowering proteinuria, compared with other antihypertensive agents.[15] ACEIs and ARBs should be started at a low dose and the dose should be titrated upward slowly to minimize the risk of AKI (see Chapter 26). Ideally, the dose of ACEIs and ARBs should be increased to achieve a 30% to 50% reduction in urinary albumin excretion, but this may be limited by side effects, such as hyperkalemia, in patients with CKD. Thiazide diuretics have complementary effects when added to ACEIs and ARBs.[16] While many clinicians feel that thiazide diuretics are ineffective with GFR less than 30 mL/min/1.73 m^2 (0.29 mL/s/m^2), some evidence suggests that thiazide diuretics may be effective in lowering blood pressure with lower GFR.[17] Other drug classes should be considered when compelling indications warrant or if blood pressure goals are not achieved.

In patients with CKD G5 who are receiving hemodialysis (HD), cardiovascular mortality is affected by blood pressure both before and after HD.[18] Predialysis blood pressure has a U-shaped association between systolic blood pressure and mortality. Systolic blood pressures less than 120 mm Hg and greater than 150 mm Hg are both associated with increased mortality.[18] Furthermore, as many as 20% to 30% of people can experience hypotension during dialysis, which can cause ischemia to the heart, GI tract, and the brain, increase clotting of venous access, and increase mortality.[18] Current guidelines do not define a specific blood pressure goal before or after dialysis due to lack of clinical evidence.[19] Some evidence suggests that blood pressure on non-HD days may be a more appropriate measure and correlates better with cardiovascular outcomes.[18]

Because hypertension and kidney dysfunction are linked, blood pressure control can be more difficult to attain in patients with CKD compared with patients with normal kidney function. All antihypertensive agents have similar effects on reducing blood pressure. However, two or more agents are generally required to achieve the blood pressure goal of less than 130/80 mm Hg in CKD patients.[15] Timing of blood pressure medications may also be important. Studies suggest that administration of antihypertensive medications at bedtime can decrease proteinuria by more than 30% and decrease cardiovascular risk by 14% in people with CKD compared with taking all antihypertensive medications in the morning.[20]

▶ *Reduction in Proteinuria*

Proteinuria refers to the presence of general protein in the urine. Albumin is the most common type or protein lost in the urine in patients with CKD. While older studies refer to reductions in proteinuria, new guidelines focus specifically on albuminuria. Throughout this chapter, the two terms are used interchangeably. Albuminuria in CKD predicts long-term renal and cardiovascular prognosis.[17] The ability of antihypertensive agents to reduce protein excretion differs. ACEIs and ARBs decrease glomerular capillary pressure and volume because of their effects on angiotensin II. This, in turn, reduces the amount of protein filtered through the glomerulus, independent of the reduction in blood pressure,[17] which ultimately decreases the progression of CKD. The ability of ACEIs and ARBs to reduce proteinuria is greater than that of other antihypertensives, up to 35% to 40%,[17] making ACEIs and ARBs the antihypertensive agents of choice for all patients with CKD with an AER of 30 mg/day or more, unless contraindicated. ACEIs and ARBs have been demonstrated to slow the progression of CKD with GFR less than 50 mL/min/1.73 m^2 (0.49 mL/s/m^2).[16] Studies investigating combination of ACEIs and ARBs have shown a wide variety of results compared to monotherapy with either agent. Some studies show the combination reduces proteinuria more than monotherapy, but this does not appear to reduce the progression of CKD. Current guidelines recommend avoiding combination of ACEIs and ARBs because of increased risks of hyperkalemia and AKI.[21]

The nondihydropyridine calcium channel blockers (CCBs, eg, diltiazem, verapamil) have been shown to also decrease protein excretion and decrease the progression of CKD. Dihydropyridine CCBs (eg, amlodipine, nifedipine, felodipine) however, do not have the same effects on protein excretion and should only be used in combination with ACEIs and ARBs.[16]

▸ *Hyperlipidemia Treatment*

Hyperlipidemia plays a role in the development of cardiovascular disease (CVD) in patients with CKD. Because data do not support the use of LDL-C levels to guide treatment of hyperlipidemia, the KDIGO guidelines recommend starting statins for all patients with non–dialysis-dependent CKD aged 50 years and older, regardless of GFR category.[22] Ezetimibe should be considered when GFR is less than 60 mL/min/1.73 m^2 (0.58 mL/s/m^2). Statins should also be used for patients aged 18 to 49 years who have known coronary artery disease, DM, prior ischemic stroke, or more than a 10% estimated 10-year incidence of coronary death or nonfatal myocardial infarction.[22] However, because of the lack of efficacy in reducing cardiovascular events and the risk of adverse effects associated with statins in patients with ESKD, statins should not be initiated in patients on dialysis, unless they were receiving statins prior to starting dialysis.[22]

Outcome Evaluation

The KDIGO guidelines recommend intervals for monitoring GFR and albuminuria in patients with CKD, based on the CKD stage and the degree of albuminuria.[1] In general, patients should be monitored more frequently as CKD stage and the severity of albuminuria increase.

Patients with CKD G3a should be monitored every 12 months until albuminuria is detected, then the frequency of monitoring should be increased to every 4 to 6 months, based on the severity of albuminuria. As CKD progresses, the frequency of monitoring should be increased to every 3 to 6 months.

Monitor SCr and potassium levels and blood pressure within 1 week after initiating ACEI or ARB therapy. Discontinue the medication and switch to another agent if a sudden increase in SCr greater than 30% occurs, uncontrollable hyperkalemia develops, or the patient becomes hypotensive. Titrate the dose of the ACEI or ARB every 1 to 3 months to effect using the maximum tolerable dose. If blood pressure is not reduced to goal, add another agent to the regimen. Refer the patient to a nephrologist to manage complications associated with CKD. As kidney function declines to CKD G4, begin discussion to prepare the patient for RRT.

Patient Encounter 1

A 38-year-old Asian female presents to the clinic for a routine checkup. She has no complaints today.

PMH: Hypertension, diagnosed 8 years ago; type 2 diabetes mellitus, diagnosed 5 years ago

SH: no history of smoking; drinks alcohol occasionally (socially)

Meds: Amlodipine 10 mg orally daily; atenolol 50 mg orally daily; atorvastatin 20 mg orally daily; glipizide 5 mg orally two times daily

ROS: Unremarkable.

PE:

VS: BP 158/98 mm Hg; P 82 bpm; T 98.8°F (37.1°C); ht 5′6″ (168 cm); wt 170 lb (77.1 kg)

CV: RRR, normal S_1, S_2; no murmurs, rubs or gallops; lungs clear

Abd: No organomegaly, bruits or tenderness, (+) bowel sounds; heme (–) stool

Exts: negative for pedal edema bilaterally; no lesions

Labs (Fasting): Sodium 145 mEq/L (mmol/L); potassium 4.3 mEq/L (mmol/L); chloride 105 mEq/L (mmol/L); carbon dioxide 23 mEq/L (mmol/L); blood urea nitrogen (BUN) 28 mg/dL (10 mmol/L); serum creatinine (SCr) 1.8 mg/dL (159 μmol/L); fasting glucose 201 mg/dL (11.2 mmol/L); total cholesterol 260 mg/dL (6.72 mmol/L); low-density lipoprotein cholesterol (LDL-C) 176 mg/dL (4.55 mmol/L); high-density lipoprotein cholesterol (HDL-C) 24 mg/dL (0.62 mmol/L); triglycerides 300 mg/dL (3.39 mmol/L); urine albumin:creatinine 52 mg/g creatinine (5.9 mg/mmol creatinine)

What risk factors does the patient have for the development of CKD?

What signs and symptoms are consistent with CKD?

How would you classify her CKD?

What lifestyle modifications would you recommend for this patient with CKD?

What pharmacologic alternatives are available for this patient for treatment of CKD?

CONSEQUENCES OF CKD AND ESKD

Anemia of CKD

The progenitor cells of the kidney produce 90% of the hormone EPO, which stimulates red blood cell (RBC) production. **KEY CONCEPT** Reduction in the number of functioning nephrons decreases renal production of EPO, which is the primary cause of anemia in patients with CKD. The development of anemia of CKD results in decreased oxygen delivery and utilization, leading to increased cardiac output and left ventricular hypertrophy (LVH), which increase the cardiovascular risk and mortality in patients with CKD. A decline in hematocrit (Hct) from 30% (0.3) to 27% (0.27) results in an increased relative risk (RR) for mortality of 1.33.[23]

▸ *Epidemiology and Etiology*

The World Health Organization defines anemia as an Hgb level less than 13 g/dL (130 g/L; 8.07 mmol/L) in males and less than 12 g/dL (120 g/L; 7.45 mmol/L) in females. In addition to

Clinical Presentation and Diagnosis of Anemia of CKD

General

Anemia of CKD generally presents with fatigue and decreased quality of life.

Symptoms

Anemia of CKD is associated with symptoms of cold intolerance, shortness of breath, and decreased exercise capacity.

Signs

Cardiovascular: Left ventricular hypertrophy, ECG changes, congestive heart failure.

Neurologic: Impaired mental cognition.

Genitourinary: Sexual dysfunction.

Laboratory Tests

Decreased RBC count, Hgb, and Hct.

Decreased serum iron level, TSat and serum ferritin, and increased TIBC.

Patient Encounter 2, Part 1

A 54-year-old African American man with a history of diabetes presents to your clinic for a routine checkup. He complains of getting fatigued easily at work. He works in a bank and notes that he is not able to keep up with his work. He notes that he feels winded when he walks even short distances between his desk and the fax machine and printer. He notes his shoes are fitting tightly and his socks leaves indentations on his legs.

Current meds: Lisinopril 20 mg orally daily; furosemide 20 mg orally daily; levothyroxine 125 mcg orally daily; glipizide 10 mg po BID, ferrous sulfate 325 mg orally two times daily.

ROS: Fatigue daily throughout the day with minimal exertion; otherwise unremarkable.

PE:

VS: BP 127/82 mm Hg; P 88 bpm; T 97.5°F (36.4°C); ht 5′10″ (178 cm); wt 264 lb (120 kg)

CV: RRR, normal S_1, S_2

Abd: No organomegaly, bruits or tenderness; (+) bowel sounds; heme (–) stool

Ext: 2+ pedal edema bilaterally

Labs: Sodium 138 mEq/L (mmol/L); potassium 4.1 mEq/L (mmol/L); chloride 101 mEq/L (mmol/L); carbon dioxide 21 mEq/L (mmol/L); BUN 18 mg/dL (6.4 mmol/L); Scr 2.2 mg/dL (194 μmol/L); glucose 140 mg/dL (7.8 mmol/L); white blood cell (WBC) count 4.8×10^3 cells/mm^3 (4.8×10^9/L); red blood cell (RBC) count 2.5×10^6 cells/mm^3 (2.5×10^{12}/L); Hgb 8.2 g/dL (82 g/L; 5.09 mmol/L); Hct 25% (0.25); platelets 278×10^3 cells/mm^3 (278×10^9/L)

What signs and symptoms are consistent with anemia of CKD?

What additional information could you request to determine other causes of anemia in this patient?

decreased EPO production, a number of factors contribute to the development of anemia including deficiencies in iron, vitamin B_{12} or folate, hemolysis, bleeding, or bone marrow resistance to EPO. Many of these can be detected by alterations in RBC indices, which should be included in the evaluation for anemia (see Chapter 69). A complete blood cell count is also helpful in evaluating anemia to determine overall bone marrow function. The prevalence of anemia correlates with the degree of kidney dysfunction. Only 8.7% of patients with CKD G1 have anemia, whereas the number increases to 54.2% with CKD G5 without dialysis.[23]

▶ *Pathophysiology*

The primary cause of anemia in patients with CKD is a decrease in EPO production. With normal kidney function, as Hgb, Hct, and tissue oxygenation decrease, the plasma concentration of EPO increases exponentially. As the number of functioning nephrons decrease, EPO production also decreases. Thus, as Hgb, Hct, and tissue oxygenation decrease in patients with CKD, plasma EPO levels remain constant within the normal range but low relative to the degree of hypoxia present. The result is a normochromic, normocytic anemia.

Several other factors contribute to the development of anemia in patients with CKD. Uremia, the accumulation of toxins that results from declining kidney function, decreases the lifespan of RBCs from a normal of 120 days to as low as 60 days in patients with CKD G5. Iron deficiency and blood loss from frequent regular laboratory testing and HD also contribute to the development of anemia in patients with CKD.

▶ *Treatment*

Patients with CKD should be evaluated for anemia when the GFR falls below 60 mL/min (1.0 mL/s) or if the SCr rises above 2 mg/dL (177 μmol/L). An anemia workup should be performed if the Hgb is less than 13 g/dL (130 g/L; 8.07 mmol/L) in males or less than 12 g/dL (120 g/L; 7.45 mmol/L) in females. The workup for anemia should rule out other potential causes for anemia (see Chapter 69). Abnormalities found during the anemia workup should be corrected before initiating erythropoiesis-stimulating agents (ESAs), particularly iron deficiency, because iron is an essential component of RBC production. If Hgb is below 10 g/dL (100 g/L; 6.21 mmol/L) when all other causes of anemia have been corrected, EPO deficiency should be assumed. EPO levels are not routinely measured and have little clinical significance in monitoring progression and treatment of anemia in patients with CKD.

Nonpharmacologic Therapy Approximately 1 to 2 mg of iron is absorbed daily from the diet. This small amount is generally not adequate to preserve adequate iron stores to promote RBC production in patients with CKD-related anemia. RBC transfusions have been used in the past as the primary means to maintain Hgb and Hct levels in patients with anemia of CKD. This treatment is still utilized today in patients with severe anemia, when rapid Hgb correction is needed, especially for patients with cardiovascular disease, or if patients have contraindications to ESAs.

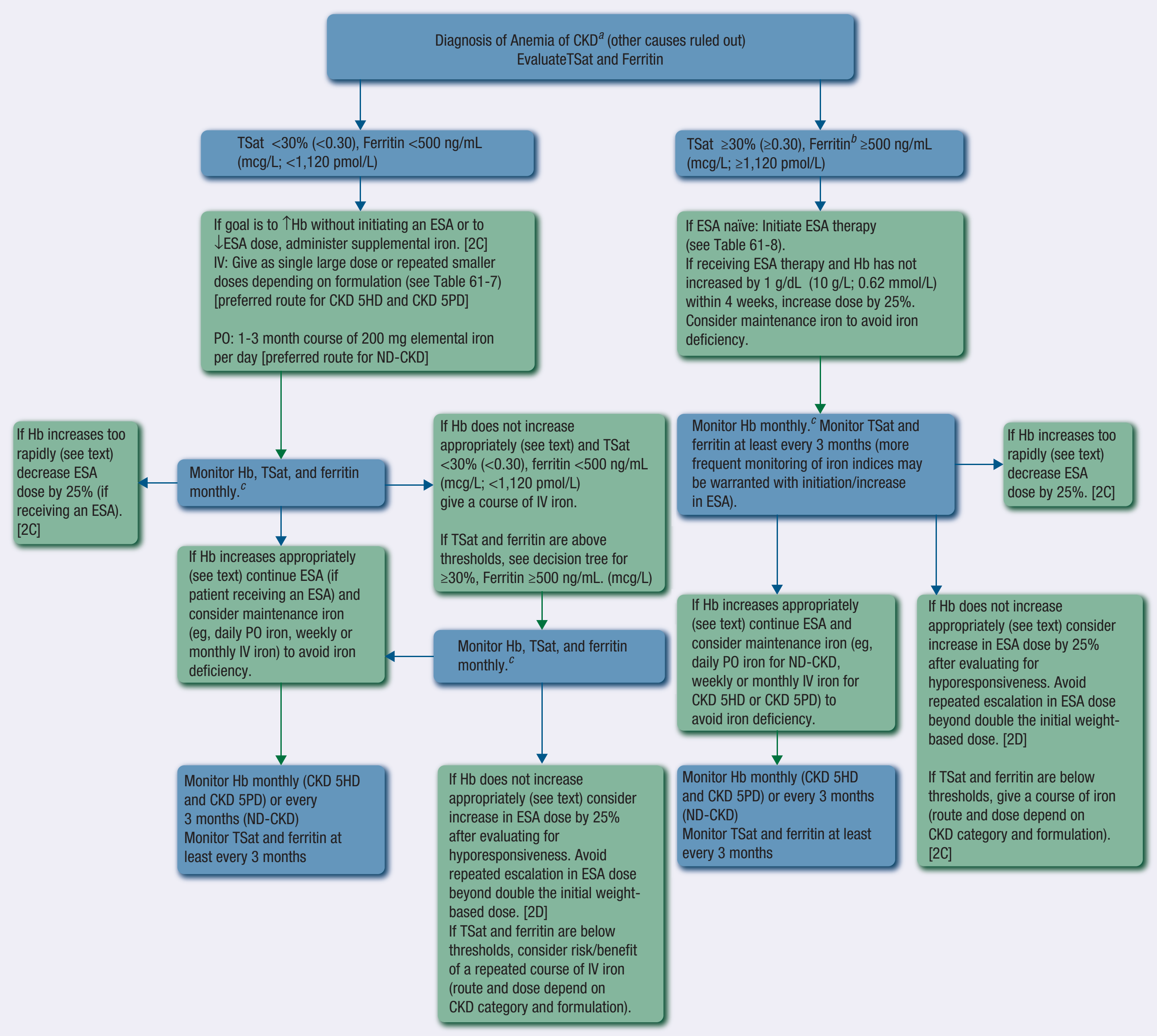
Pharmacologic Therapy The first-line treatment for anemia of CKD involves replacement of iron stores with iron supplements. When iron supplementation alone is not sufficient to increase Hgb levels, ESAs are necessary to replace EPO. ESAs are synthetic formulations of EPO produced by recombinant human DNA technology. Use of ESAs increases the iron demand for RBC production and iron deficiency is common, requiring iron supplementation to correct and maintain adequate iron stores to promote RBC production. The approach to the management of anemia of CKD with iron supplementation and ESAs is illustrated in Figure 27–2.

Iron Supplementation. Iron deficiency is a common cause of anemia in CKD. Use of ESAs can lead to iron deficiency if iron stores are not adequately maintained. The markers of iron stores that are used to determine iron deficiency include serum ferritin levels and transferrin saturation (TSat). Ferritin is an intracellular protein that stores iron and is used as an indirect marker of the total amount of iron stored in the body. Transferrin is the primary transport protein for iron in the bloodstream. The saturation of transferrin reflects how much serum iron is bound to transferrin.

According to the KDIGO guidelines, iron supplementation should be considered when:

- Serum ferritin levels are less than 500 ng/mL (mcg/L; 1124 pmol/L)
- Transferrin saturation (TSat) is less than 30% (0.30).[24]

Serum ferritin is an acute phase reactant that may become elevated with inflammation and infection. Thus, when serum ferritin is normal or elevated in conjunction with TSat levels less than 30% (0.30), treatment should be based on the clinical picture of the patient. Iron supplementation may be indicated if Hgb levels are below the goal level but avoided if the patient has an active infection.



Diagnosis of Anemia of CKD[a] (other causes ruled out)
EvaluateTSat and Ferritin

TSat <30% (<0.30), Ferritin <500 ng/mL (mcg/L; <1,120 pmol/L)

If goal is to ↑Hb without initiating an ESA or to ↓ESA dose, administer supplemental iron. [2C]
IV: Give as single large dose or repeated smaller doses depending on formulation (see Table 61-7) [preferred route for CKD 5HD and CKD 5PD]

PO: 1-3 month course of 200 mg elemental iron per day [preferred route for ND-CKD]

Monitor Hb, TSat, and ferritin monthly.[c]

If Hb increases too rapidly (see text) decrease ESA dose by 25% (if receiving an ESA). [2C]

If Hb does not increase appropriately (see text) and TSat <30% (<0.30), ferritin <500 ng/mL (mcg/L; <1,120 pmol/L) give a course of IV iron.

If TSat and ferritin are above thresholds, see decision tree for ≥30%, Ferritin ≥500 ng/mL. (mcg/L)

If Hb increases appropriately (see text) continue ESA (if patient receiving an ESA) and consider maintenance iron (eg, daily PO iron, weekly or monthly IV iron) to avoid iron deficiency.

Monitor Hb, TSat, and ferritin monthly.[c]

Monitor Hb monthly (CKD 5HD and CKD 5PD) or every 3 months (ND-CKD)
Monitor TSat and ferritin at least every 3 months

If Hb does not increase appropriately (see text) consider increase in ESA dose by 25% after evaluating for hyporesponsiveness. Avoid repeated escalation in ESA dose beyond double the initial weight-based dose. [2D]
If TSat and ferritin are below thresholds, consider risk/benefit of a repeated course of IV iron (route and dose depend on CKD category and formulation).

TSat ≥30% (≥0.30), Ferritin[b] ≥500 ng/mL (mcg/L; ≥1,120 pmol/L)

If ESA naïve: Initiate ESA therapy (see Table 61-8).
If receiving ESA therapy and Hb has not increased by 1 g/dL (10 g/L; 0.62 mmol/L) within 4 weeks, increase dose by 25%.
Consider maintenance iron to avoid iron deficiency.

Monitor Hb monthly.[c] Monitor TSat and ferritin at least every 3 months (more frequent monitoring of iron indices may be warranted with initiation/increase in ESA).

If Hb increases too rapidly (see text) decrease ESA dose by 25%. [2C]

If Hb increases appropriately (see text) continue ESA and consider maintenance iron (eg, daily PO iron for ND-CKD, weekly or monthly IV iron for CKD 5HD or CKD 5PD) to avoid iron deficiency.

Monitor Hb monthly (CKD 5HD and CKD 5PD) or every 3 months (ND-CKD)
Monitor TSat and ferritin at least every 3 months

If Hb does not increase appropriately (see text) consider increase in ESA dose by 25% after evaluating for hyporesponsiveness. Avoid repeated escalation in ESA dose beyond double the initial weight-based dose. [2D]

If TSat and ferritin are below thresholds, give a course of iron (route and dose depend on CKD category and formulation). [2C]

FIGURE 27–2. Algorithm for management of anemia of CKD. (CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; ND-CKD, nondialysis CKD patients; TSat, transferrin saturation.) [a]Clinical judgement should be used to determine if iron supplementation should be given when ferritin > 500 ng/mL (mcg/L; 1,124 pmol/L). [c]Weekly monitoring of Hb may be warranted. Wait at least 1 week after an IV dose of iron to measure TSat and ferritin. (From Hudson JQ, Wazny LD, Komenda P. Chronic kidney disease. In: DiPiro JT, Yee GC, Posey M, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill Education; 2020, with permission.)

Oral iron supplements are less costly than IV supplements and are generally the first-line treatment for iron supplementation for patients with CKD not receiving HD. When administering iron by the oral route, 200 mg of elemental iron should be delivered daily in divided doses to increase iron stores.[24]

When oral iron is not effective to increase iron stores or for patients receiving HD, IV iron should be administered. Table 27–4 lists the FDA-approved doses of the currently available IV iron products. Patients receiving HD have ongoing blood losses with each HD session, which can lead to iron losses of 1 to 2 g/year. For HD, IV iron may be administered episodically based on routine surveillance of iron stores as a total of 1 g of IV iron, administered in small sequential doses to replete iron stores. An alternative method to administer IV iron is to give smaller maintenance doses of iron weekly or with each dialysis session (eg, iron sucrose 20–100 mg/week; sodium ferric gluconate 62.5–125 mg/week). The latter approach of giving smaller maintenance doses may result in lower cumulative doses of iron and lower doses of ESAs.[24]

IV iron preparations are equally effective in increasing iron stores. Anaphylaxis may occur with all IV preparations, but most notably with iron dextran, which can also cause delayed reactions,

Table 27–4

IV Iron Products

Iron Formulation (Product)	FDA-Approved Indications	FDA-Approved Dosing	Warnings	Dose Ranges[a]	How Supplied
Ferric carboxymaltose (Injectafer®)	Adults with non–dialysis-dependent CKD	IV push: 750 mg over 10 minutes IV infusion: 750 mg in 100–250 mL of 0.9% NaCl over at least 15 minutes	General	1500 mg (2 doses of 750 mg separated by at least 7 days)	15-mL vials containing 750 mg elemental iron
Ferric derisomaltose (Monoferric®)	Adults with non–dialysis-dependent CKD	IV infusion: Patients ≥ 50 kg: 1000 mg; Patients < 50 kg: 20 mg/kg actual body weight	General	1000 mg (single dose)	1-mL, 5-mL, 10-mL vials (100 mg iron/mL)
Ferric gluconate (Ferrlecit®, Sodium ferric gluconate)	Adult and pediatric HD patients age 6 years and older receiving ESA therapy	IV push (adult): 125 mg over 10 minutes	General	6.25–500 mg	5-mL ampules containing 62.5 mg elemental iron (12.5 mg/mL)
		IV infusion (adult): 125 mg in 100 mL of 0.9% NaCl over 60 minutes			
		IV infusion (pediatric): 1.5 mg/kg in 25 mL of 0.9% NaCl over 60 minutes; maximum dose 125 mg			
Ferumoxytol (Feraheme”)	Adults with iron-deficiency anemia associated with CKD	infusion: 510 mg (17 mL) in 50–200 mL 0.9% NaCl or 5% Dextrose over at least 15 minutes, followed by a second 510-mg infusion 3–8 days after the initial infusion	Black box (risk of anaphylactic reactions)	1020 mg (2 doses of 510 mg separated by 3–8 days)	17 mL vials containing 510 mg (0 mg/mL)
Iron dextran (INFeD®, Dexferrum®)	Patients with iron deficiency in whom oral iron is unsatisfactory	IV push: 100 mg over 2 minutes (25 mg test dose required)	Black box (risk of anaphylactic reactions)	25–1000 mg	2-mL vials containing 50 mg elemental iron per mL
Iron sucrose (Venofer®)	HD patients with CKD receiving ESA therapy	IV push: 100 mg over 2–5 minutes	General	25–500 mg	5-mL single-dose vials containing 100 mg elemental iron (20 mg/mL)
		IV infusion: 100 mg in maximum of 100 mL of 0.9% NaCl over 15 minutes			
	Nondialysis-CKD patients receiving or not receiving ESA therapy	IV push: 200 mg over 2–5 minutes on five different occasions within 14-day period			
	PD patients receiving ESA therapy	IV infusion: 2 infusions 14 days apart, of 300 mg in maximum of 250 mL of 0.9% NaCl over 1.5 hour, followed by 1 infusion 14 days later, of 400 mg in maximum of 250 mL of 0.9% NaCl over 2.5 hours			

CKD, chronic kidney disease; ESA, erythropoietin-stimulating agent; HD, hemodialysis; PD, peritoneal dialysis.

[a] Small dosing ranges (eg, 25–100 mg/week) generally used for maintenance regimens. Larger doses (eg, 1 g) should be administered in divided doses.

such as arthralgias and myalgias. A test dose of 25 mg iron dextran should be administered 30 minutes before the full dose to monitor for potential anaphylactic reactions, although anaphylactic reactions can occur in patients who safely received prior doses of iron dextran. Ferumoxytol also carries a warning for serious allergic reactions and should be closely monitored, but does not require a test dose. Sodium ferric gluconate, iron sucrose, and ferric carboxymaltose are associated with fewer severe reactions and a much lower risk of anaphylaxis and do not require a test dose, making them the preferred agents in CKD. The most common side effects seen with these preparations include hypotension, flushing, nausea, and injection site reactions.

After administering a 1g course of IV iron, iron status should be monitored to determine the effectiveness of the treatment. Serum ferritin and TSat should be monitored no sooner than 1 week after the last dose of IV iron. If Hgb does not increase after a course of IV iron or serum ferritin is not greater than 500 ng/mL (mcg/L; 1124 pmol/L) and TSat greater than 30% (0.30), an additional 1 g of IV iron may be administered, based on the clinical situation.

Erythropoiesis-Stimulating Agents. ESAs may be considered if Hgb levels remain persistently low to improve symptoms of anemia. In patients not receiving dialysis, the decision to initiate ESAs should be based on the rate of Hgb decline, prior response to anemia treatment, risks associated with ESAs and the patient's symptoms. The KDIGO guidelines recommend considering initiating ESAs when Hgb is less than 10 g/dL (100 g/L; 6.21 mmol/L).[24] However, the target for Hgb is unclear because use of ESAs to increase Hgb levels beyond 12 g/dL (120 g/L; 7.45 mmol/L) is associated with increased mortality.[24] The ESAs currently available in the United States are listed in Table 27–5. Epoetin α and epoetin β (which is available outside the United States) have the same biological activity as endogenous EPO. Darbepoetin alfa has 2 additional carbohydrate side chains that increase the half-life compared with epoetin alfa and endogenous EPO, allowing for less frequent dosing than that of epoetin alfa. Methoxy PEG-epoetin beta has the addition of an amide bond that produces a longer half-life than the other ESAs and is referred to as a continuous EPO receptor activator (CERA). All ESAs are equivalent in their efficacy and have a similar adverse-effect profile.

The most common adverse effect seen with ESAs is increased blood pressure, which may require antihypertensive agents to control blood pressure. Caution should be used when initiating an ESA in patients with very high blood pressures (> 180/100 mm Hg). If blood pressures are refractory to antihypertensive agents, ESAs may need to be withheld. Seizures and pure red cell aplasia have also been reported in patients initiating ESA therapy, and has been reported more with the CERA product.

Subcutaneous (SC) administration of ESA is the preferred route of administration for all agents because it produces a more predictable and sustained response than IV administration, and lower doses of ESAs are generally needed. IV administration is often utilized in patients who have established IV access or are receiving HD. Starting doses of ESAs depend on the Hgb level, the target Hgb level, the rate of Hgb increase, and clinical circumstances. The initial increase in Hgb should be 1 to 2 g/dL (10–20 g/L; 0.62–1.24 mmol/L) per month.[24] The recommended starting dose of the ESAs are listed in Table 27–5.

When prescribing ESAs, clinicians should not attempt to target "normal" Hgb levels (ie, > 13 g/dL [130 g/L; 8.07 mmol/L] in males; > 12 g/dL [120 g/L; 7.45 mmol/L] in females). Several clinical trials have demonstrated that targeting Hgb levels greater than 13 g/dL (130 g/L; 8.07 mmol/L) resulted in more cardiovascular complications or death, compared with target Hgb levels less than 11 g/dL (110 g/L; 6.83 mmol/L).[23] Further studies are needed to evaluate the appropriate target level for Hgb. Nonetheless, based on these findings, the US FDA recommended addition of a black box warning to the product information for all ESAs indicating the maximum target Hgb should not exceed 11 g/dL (110 g/L; 6.83 mmol/L) and requires a medication guide be given to patients who are receiving ESAs. However, KDIGO suggests a maximum threshold of 11.5 g/dL (115 g/L; 7.14 mmol/L).[23]

▶ *Outcome Evaluation*

The outcomes to monitor for anemia of CKD include Hgb, iron status, and the need for blood transfusions. Hemoglobin should be monitored every 3 months in patients with CKD not on dialysis and those receiving PD and monthly in patients receiving HD. Evaluate Hgb monthly when ESA therapy is initiated or the dose is adjusted to ensure Hgb does not exceed 11.5 g/dL (115 g/L; 7.14 mmol/L).[24] The ESA dose can increase monthly if Hgb is below goal. Once a stable Hgb is attained, evaluate Hgb every 3 months thereafter. When a patient begins or increases the dose of ESA therapy, monitor iron stores monthly to ensure

Table 27–5

Erythropoiesis Stimulating Agents in Chronic Kidney Disease[a]

Drug	Brand Name	Starting Dose	Route of Administration	Half-Life (Hours)
Epoetin alfa Epoetin alfa-epbx	Epogen®, Procrit® Retacrit®	Adults: 50–100 U/kg three times per week Pediatrics: 50 U/kg three times per week	IV or SC	8.5 (IV) 24 (SC)
Darbepoetin alfa	Aranesp®	ND-CKD: 0.45 mcg/kg once every 4 weeks Dialysis: 0.45 mcg/kg once per week or 0.75 mcg/kg once every 2 weeks Pediatrics: 0.45 mcg/kg once weekly; may give 0.75 mcg/kg once every 2 weeks for nondialysis	IV or SC	25 (IV) 48 (SC)
Methoxy PEG-epoetin beta	Mircera®	0.6 mcg/kg every 2 weeks; once Hgb stabilizes, double the dose and administer monthly (eg, if administering 0.6 mcg/kg every 2 weeks, give 1.2 mcg/kg every month)	IV or SC	134 (IV) 139 (SC)

[a]Adapted from Hudson JQ, Wazny LD, Komenda P. Chronic kidney disease. In: DiPiro JT, Yee GC, Posey M, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill Education; 2020, with permission.

CKD, chronic kidney disease; ND-CKD, nondialysis CKD; PEG, polyethylene glycol; SC, subcutaneous.

Patient Encounter 2, Part 2

The patient returns to your clinic in 1 week and states that his symptoms have not changed. He is asking about the results of his laboratory studies.

Labs: WBC 4.2 × 10^3 cells/mm^3 (4.2 × 10^9/L); red blood cell (RBC) count 2.6 × 10^6 cells/mm^3 (2.6 × 10^{12}/L); Hgb 8.4 g/dL (84 g/L; 5.21 mmol/L); Hct 27% (0.27); mean corpuscular volume (MCV) 86 fL; mean corpuscular hemoglobin concentration (MCHC) 31 g/dL (310 g/L); platelets 298 × 10^3 cells/mm^3 (298 × 10^9/L); iron 131 mcg/dL (23.4 μmol/L); total iron binding capacity (TIBC) 390 mcg/dL (69.8 μmol/L); ferritin 662 ng/mL (mcg/L; 1487 pmol/L); transferrin saturation (TSat) 36% (0.36); stool guaiac negative × 3

What treatment would you recommend for this patient for treatment of anemia?

How would you evaluate the effectiveness of treatment of anemia?

adequate iron stores are present for erythropoiesis and limit dosing of ESAs. When the goal Hgb is reached, monitor iron stores every 3 months. Serum ferritin and TSat should be monitored no sooner than 1 week after the last dose of IV iron is administered.

CKD-Mineral and Bone Disorder and Secondary Hyperparathyroidism

▶ *Epidemiology and Etiology*

Increases in parathyroid hormone (PTH) occur early as kidney function begins to decline. The actions of PTH on bone turnover lead to CKD-mineral and bone disorders (CKD-MBD). The majority of patients with CKD G3-G5 have CKD-MBD.[25]

▶ *Pathophysiology*

As kidney function declines in patients with CKD, decreased phosphorus excretion disrupts the balance of calcium and phosphorus homeostasis. Fibroblast growth factor 23 (FGF-23) is a hormone produced by osteocytes and osteoblasts that is stimulated by increased phosphate and calcitriol. In CKD, elevated phosphate concentrations increase expression of FGF-23, which promotes phosphorus excretion and downregulates vitamin D activation in the kidney.[25] Decreased vitamin D activation in the kidney also decreases calcium absorption from the GI tract. Each of these stimulates the parathyroid glands to secrete parathyroid hormone. KEY CONCEPT The parathyroid glands release PTH in response to decreased serum calcium and increased serum phosphorus levels. The actions of PTH include the following:

- Increasing calcium resorption from bone
- Increasing calcium reabsorption from the proximal tubules in the kidney
- Decreasing phosphorus reabsorption in the proximal tubules in the kidney
- Stimulating activation of vitamin D by 1-α-hydroxylase to calcitriol (1,25-dihydroxyvitmin D_3) to promote calcium absorption in the GI tract and increased calcium mobilization from bone

All of these actions are directed at increasing serum calcium levels and decreasing serum phosphorus levels, although the activity of calcitriol also increases phosphorus absorption in the GI tract and mobilization from the bone, which can worsen hyperphosphatemia. Calcitriol also decreases PTH levels through a negative feedback loop. These measures are sufficient to correct serum calcium and phosphorus levels in the earlier stages of CKD. However, secondary hyperparathyroidism (sHPT) can still present in early stages of CKD, despite normal calcium and phosphorus levels, due to the effects of FGF-23.[25] As CKD worsens, increased FGF-23 and phosphorus and decreased calcitriol levels lead to excessive production of PTH, resulting in hyperplasia of the parathyroid glands, which decreases the sensitivity of the parathyroid glands to serum calcium levels and calcitriol feedback, further promoting sHPT. The most dramatic consequences of sHPT are vascular calcifications and alterations in bone turnover, which leads to renal osteodystrophy (ROD). The pathogenesis of sHPT and CKD-MBD are depicted in Figure 27–3.

Clinical Presentation and Diagnosis of sHPT and ROD

General

Onset of sHPT and ROD is subtle and may not be associated with symptoms.

Symptoms

sHPT and ROD are usually asymptomatic in early disease. Calcification in the joints can be associated with decreased range of motion.

Conjunctival calcifications are associated with a gritty sensation in the eyes, redness, and inflammation.

Signs

Cardiovascular: Increased stroke index, heart rate, and diastolic and mean arterial pressures.

Musculoskeletal: Bone pain, muscle weakness.

Dermatologic: Pruritus.

Laboratory Tests

Increased serum phosphorus levels.

Low to normal serum calcium levels.

Increased PTH levels.

Decreased vitamin D levels.

Diagnostic Tests

Radiographic studies show calcium–phosphate deposits in joints and/or cardiovascular system.

Bone biopsy of the iliac crest (not routinely performed)

▶ *Treatment*

General Approach KEY CONCEPT Diagnosis and management of bone disease in CKD is based on corrected serum levels of calcium and phosphorus, and intact PTH levels (iPTH). KDIGO guidelines recommend preventing hyperphosphatemia and avoiding hypercalcemia, while maintaining PTH levels as close to normal as possible in people with CKD.[26]

Current recommendations suggest that treatment of CKD-MBD should take into consideration evaluations of calcium, phosphorus, and PTH level collectively and trends over time.[26] When phosphorus levels remain elevated, phosphorus-lowering treatment should be started. Management of sHPT often requires

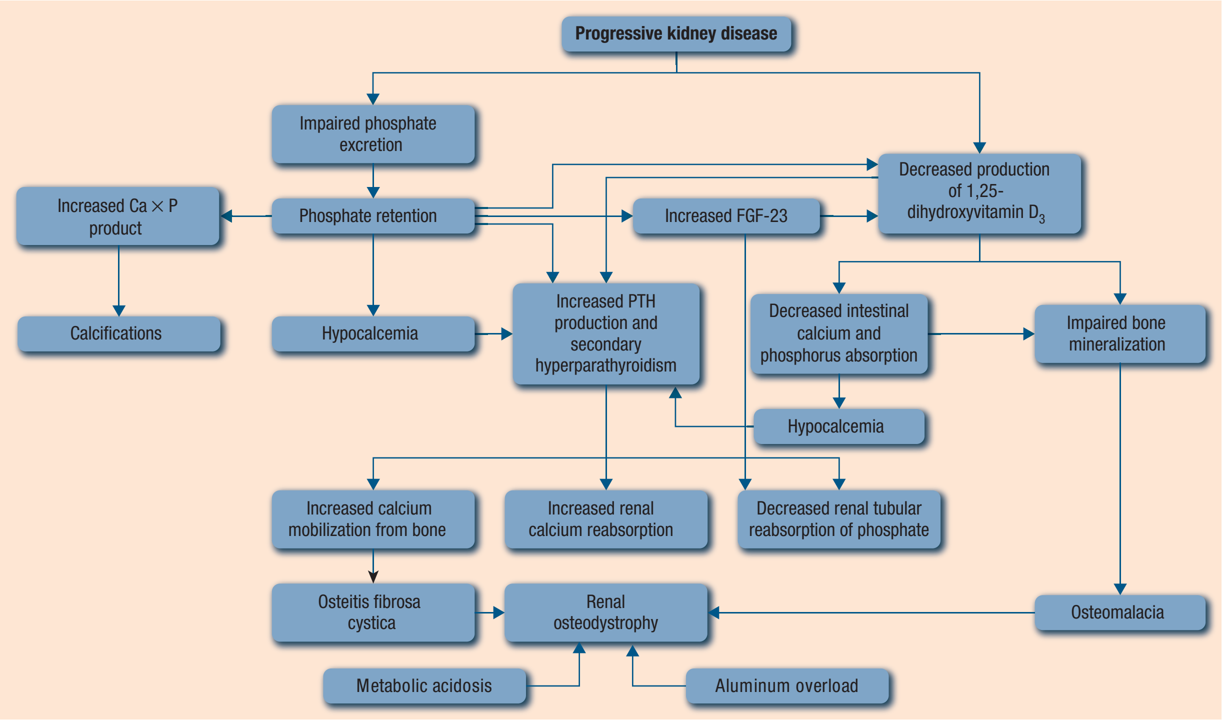

Progressive kidney disease
Impaired phosphate excretion
Decreased production of 1,25-dihydroxyvitamin D_3
Increased Ca × P product
Phosphate retention
Increased FGF-23
Calcifications
Hypocalcemia
Increased PTH production and secondary hyperparathyroidism
Decreased intestinal calcium and phosphorus absorption
Impaired bone mineralization
Hypocalcemia
Increased calcium mobilization from bone
Increased renal calcium reabsorption
Decreased renal tubular reabsorption of phosphate
Osteitis fibrosa cystica
Renal osteodystrophy
Osteomalacia
Metabolic acidosis
Aluminum overload

FIGURE 27–3. Pathogenesis of CKD-MBD. (Ca, calcium; FGF-23, fibroblast growth factor-23, PTH, parathyroid hormone.) [a]FGF-23 also increases in response to 1,25-dihydroxyvitamin D_3. [b]These adaptations are lost as kidney failure progresses. (From Hudson JQ, Wazny LD, Komenda P. Chronic kidney disease. In: DiPiro JT, Yee GC, Posey M, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill Education; 2020, with permission.)

treatment with vitamin D analogs or calcimimetics in addition to phosphorus management.

Nonpharmacologic Therapy The first-line treatment for the management of hyperphosphatemia is dietary phosphorus restriction to 800 to 1000 mg/day in patients with CKD G3 or higher who have phosphorus levels at the upper limit of the normal range or elevated iPTH levels.[26] Many foods high in phosphorus are also high in protein, which can make it difficult to restrict phosphorus intake while maintaining adequate protein intake to avoid malnutrition. HD and peritoneal dialysis (PD) can remove up to 2 to 3 g of phosphorus per week. However, this is usually insufficient to control hyperphosphatemia, and pharmacologic therapy is necessary in addition to dialysis treatment.

Other nonpharmacologic strategies to manage sHPT and CKD-MBD include restriction of aluminum exposure and parathyroidectomy. Chronic ingestion of aluminum-containing antacids and other aluminum-containing products should be avoided in patients with CKD G4 and G5 (GFR less than 30 mL/min/1.73 m^2 [0.29 mL/s/m^2]) because of the risk of aluminum toxicity and potential uptake into the bone

Parathyroidectomy is a treatment of last resort for sHPT, but should be considered in patients with persistently elevated iPTH levels above 800 pg/mL (ng/L; 85.6 pmol/L) that is refractory to medical therapy to lower serum PTH and/or phosphorus levels. A portion or all of the parathyroid tissue may be removed. After parathyroidectomy, serum calcium levels can decrease dramatically due to the low levels of PTH after the parathyroid tissue is removed, which decreases intestinal calcium absorption and bone resorption. Therefore, serum ionized calcium levels should be monitored frequently (every 4–6 hours for the first 48–72 hours) in patients receiving a parathyroidectomy. Calcium supplementation is usually necessary, administered IV initially, then orally (with vitamin D supplementation) once normal calcium levels are attained for several weeks to months after the procedure.

Pharmacologic Therapy

Phosphate-Binding Agents. When serum phosphorus levels cannot be controlled by restriction of dietary intake, phosphate-binding agents are used to bind dietary phosphate in the GI tract to form an insoluble complex that is excreted in the feces. Phosphorus absorption is decreased, thereby decreasing serum phosphorus levels. The drugs used for binding dietary phosphate are listed in Table 27–6. The selection of the phosphate binding agent should be on sequential assessment of calcium and PTH levels in addition to the phosphorus level. These agents should be administered with each meal and can be tailored to the amount of phosphorus that is typically ingested during each meal. For example, patients can take a smaller dose with smaller meals or snacks, and a larger dose with larger meals. Although phosphate binders are not FDA approved for patients with CKD who are not receiving dialysis, they are used clinically when phosphorus levels are elevated, regardless of the GFR category.

Sevelamer and lanthanum phosphate binders do not contain calcium, iron, or aluminum. These agents are particularly useful in patients with hyperphosphatemia who have elevated serum calcium levels or who have vascular or soft tissue calcifications. Sevelamer is a cationic polymer that is not systemically absorbed and binds to phosphate in the GI tract, and it prevents absorption and promotes excretion of phosphate through the GI tract via the feces. Sevelamer carbonate has an added benefit of reducing LDL-C levels,[25] and correction of metabolic acidosis. The most common side effects of sevelamer are GI complaints including nausea, constipation, and diarrhea.

Table 27–6

Phosphate-Binding Agents Used to Treat Hyperphosphatemia in CKD

Compound	Trade Name	Dosage Form	Compound Content (mg)	Elemental Compound Content (mg)	Starting Dose	Comments
Resin-based binders						
Sevelamer carbonate	Renvela®	Tablet, Powder for suspension	800		800 mg three times a day with meals	First-line agent; lowers LDL-C More expensive than calcium products; preferred in patients at risk for extraskeletal calcification May require large doses to control phosphorus levels
Elemental-based binders						
Lanthanum	Fosrenol®	Chewable tablet	500, 750, 1000	–	750–1500 mg three times a day with meals	Second-line agent; more expensive than calcium products; preferred in patients at risk for extraskeletal calcification Most patients require 1500–3000 mg/day to control phosphorus
Iron-based binders						
Ferric citrate	Auryxia®	Tablet	210	1 g ferric citrate	420 mg (2 tablets) three times a day with meals	Maximum dose is 12 tablets per day; iron is systemically absorbed
Sucroferric oxyhydroxide	Velphoro®	Chewable tablet	500	–	500 mg three times a day with meals	Do not use with levothyroxine; separate from doxycycline and alendronate by 1 hour
Calcium-containing binders						
Calcium carbonate (40% elemental calcium)	Tums®	Chewable tablet	500, 750, 1000, 1250	200, 300, 400, 500	0.5–1 g (elemental calcium) three times a day with meals	First-line agent; dissolution characteristics and phosphorus-binding effect may vary from product to product; try to limit daily intake of elemental calcium to 1500 mg/day Approximately 39 mg phosphorus bound per 1 g calcium carbonate
	Oscal®-500	Tablet	1250	500		
	Caltrate® 600	Tablet	1500	600		
	Nephro-Calci”	Tablet	1500	600		
	LiquiCal”	Liquid gelcap	1200	480		
	Calci-Chew®	Chewable tablet	1250	500		
Calcium acetate (25% elemental calcium)	PhosLo®	Capsule, Tablet	667	167	0.5–1 g (elemental calcium) three times a day with meals	First-line agent; comparable efficacy to calcium carbonate with one-half the dose of elemental calcium; do not exceed 1500 mg elemental calcium intake per day Approximately 45 mg phosphorus bound per 1 g calcium acetate By prescription only
	Phoslyra®	Solution	667/5 mL			
Aluminum-based binders						
Aluminum hydroxide	AlternaGel® Amphojel®	Suspension	Various	–	300–600 mg three times a day with meals	Third-line agents; do not use concurrently with citrate-containing products Reserve for short-term use (4 weeks) in patients with hyperphosphatemia not responding to other binders

CKD, chronic kidney disease; LDL-C, low-density lipoprotein cholesterol.

Lanthanum is a naturally occurring trivalent rare earth element (atomic number 57). Lanthanum carbonate quickly dissociates in the acidic environment of the stomach, where the lanthanum ion binds to dietary phosphorus, forming an insoluble compound that is excreted in the feces. Lanthanum has been shown to be as effective as other phosphate binders and may improve bone turnover, compared with calcium-containing products. Side effects of lanthanum include nausea, peripheral edema, and myalgias.

Sucroferric oxyhydroxide and ferric citrate are iron-based phosphate binders that lower phosphate levels. Sucroferric oxyhydroxide is an insoluble form of iron that binds to phosphate in the GI tract and has been shown to be as effective as other phosphate binders but has a benefit of a lower pill burden.[27] Sucroferric oxyhydroxide is not absorbed from the GI tract, so it does not affect serum iron levels. Ferric citrate also lowers phosphate as effectively as other phosphate binders. Unlike sucroferric oxyhydroxide, ferric citrate is absorbed from the GI tract and can also increase serum ferritin and TSAT levels. The major side effects associated with both products are GI side effects, namely, diarrhea.[27]

Calcium-containing phosphate binders (CCPBs), including calcium carbonate and calcium acetate, are effective in decreasing serum phosphate levels, as well as in increasing serum calcium levels. Calcium acetate binds more phosphorus than the carbonate salt, making it a more potent agent for binding dietary phosphate. Calcium carbonate can also aid in the correction of metabolic acidosis, another complication of kidney failure. Calcium citrate is usually not used as a phosphate-binding agent because the citrate salt can increase aluminum absorption. However, use of CCPBs can cause hypercalcemia, even at low doses, which can lead to vascular calcification and cardiovascular events in people with CKD. Furthermore, studies have shown an increase in mortality associated with CCPBs compared to non-CCPBs in both predialysis and dialysis patients.[26] Therefore, current guidelines recommend restricting the dose of CCPBs in all stages of CKD.[26] The most common adverse effects of CCPBs are constipation and hypercalcemia.

Aluminum-containing phosphate-binding agents are not recommended for chronic use in patients with CKD to avoid aluminum accumulation, leading to encephalopathy, bone disease, and anemia. These agents may be used for a short course of therapy (< 4 weeks) for significantly elevated phosphorus levels in AKI or refractory hyperphosphatemia in patients with CKD.

Vitamin D Therapy. Vitamin D regulates many processes in the body, including calcium and phosphorus absorption from the GI tract and kidney, PTH secretion, maintaining muscle, cardiovascular, immune and brain function, and glucose control. Vitamin D is activated in various tissues, with the liver and kidney being primary sites. In CKD, a decrease in renal metabolism of vitamin D decreases circulating concentrations of the activated form of vitamin D, calcitriol (1,25-dihydroxyvitamin D) and its precursor 25-hydroxyvitamin D. Vitamin D deficiency begins early in CKD and increases as kidney function declines.[28] PTH levels rise as early as CKD G3 as a result of low calcitriol concentrations.

Exogenous vitamin D compounds that mimic the activity of calcitriol act directly on the parathyroid gland to decrease PTH secretion by upregulation of the vitamin D receptor in the parathyroid gland, which decreases parathyroid gland hyperplasia and PTH synthesis and secretion. This is particularly useful when reduction of serum phosphorus levels does not sufficiently reduce PTH levels.

Vitamin D supplements (Table 27–7) can be used to lower serum PTH levels in patients with CKD. Ergocalciferol, cholecalciferol, and calcifediol have been shown to be effective in lowering PTH secretion in patients with CKD G3, and are useful in later stages of CKD to maintain adequate 25-hydroxyvitamin D levels for extrarenal functions.[26,28] In CKD G4 and G5, renal 1α-hydroxylation of vitamin D decreases and thus activated vitamin D analogs must be used to decrease PTH secretion in severe hyperparathyroidism.[26] Synthetic calcitriol has the same biologic activity as endogenous calcitriol. Doxercalciferol (1-α-hydroxyvitamin D_2) is another vitamin D analog that is hydroxylated in the liver to 1,25-dihydroxyvitamin D_2, which has the same biologic activity as calcitriol. Both calcitriol and doxercalciferol upregulate vitamin D receptors in the intestines, which increases calcium and phosphorus absorption, increasing the risk of hypercalcemia and hyperphosphatemia. It is important that serum calcium and phosphorus levels are within the normal range for the stage of CKD prior to starting either of these therapies. Paricalcitol (19-nor-1,25-dihydroxyvitamin D_2) is a vitamin D analog that has equal efficacy to calcitriol. Alfacalcidol

Table 27–7

Available Treatments for Secondary Hyperparathyroidism

Generic Name	Trade Name	Dosage Range	Dosage Forms	Frequency of Administration
Vitamin D (prohormone)				
Ergocalciferol	Vitamin D_2	400–50,000 IU	PO	Daily (doses of 400–2000 IU) Weekly or monthly for higher doses (50,000 IU)
Cholecalciferol	Vitamin D_3			
Calcifediol	Rayaldee®	30–60 mcg	PO	Daily
Active vitamin D				
Calcitriol	Calcijex®	0.5–5 mcg	IV	Three times per week
	Rocaltrol®	0.25–5 mcg	PO	Daily, every other day, or three times per week
Vitamin D analogs				
Paricalcitol	Zemplar®	1–4 mcg	PO	Daily or three times per week
		2.5–15 mcg	IV	Three times per week
Doxercalciferol	Hectorol®	5–20 mcg	PO	Daily or three times per week
		2–8 mcg	IV	Three times per week
Calcimimetics				
Cinacalcet	Sensipar”	30–180 mg	PO	Daily
Etelcalcitide	Parsabiv”	2.5–15 mg	IV	3 times per week

Patient Encounter 3

A 52 year-old Hispanic female with a history of hypertension presents to your clinic for a routine follow-up. She has no complaints at this time.

PMH: hypertension, diagnosed 12 years ago; hyperlipidemia

Current meds: Aspirin 81 mg orally daily; atorvastatin 40 mg orally daily; carvedilol 12.5 mg orally twice daily; lisinopril 20 mg orally daily; sodium bicarbonate 1300 mg orally twice daily; Ergocalciferol 50,000 units orally once a week or calcitriol 0.5 mcg orally daily.

ROS: Unremarkable.

PE:

VS: BP 136/84 mm Hg; P 70 bpm; T 96.3°F (35.7°C); ht 5′7″ (170 cm); wt 178 lb (80.7 kg)

CV: RRR, normal S_1, S_2

Abd: No organomegaly, bruits, tenderness; (+) bowel sounds; heme (–) stool

Ext: 2+ edema bilaterally

Labs: Sodium 139 mEq/L (mmol/L); potassium 5.2 mEq/L (mmol/L); chloride 109 mEq/L (mmol/L); carbon dioxide 24 mEq/L (27 mmol/L); BUN 42 mg/dL (15 mmol/L urea); SCr 3.4 mg/dL (301 μmol/L); glucose 98 mg/dL (5.4 mmol/L); calcium 8.8 mg/dL (2.2 mmol/L); phosphate 7.4 mg/dL (2.39 mmol/L); intact parathyroid hormone (iPTH) 458 pg/mL (ng/L; 48.6 pmol/L); WBC 5.6×10^3 cells/mm^3 (5.6×10^9/L); RBC 3.9×10^6 cells/mm^3 (3.9×10^{12}/L); Hgb 9.8 g/dL (98 g/L; 6.08 mmol/L); Hct 29% (0.29); platelets 272×10^3 cells/mm^3 (272×10^9/L)

What signs are consistent with CKD mineral and bone disorder (MBD)?

What treatment would you recommend for CKD-MBD?

(1-α-hydroxyvitamin D_3), falecalcitriol, and 22-oxacalcitriol (maxacalcitol) are only available outside the United States.

Calcimimetics. Cinacalcet and etelcalcetide are calcimimetics that increase the sensitivity of receptors on the parathyroid gland to serum calcium levels to reduce PTH secretion but have no effect on intestinal absorption of calcium or phosphorus. Calcimimetics also reduce FGF-23 and serum calcium levels.[29] Thus, calcimimetics are beneficial for patients with elevated PTH levels who have increased calcium or phosphorus levels or cannot use vitamin D therapy. Cinacalcet is an oral calcimimetic that is most widely used for sHPT. Etelcalcetide is an injectable agent that lowers PTH levels and serum calcium levels to a greater degree than cinacalcet.[29] Gastrointestinal side effects, including nausea and vomiting, are the most common side effects for both agents. Hypocalcemia resulting from calcimimetics can result in QTc prolongation[29] and may lower the seizure threshold in patients with seizure disorders.

▶ *Outcome Evaluation*

KDIGO guidelines recommend monitoring serum calcium, phosphorus, and PTH levels early in CKD, with increasing frequency as renal function declines. Calcium and phosphorus levels should be monitored every 6 to 12 months in CKD G3a to G3b; every 3 to 6 months in CKD G4, and every 1 to 3 months in CKD G5. PTH levels should be monitored every 6 to 12 months for CKD G3-G4 and every 3 to 6 months in CKD G5.[26]

Monitor serum calcium and phosphorus levels regularly in patients receiving phosphate-binding agents. When initiating therapy, monitor serum levels every 1 to 4 weeks, depending on the severity of hyperphosphatemia. Titrate doses of phosphate binders to maintain phosphorus levels near normal. Once target levels are achieved, monitor phosphorus and corrected serum calcium or ionizsed calcium levels every 1 to 3 months. Monitor-iPTH levels monthly while initiating vitamin D therapy, then every 3 months once stable iPTH levels are achieved. When starting or increasing the dose of cinacalcet, monitor serum calcium and phosphorus levels within 1 week; iPTH levels should be monitored within 1 to 4 weeks. Once target levels are achieved, decrease monitoring to every 3 months.

Impaired Electrolyte and Acid-Base Homeostasis

The kidney is responsible for regulating homeostasis for sodium, potassium, water, and acid-base. Reductions in the number of functioning nephrons decrease glomerular filtration regulation of electrolytes and acid secretion.

▶ *Pathophysiology*

As the number of functioning nephrons decreases, the remaining nephrons are able to increase excretion of sodium, water, potassium, and hydrogen ions. However, this is limited and as the number of functioning nephrons decreases as CKD progresses, total excretion of electrolytes and fluid eventually decreases.

Sodium and water balance is maintained by natriuretic peptides, namely, atrial natriuretic peptide (ANP), which increases sodium excretion in the kidneys. The relative increase in sodium excretion by a smaller number of functioning nephrons results in an osmotic diuresis that promotes water excretion but impairs the ability of the kidneys to concentrate and dilute urine. Thus, urine becomes fixed at an osmolality close to that of the plasma, approximately 300 mOsm/kg (mmol/kg) and presents as nocturia. Sodium and fluid retention increases intravascular volume and raises systemic blood pressure, which can present as early as CKD G3a to G3b.[30]

Potassium excretion occurs in both the distal tubules of the kidney and in the GI tract, which is mediated by aldosterone stimulation. Aldosterone increases in response to rising serum potassium, which then increases potassium excretion in both the functioning nephrons and GI tract. This maintains serum potassium concentrations within the normal range through CKD G1 to G4. Hyperkalemia begins to develop when GFR falls below 20% of normal, when the number of functioning nephrons and renal potassium secretion is so low that the capacity of the GI tract to excrete potassium has been exceeded.[31]

Medications can increase the risk of hyperkalemia in patients with CKD, including ACEI and ARBs, used for the treatment of proteinuria and hypertension. Potassium-sparing diuretics, used for the treatment of edema and chronic heart failure, can also exacerbate the development of hyperkalemia, and they should be used with caution in patients with CKD G3 or higher.

Hydrogen ions are excreted at the same rate of production by the kidney via buffers in the urine created by ammonia generation and phosphate excretion to maintain the pH of body fluids within a very narrow range. As kidney function declines, bicarbonate reabsorption is maintained, but hydrogen excretion is decreased because the ability of the kidney to generate ammonia is impaired. The positive hydrogen balance leads to metabolic acidosis, which is characterized by a serum bicarbonate level of 15 to 20 mEq/L (mmol/L), and an elevated anion gap greater than 17 mEq/L (mmol/L), resulting in a pH less than 7.35. Metabolic acidosis generally presents when the GFR declines below 25 mL/min/1.73 m^2 (0.24 mL/s/m^2).[32]

Metabolic acidosis contributes to various complications associated with CKD. Metabolic acidosis can directly cause bone disease, particularly in children, and contribute significantly to the bone disease induced by secondary hyperparathyroidism, as discussed previously. Metabolic acidosis also decreases hepatic albumin synthesis, which contributes to hypoalbuminemia and muscle wasting. Furthermore, metabolic acidosis can accelerate progression of CKD by causing tubular injury. Reversal of metabolic acidosis has been demonstrated to decrease progression of CKD, improve bone disease and increase serum albumin concentrations.[32]

▶ *Treatment*

Nonpharmacologic Treatment The kidney is unable to adjust to abrupt changes in sodium and potassium intake in patients with severe CKD. Electrolyte disorders resulting from an acute increase in intake can be more severe and prolonged.

Clinical Presentation and Diagnosis of Electrolyte and Acid-Base Abnormalities

General

Alterations in sodium and water balance in CKD manifests as increased edema.

Hyperkalemia is generally asymptomatic in patients with CKD until serum potassium levels are greater than 5.5 mEq/L (mmol/L), when cardiac abnormalities present.

Metabolic acidosis is generally asymptomatic in patients with CKD.

Symptoms

Nocturia can present in CKD G3a-G3b.

Edema generally presents in CKD G4 or later.

Mild hyperkalemia and metabolic acidosis are generally not associated with overt symptoms.

Symptoms of hyperkalemia generally appear when GFR falls below 20 ml/min/1.73m^2 (0.19 ml/s/m^2), such as muscle weakness, fatigue, nausea, and paresthesias.

Symptoms of chronic metabolic acidosis present as bone abnormalities and growth retardation in children.

Signs

Cardiovascular:

Sodium: Worsening hypertension, edema.

Potassium: ECG changes (peaked T waves, widened QRS complex, loss of P wave).

Genitourinary: Sodium abnormalities result in change in urine volume and consistency.

Laboratory Tests

Sodium: Increased blood pressure; sodium levels remain within the normal range; urine osmolality is generally fixed at 300 mOsm/kg (mmol/kg).

Potassium: Increased serum potassium levels.

Metabolic acidosis: Decreased serum bicarbonate levels (CO_2); decreased pH.

Sodium and Water. Patients with CKD should be advised to refrain from adding salt to their diet but should not restrict sodium intake. Changes in sodium intake should occur slowly over a period of several days to allow adequate time for the kidney to adjust urinary sodium content. Sodium restriction produces a negative sodium balance, which causes fluid excretion to restore sodium balance. The resulting volume contraction can decrease perfusion of the kidney and hasten the decline in GFR. Saline-containing IV solutions should be used cautiously in patients with CKD because the salt load may precipitate volume overload.

Fluid restriction is generally unnecessary as long as sodium intake is controlled. The thirst mechanism remains intact in CKD to maintain total body water and plasma osmolality near normal levels. Fluid intake should be maintained at the rate of urine output to replace urine losses, usually fixed at approximately 2 L/day as urine concentrating ability is lost. Significant increases in free water intake orally or IV can precipitate volume overload and hyponatremia. Patients with CKD G5 require RRT to maintain normal volume status. Fluid intake is often limited in patients receiving HD to prevent fluid overload between dialysis sessions.

Diuretic therapy is often necessary to prevent volume overload in patients with CKD who still produce urine. When GFR falls below 30 mL/min/1.73 m^2 (0.29 mL/s/m^2), thiazide diuretics alone may not be effective in reducing fluid retention.[21] Loop diuretics are most frequently used to increase sodium and water excretion. As CKD progresses, higher doses, as much as 80 to 1000 mg/day of oral furosemide, or continuous infusion of loop diuretics may be needed, or combination therapy with loop and thiazide diuretics to increase sodium and water excretion.[17]

Potassium. Patients who develop hyperkalemia should restrict dietary intake of potassium to 50 to 80 mEq (mmol) per day. Potassium concentrations can also be altered in the dialysate for patients receiving HD and PD to manage hyperkalemia. Because GI excretion of potassium plays a large role in potassium homeostasis in patients with CKD G5, a good bowel regimen is essential to minimize constipation. Severe hyperkalemia is most effectively managed by HD.

Acute hyperkalemia can be managed medically until dialysis can be initiated. Loop diuretics, some potassium-binding agents, and fludrocortisone are useful in the management of hyperkalemia in patients with CKD. Acute hyperkalemia that results in cardiac abnormalities can be managed with calcium, insulin, and dextrose; sodium bicarbonate; or β_2-agonist. The management of hyperkalemia is discussed in more detail in Chapter 28. Potassium-binding agents are particularly useful in CKD to lower potassium levels. Potassium-binding agents decrease potassium levels by exchanging ions in the GI tract to enhance GI excretion of potassium. Sodium polystyrene sulfonate (SPS) exchanges potassium for sodium; however, it is poorly tolerated because of GI side effects. Newer agents are better tolerated and are preferred for managing potassium levels in CKD. Patiromer exchanges potassium for calcium, primarily in the colon. The recommended dose of patiromer is 8.4 g once daily and can be titrated up to 25.2 g/day. Doses of patiromer should be separated from other medications by at least 3 hours. Both SPS and patiromer have a longer onset of action and are not suitable for acute treatment of hyperkalemia. Sodium zirconium cyclosilicate (SZC) exchanges potassium for sodium and hydrogen ions in the lower intestines and colon. Potassium levels are reduced within 1 hour of administration, making it useful for acute management of hyperkalemia in addition to long-term management. The recommended dose of SZC is 10 g once daily for chronic hyperkalemia but can be administered more frequently for acute hyperkalemia. Patiromer and SZC are associated with GI side effects, including constipation, diarrhea, nausea, and abdominal discomfort, but side effects are more pronounced with patiromer. SZC can also cause edema, which can be managed with diuretics. Use of potassium-binding agents can reduce the hyperkalemic effects of ACEIs and ARBs and prolong their use in latter stages of CKD.[33]

Metabolic Acidosis. Pharmacologic therapy with sodium bicarbonate or citrate/citric acid preparations may be needed in patients with CKD G3 or higher to replenish body stores of bicarbonate. Calcium carbonate, used to bind phosphorus in sHPT, also aid in increasing serum bicarbonate levels, in conjunction with other agents. The management of acidosis is discussed in more detail in Chapter 29.

▶ *Outcome Evaluation*

Monitor serum electrolytes and bicarbonate levels regularly. Monitor edema after initiation of diuretic therapy. Monitor fluid intake to ensure obligatory losses are being met and avoid dehydration. If adequate diuresis is not attained with a single agent, consider combination therapy with another diuretic, such as a loop plus thiazide diuretic. In patients with cardiac abnormalities due to elevated potassium levels, monitor ECG continuously until serum potassium levels drop below 5 mEq/L (mmol/L) or cardiac abnormalities resolve. Evaluate serum potassium and glucose levels within 1 hour in patients who receive insulin and dextrose therapy. Evaluate serum potassium levels within 2 to 4 hours after treatment with patiromer, SPS or diuretics. Repeat doses of diuretics or SPS if necessary, until serum potassium levels fall below 5 mEq/L (mmol/L). Monitor blood pressure and serum potassium levels in 1 week after starting fludrocortisone. Correct metabolic acidosis slowly to prevent the development of metabolic alkalosis or other electrolyte abnormalities.

RENAL REPLACEMENT THERAPY

Patients who progress to ESKD require RRT. The modalities that are used for RRT are dialysis, including HD and PD, and kidney transplantation. The USRDS reported that the number of patients with ESKD was 726,331, with 124,675 new cases diagnosed in 2016.[3] The mortality rate of patients with ESKD was 134 per 1000-patient years in 2016, which is decreased from 190 per 1000-patient years in 2001.[3] The modality of RRT influences mortality considerably, with a mortality of 163 per 1000-patient years with dialysis, compared to 29 per 1000-patient years mortality with transplant.[3] The improved survival makes kidney transplantation the preferred method of RRT; however, organ availability limits the number of patients who can receive a kidney transplant. Only 2.5% of patients with newly diagnosed ESKD receive kidney transplants each year.[3] Therefore, the most common form of RRT is dialysis, accounting for more than 97% of all patients with ESKD.[3] The principles and complications associated with dialysis are discussed later. Chapter 55 discusses the principles of kidney transplantation.

Indications for Dialysis

KEY CONCEPT Planning for dialysis should begin when GFR falls less than 30 mL/min/1.73 m^2 (0.29 mL/s/m^2) (CKD G4), when progression to ESKD is inevitable, to allow time to educate the patient and family on the treatment modalities for renal replacement and establish the appropriate access for the modality of choice.[34] Ideally, initiation of dialysis should be done at a point when the patient is ready to undergo treatment, rather than when the patient is in emergent need of dialysis.

Initiation of dialysis depends on the patient's clinical status and not based solely on laboratory values. Symptoms that may indicate the need for dialysis include persistent anorexia, nausea, vomiting, fatigue, and pruritus. Other criteria that indicate the need for dialysis include declining nutritional status, declining serum albumin levels, electrolyte abnormalities, particularly hyperkalemia, and volume overload, which may manifest as chronic heart failure and uncontrolled hypertension. Blood urea nitrogen (BUN) and SCr levels may be used as a guide for the initiation of dialysis, but they should not be the absolute indicator. Dialysis is initiated in most patients after the GFR falls below 15 mL/min/1.73 m^2 (0.14 mL/s/m^2).[34] Patients should determine which modality of dialysis to use based on their own preferences. Advantages and disadvantages of HD and PD are listed in Tables 27–8 and 27–9, respectively.

The goals of dialysis are to remove toxic metabolites to decrease uremic symptoms, correct electrolyte abnormalities, restore acid–base status, and maintain volume status to ultimately improve quality of life and decrease the morbidity and mortality associated with ESKD.

Table 27–8

Advantages and Disadvantages of Hemodialysis

Advantages

1. Higher solute clearance allows intermittent treatment
2. Parameters of adequacy of dialysis are better defined and therefore underdialysis can be detected early
3. The technique's failure rate is low
4. Even though intermittent heparinization is required, hemostasis parameters are better corrected with hemodialysis than peritoneal dialysis
5. In-center hemodialysis enables closer monitoring of the patient

Disadvantages

1. Requires multiple visits each week to the hemodialysis center, which translates into loss of control by the patient
2. Dysequilibrium, dialysis, hypotension, and muscle cramps are common. May require months before patient adjusts to hemodialysis
3. Infections in hemodialysis patients may be related to the choice of membranes; the complement-activating membranes are more deleterious
4. Vascular access is frequently associated with infection and thrombosis
5. Decline of residual renal function is more rapid compared with peritoneal dialysis

From Sowinski KM, Churchwell MD, Decker BS. Hemodialysis and peritoneal dialysis. In: DiPiro JT, Yee GC, Posey M, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020, with permission.

Hemodialysis

HD is the most common method of RRT, initiated in 88% of US patients with newly diagnosed ESKD each year, with a total of 428,588 patients receiving HD in 2014.[3] Home HD is becoming increasingly more popular, but most patients continue to receive HD from a dialysis center.

Table 27–9

Advantages and Disadvantages of Peritoneal Dialysis

Advantages

1. More hemodynamic stability (blood pressure) due to slow ultrafiltration rate
2. Increased clearance of larger solutes, which may explain good clinical status in spite of lower urea clearance
3. Better preservation of residual renal function
4. Convenient intraperitoneal route of administration of drugs such as antibiotics and insulin
5. Suitable for elderly and very young patients who may not tolerate hemodialysis well
6. Freedom from the "machine" gives the patient a sense of independence (for continuous ambulatory peritoneal dialysis)
7. Less blood loss and iron deficiency, resulting in easier management of anemia or reduced requirements for erythropoietin and parenteral iron
8. Systemic heparin not required
9. Subcutaneous versus IV erythropoietin or darbepoetin is usual, which may reduce overall doses and be more physiologic

Disadvantages

1. Protein and amino acid losses through the peritoneum and reduced appetite owing to continuous glucose load and sense of abdominal fullness predispose to malnutrition
2. Risk of peritonitis
3. Catheter malfunction, and exit site and tunnel infection
4. Inadequate ultrafiltration and solute dialysis in patients with a large body size, unless large volumes and frequent exchanges are employed
5. Patient burnout and high rate of technique failure
6. Risk of obesity with excessive glucose absorption
7. Mechanical problems such as hernias, dialysate leaks, hemorrhoids, or back pain may occur
8. Extensive abdominal surgery may preclude peritoneal dialysis
9. No convenient access for IV iron administration

From Sowinski KM, Churchwell MD, Decker BS. Hemodialysis and peritoneal dialysis. In: DiPiro JT, Yee GC, Posey M, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020, with permission.

▸ *Principles of Hemodialysis*

KEY CONCEPT Hemodialysis involves the exposure of blood to a semipermeable membrane (dialyzer) against which a physiologic solution (dialysate) is flowing (Figure 27–4). The dialyzer is composed of thousands of capillary fibers made up of the semipermeable membrane, which are enclosed in the dialyzer, to increase the surface area of blood exposure to maximize the efficiency of removing substances. The dialysate is composed of purified water and electrolytes, and it is run through the dialyzer countercurrent to the blood on the other side of the semipermeable membrane. The process allows for the removal of several substances from the bloodstream, including water, urea, creatinine, electrolytes, uremic toxins, and some drugs. Sterilization is not required for dialysate because the membrane prevents bacteria from entering into the bloodstream. However, if the membrane ruptures during HD, infection becomes a major concern for the patient.

Three types of membranes used for dialysis are classified by the size of the pores and the ability to remove solutes from the bloodstream: low flux, high efficiency, and high flux. Low flux membranes have small pores, which limit solute removal to relatively small molecules, such as creatinine and urea. High-efficiency membranes also have small pores but have a higher surface area

Patient Encounter 4, Part 1

A 33-year-old Caucasian male with a history of focal segmental glomerulosclerosis (FSGS) presents to the clinic with complaints that he "feels terrible and exhausted and foggy." He has not felt like eating for several weeks and has lost 12 lb (5.5 kg) in the last 2 months. As of yesterday, he is unable to keep any food down and has been very nauseous and vomiting.

PMH: FSGS; hypertension; anxiety

Current medications: Venlafaxine XR 150 mg orally daily; vitamin D_3 2000 international units orally daily; lisinopril 20 mg orally daily; metoprolol 50 mg orally twice daily; calcium acetate 1,334 mg orally three times daily with meals; pravastatin 40 mg orally daily.

ROS: Lethargic male in mild distress.

PE:

VS: BP 178/108 mm Hg; P 86 bpm; T 97.2°F (36.2°C); ht 5′10″ (178 cm); wt 150 lb (68 kg)

CV: RRR, normal S_1, S_2, present

Lungs: negative for crackles at bases; negative for inspiratory wheezes

Ext: 4+ bilateral lower extremity edema present to mid-thigh

Labs: Sodium 138 mEq/L (mmol/L); potassium 7.2 mEq/L (mmol/L); chloride 106 mEq/L (mmol/L); carbon dioxide 10 mEq/L (mmol/L); BUN 108 mg/dL (38.5 mmol/L); SCr 8.1 mg/dL (716 μmol/L); glucose 62 mg/dL (3.4 mmol/L); calcium 9.8 mg/dL (2.45 mmol/L); phosphate 5.6 mg/dL (1.81 mmol/L); iPTH 315 pg/mL (ng/L; 33.7 pmol/L); WBC 6.8×10^3 cells/mm^3 (6.8×10^9/L); RBC 4.0×10^6 cells/mm^3 (4.0×10^{12}/L); Hgb 10.4 g/dL (104 g/L; 6.46 mmol/L); Hct 30% (0.30); platelets 278×10^3 cells/mm^3 (278×10^9/L)

What indications does the patient have for dialysis?

What options for renal replacement therapy exist for the patient?

What are the advantages and disadvantages of each modality for renal replacement therapy?

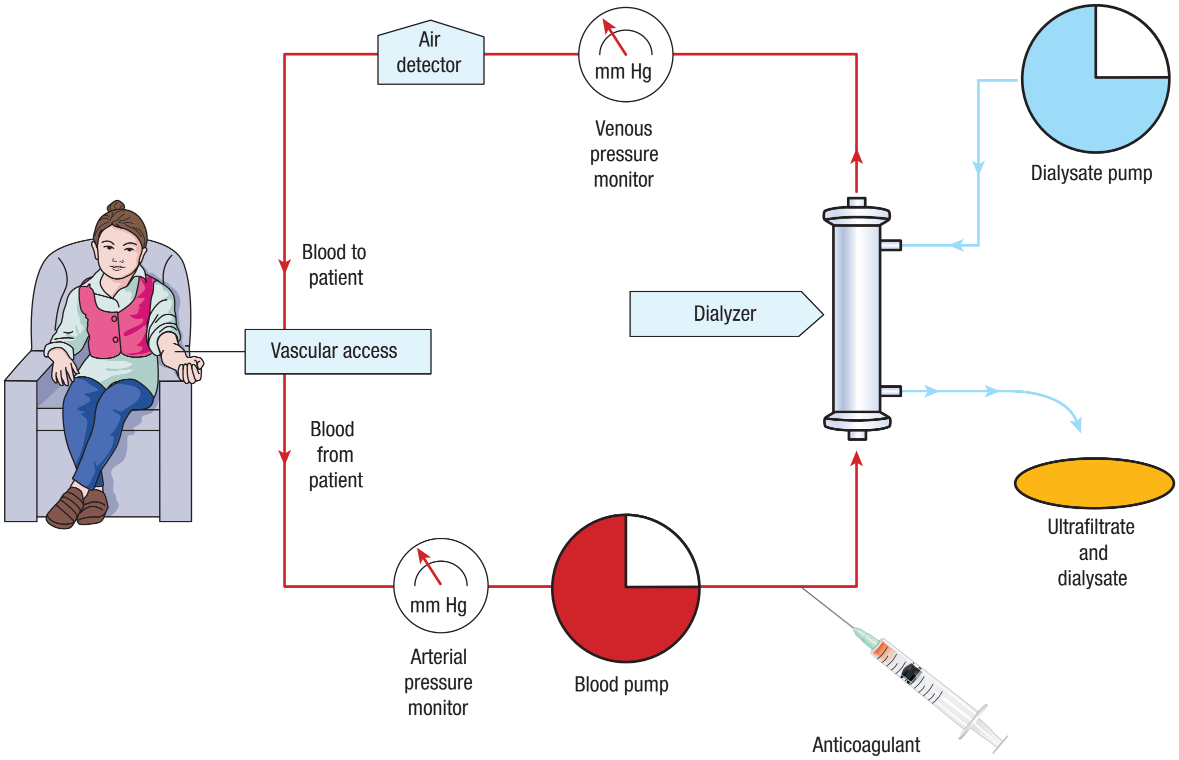


FIGURE 27–4. In hemodialysis, the patient's blood is pumped to the dialyzer at a rate of 300 to 600 mL/min. An anticoagulant (usually heparin) is administered to prevent clotting in the dialyzer. The dialysate is pumped at the rate of 500 to 1000 mL/min through the dialyzer countercurrent to the flow of blood. The rate of fluid removal from the patient is controlled by adjusting the pressure in the dialysate compartment. (From Sowinski KM, Churchwell MD, Decker BS. Hemodialysis and peritoneal dialysis. In: DiPiro JT, Yee GC, Posey M, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020, with permission.)

that increases removal of small molecules, such as water, urea, and creatinine from the blood. The most widely used dialyzers are high-flux membranes which larger pores that allow for the removal of substances with higher molecular-weight, including some drugs, such as vancomycin.

Three primary processes are utilized for the removal of substances from the blood:

- Diffusion is the movement of a solute across the dialyzer membrane from an area of higher concentration (usually the blood) to a lower concentration (usually the dialysate). This process removes small molecules from the bloodstream, such as electrolytes. At times, solutes can be added to the dialysate that are diffused into the bloodstream. Changing the composition of the dialysate allows for control of the amount of electrolytes that are being removed.
- Ultrafiltration is the movement of solvent (plasma water) across the dialyzer membrane by applying hydrostatic or osmotic pressure, and it is the primary means for removing water from the bloodstream. Changing the hydrostatic pressure applied to the dialyzer or the osmotic concentration of the dialysate allows for control of the amount of water being removed.
- Convection is the movement of dissolved solutes across the dialyzer membrane by "dragging" the solutes along a pressure gradient with a fluid transport and is the primary means for larger molecules to be removed from the bloodstream. Changing the pore size of the dialyzer membrane alters the efficiency of convection and allows for control of the amount of water removed in relation to the amount of solute being removed.

▶ *Vascular Access*

Long-term permanent access to the bloodstream is a key component of HD. There are three primary techniques used to obtain permanent vascular access in patients receiving HD: arteriovenous fistulas (AVFs), arteriovenous grafts (AVGs), and central venous catheters. An AVF is the preferred access method because it has the longest survival rate and the fewest complications. An AVF is made by creating an **anastomosis** between an artery and a vein, usually in the forearm of the nondominant arm (Figure 27–5). An AVG results in a similar access site but uses a synthetic graft, usually made of polytetrafluoroethylene, to connect the artery and vein in the forearm (Figure 27–5). The advantages of the AVG are that it is able to be used within 2 to 3 weeks, compared with 2 to 3 months for an AVF. However, AVGs are complicated by stenosis, thrombosis, and infections, which lead to a shorter survival time of the graft. Double-lumen venous catheters, placed in the femoral, subclavian, or jugular vein, are often used as temporary access while waiting for the AVF or AVG to mature. The catheters are tunneled beneath the skin to an exit site to reduce the risk of infection. Venous catheters can also be used as permanent access in patients in whom arteriovenous access cannot be established. However, venous catheters carry the greatest risk of complications, namely, thrombosis and infections.

▶ *Complications of Hemodialysis*

Complications associated with HD include hypotension, muscle cramping, thrombosis, infection, and vitamin depletion. The physiology of these complications is described below and the management is listed in Table 27–10.

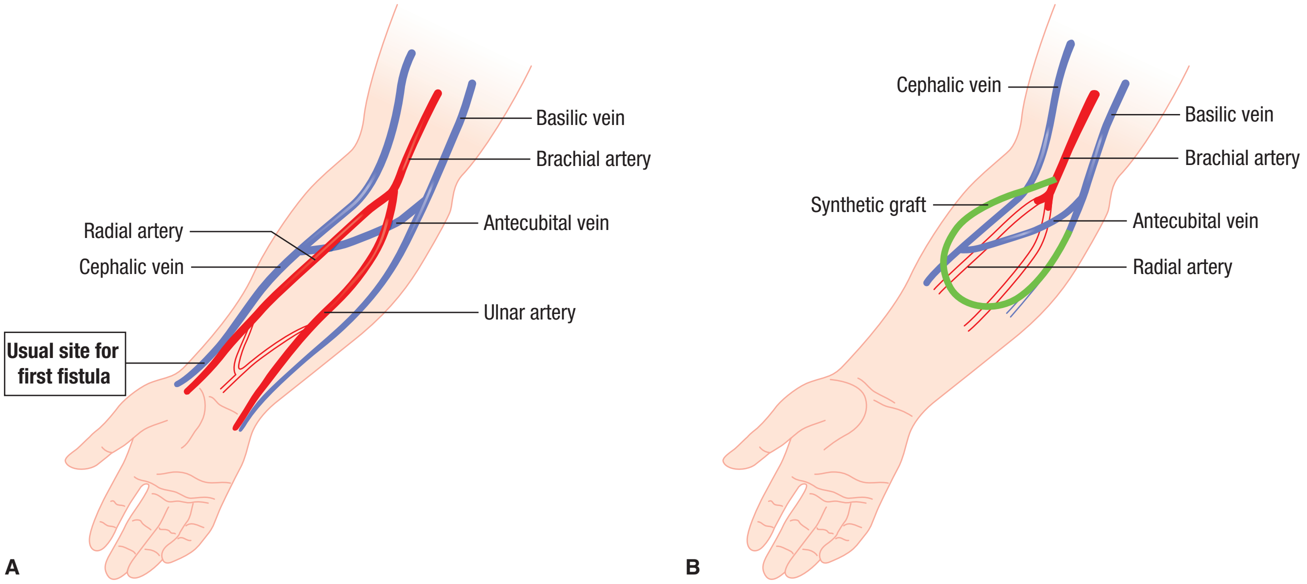


FIGURE 27–5. The predominant types of vascular access for chronic dialysis patients are (A) the arteriovenous fistula and (B) the synthetic arteriovenous forearm graft. The first primary arteriovenous fistula is usually created by the surgical anastomosis of the cephalic vein with the radial artery. The flow of blood from the higher-pressure arterial system results in hypertrophy of the vein. The most common AV graft (depicted in green) is between the brachial artery and the basilic or cephalic vein. The flow of blood may be diminished in the radial and ulnar arteries because it preferentially flows into the low pressure graft. (From Sowinski KM, Churchwell MD, Decker BS. Hemodialysis and peritoneal dialysis. In: DiPiro JT, Yee GC, Posey M, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020, with permission.)

Table 27–10

Management of Complications Associated with Hemodialysis

Hypotension	Acute treatment	Decrease ultrafiltration rate Place in Trendelenburg position (head lower than feet) Normal saline 100–200 mL Hypertonic saline (23.4%) 10–20 mL Mannitol 12.5 g
	Prevention	Accurate determination of "dry weight" Midodrine 2.5–10 mg 30 minutes prior to HD Other options with limited evidence: Levocarnitine 20 mg/kg IV after HD Sertraline 50–100 mg daily Fludrocortisone 0.1 mg before HD
Muscle cramps	Acute treatment	Normal saline 100–200 mL Hypertonic saline (23.4%) 10–20 mL Dextrose 50% 50 mL (for nondiabetic patients)
	Prevention	Decrease ultrafiltration rate Accurate determination of "dry weight" Stretching exercises, massage, flexing, compression devices Vitamin E 400 IU daily
Central Venous Catheter Thrombosis	Acute treatment	Normal saline flush Alteplase 2 mg/2 mL per catheter lumen port Reteplase 0.4 U/0.4 mL per catheter lumen port
	Prevention	Heparin lock (1000–10,000 units/1 mL) Sodium citrate 4% lock
Vitamin depletion	Prevention	Multivitamin B complex with vitamin C supplement

Hypotension Hypotension is the most common complication seen during HD. It has been reported to occur with approximately 20% to 30% of dialysis sessions.[35]

Pathophysiology. Hypotension associated with HD manifests as a symptomatic decrease in systolic blood pressure of more than 20 mm Hg or a decrease in mean arterial pressure of more than 10 mm Hg during the dialysis session. The primary cause is fluid removal from the bloodstream. Ultrafiltration removes fluid from the plasma, which promotes redistribution of fluids from extracellular spaces into the plasma. However, decreased serum albumin levels and removal of solutes from the bloodstream reduce the osmotic pressure of the plasma relative to the extracellular spaces, slowing redistribution during HD. The decreased plasma volume causes hypotension. Other factors that can contribute to hypotension include antihypertensive medications prior to HD, a target "dry weight" (the target weight after HD session is complete) that is too low, diastolic or autonomic dysfunction, low dialysate calcium or sodium, high dialysate temperature, or ingesting meals prior to or during HD. Elderly age, diabetes, autonomic neuropathy, uremia, and cardiac disease also increase the potential for hypotension.[35] The symptoms associated with hypotension during dialysis include dizziness, nausea, vomiting, abdominal pain, and muscle cramping.

Muscle Cramps Muscle cramps are reported in as many as 35% to 86% of patients receiving HD.[36] The cause is often related to excessive ultrafiltration, which causes hypoperfusion of the muscles. Other contributing factors to the development of muscle cramps include hypotension, hypoosmolality, and electrolyte and acid–base imbalances that occur during HD sessions.[36]

Thrombosis Thrombosis associated with HD most commonly occurs in patients with venous catheter access for dialysis and is a common cause of catheter failure. However, thrombosis can occur in synthetic grafts and less frequently in AVF.

Patient Encounter 4, Part 2

The patient returns to the dialysis center 1 month later for routine hemodialysis. Two hours after starting dialysis, he complains of muscle cramps

PE:

VS: BP 121/68 mm Hg; P 72 bpm; T 98.9° F (37.2° C); wt 155 lb (70.3 kg)

What is the most likely cause of his cramping?

What treatment would you recommend?

Infection Infections are an important cause of morbidity and mortality in patients receiving hHD. The cause of infection is usually related to organisms found on the skin, namely, *Staphylococcus epidermidis* and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA). Gram-negative bacteria are more commonly associated with bacteremia. The greatest risk to patients receiving HD is the development of bacteremia, which is commonly associated with coagulase negative staphylococci and gram-negative bacteria. The risk of bacteremia is up to 10 times higher with venous catheters compared to AVF.[37]

Blood cultures should be obtained for any patient receiving HD who develops a fever. Nonpharmacologic management of infections involves preventive measures with sterile technique, proper disinfection, and minimizing the use and duration of venous catheters for HD access.

Pharmacologic management of infections should cover the gram-positive organisms that most frequently cause access-related infections. Patients who have positive blood cultures should receive treatment tailored to the organism isolated. Preventive measures for access-related infections include mupirocin at the exit site and povidone-iodine ointment. The recommendations of the National Kidney Foundation (NKF) for treatment of infections associated with HD are listed in Table 27–11.[36]

Vitamin Depletion Water-soluble vitamins removed by HD contribute to malnutrition and vitamin deficiency syndromes. Patients receiving HD often require replacement of water-soluble vitamins to prevent adverse effects. The vitamins that may require replacement are ascorbic acid, thiamine, biotin, folic acid, riboflavin, and pyridoxine. Patients receiving HD should take a multivitamin B complex with vitamin C supplement, but they should not take supplements that include fat-soluble vitamins, such as vitamins A, E, or K, which can accumulate in patients with kidney failure.

Peritoneal Dialysis

PD is initiated in 9.7% of patients with newly diagnosed ESKD each year.[3] In 2016, 51,057 patients were receiving PD.[3] PD is associated with improved survival compared with HD.[3] PD preserves residual renal function, which improves cardiovascular stability and may account for the improved survival. Thus, PD may be the preferred method of dialysis in patients with residual renal function.

▶ *Principles of Peritoneal Dialysis*

PD utilizes similar principles as HD in that blood is exposed to a semipermeable membrane against which a physiologic solution is placed. In the case of PD, however, the semipermeable membrane is the peritoneal membrane, and a sterile dialysate is instilled into the peritoneal cavity. The peritoneal membrane is composed of a continuous single layer of mesothelial cells that covers the abdominal and pelvic walls on one side of the peritoneal cavity, and the visceral organs including the GI tract, liver, spleen, and diaphragm on the other side. The mesothelial cells are covered by microvilli that increase the surface area of the peritoneal membrane to approximate body surface area (1–2 m^2). Blood vessels that supply the abdominal organs, muscle, and mesentery serve as the blood component of the system.

The gaps between the mesothelial cells allow for large solutes to pass through into the bloodstream. Both the interstitium and endothelial cells of the blood vessels provide resistance to limit the solute size that is removed from the blood. Diffusion is the most important component of solute transport in PD, which is enhanced by the large surface area and volume of dialysate, as well as contact time with the peritoneal membrane. Ultrafiltration is achieved in PD by creating an osmotic pressure gradient between the dialysate and the blood. Traditionally, glucose has been used

Table 27–11

Management of Hemodialysis Access Infections[36]

AV Fistula	Treat as subacute bacterial endocarditis for 6 weeks Initial antibiotic choice should always cover gram-positive organisms (eg, vancomycin 20 mg/kg IV with serum concentration monitoring or cefazolin 20 mg/kg IV three times per week) Gram-negative coverage is indicated for patients with diabetes, HIV infection, prosthetic valves, or those receiving immunosuppressive agents (gentamicin 2 mg/kg IV with serum concentration monitoring)
Synthetic Grafts (AVG)	
Local infection	Empiric antibiotic coverage for Gram-positive, Gram-negative, and *Enterococcus* (eg, gentamicin plus vancomycin, then individualize after culture results become available); continue for 2–4 weeks
Extensive infection	Antibiotics as above plus total resection
Access less than 1-month old	Antibiotics as above plus removal of the graft
Tunneled Cuffed Catheters (Internal Jugular, Subclavian)	
Infection localized to catheter exit site	No drainage: topical antibiotics (eg, mupirocin ointment) Drainage present: Gram-positive coverage (eg, cefazolin 20 mg/kg IV three times a week)
Bacteremia with or without systemic signs or symptoms	Gram-positive coverage as above If stable and asymptomatic, change catheter and provide culture-specific antibiotic coverage for a minimum of 3 weeks

AV, arteriovenous. From Ulu MS, Ahsen A. Muscle cramps during hemodialysis: what can we do? New approaches for treatment and preventing. Eur J Gen Med. 2015;12(3):277–281.

to create the osmotic gradient, but the solutions are not biocompatible with the peritoneal membrane, resulting in cytotoxicity of the cells. Polymeric glucose derivatives such as icodextrin may be used in place of glucose to create a colloid-driven osmosis that results in ultrafiltration and convection of solute removal but are more expensive.

In PD, prewarmed dialysate is instilled into the peritoneal cavity where it "dwells" for a specified length of time (usually one to several hours, depending on the type of PD) to adequately clear metabolic waste products and excess fluids and electrolytes. At the end of the dwell time, the dialysate is drained and replaced with fresh dialysate. The continuous nature of PD provides for a more physiologic removal of waste products from the bloodstream, which mimics endogenous kidney function by limiting the fluctuations seen in serum concentrations of the waste products. Similarly, water is removed at a more constant rate, lessening the fluctuations in intravascular fluid balance and providing for more hemodynamic stability.

Several types of PD are used:

- Continuous ambulatory PD (CAPD) is the most common. The patient exchanges 1 to 3 L of dialysate every 4 to 6 hours throughout the day with a longer dwell time overnight.
- Automated PD (APD) procedures involve the use of a cycler machine that performs sequential exchanges overnight while the patient is sleeping.
- Continuous cycling PD (CCPD) performs three to five exchanges throughout the night. The final exchange remains in the peritoneal cavity to dwell for the duration of the day.
- Nightly intermittent PD (NIPD) performs six to eight exchanges throughout the night. The final exchange of dialysate is drained in the morning, and the peritoneal cavity remains empty throughout the day.
- Nocturnal tidal PD (NTPD) is similar to NIPD, with the exception that only a portion of the dialysate is exchanged throughout the night. The final exchange is drained in the morning, and the peritoneal cavity remains empty throughout the day.

▶ *Peritoneal Access*

Access to the peritoneal cavity requires placement of an indwelling catheter with the distal end of the catheter resting in the peritoneal cavity. The central portion of the catheter is generally tunneled under the abdominal wall and SC tissue where it is held in place by cuffs that provide stability and mechanical support to the catheter. The proximal portion of the catheter exits the abdomen near the umbilicus. Several types of indwelling catheters are available; the most common is the Tenckhoff catheter. Placement and handling of the catheter during PD exchanges requires a sterile environment to minimize the risk of infectious complications.

▶ *Complications of Peritoneal Dialysis*

Complications associated with PD include mechanical problems related to the PD catheter, metabolic problems associated with the components of the dialysate fluid, damage to the peritoneal membrane, and infections (Table 27–12). Strategies to manage infectious complications of PD are discussed below.

Peritonitis Peritonitis is a leading cause of morbidity in PD patients, which often leads to loss of the catheter and subsequent change to HD as the treatment modality. However, advances with connectors used during instillation and drainage of dialysate and delivery systems have dramatically decreased the incidence of peritonitis. Peritonitis can also be caused by chemical irritation or microorganisms.

Table 27–12

Common Complications During Peritoneal Dialysis

Mechanical Complications
Kinking in catheter
Catheter migration
Catheter adherence to peritoneal tissue
Excessive movement of catheter at exit site

Peritoneal Damage
Alterations in permeability of the peritoneal membrane
Sclerosis of the peritoneal membrane

Pain
Impingement of the catheter tip on visceral organs
Instillation pain
- Rapid inflow of dialysate
- Acidic pH of dialysate
- Chemical irritation from dialysate additives (eg, antibiotics)
- Low dialysate temperature

Infections
Peritonitis
Exit-site infections
Tunnel infections

Metabolic Complications
Exacerbation of diabetes mellitus from glucose load
Fluid overload
- Exacerbation of chronic heart failure
- Edema
- Pulmonary congestion

Electrolyte abnormalities
Malnutrition
- Albumin and amino acid loss
- Muscle wasting
- Increased adipose tissue
- Fibrin formation in dialysate

Weight gain

Pathophysiology. Gram-positive organisms, namely, *S. epidermidis*, are the most common cause of peritonitis. Other pathologic organisms include *S. aureus*, streptococcal species, enterococcus species, gram-negative organisms including *Escherichia coli* and *Pseudomonas* species, and fungal organisms. Peritonitis should be presumed if cloudy fluid is drained from the peritoneal cavity and the fluid should be evaluated by cultures. Antibiotic treatment should be initiated immediately, until cell counts and cultures prove otherwise.[38] Patients with peritonitis may also complain of abdominal pain, although pain may be absent in some cases.

Treatment. The International Society of Peritoneal Dialysis (ISPD) revised the recommendations for the treatment of PD-related infections in 2016.[38] Drug selection for empirical treatment of peritonitis should cover both gram-positive and gram-negative organisms specific to the dialysis center and be based on the protocols and sensitivity patterns of organisms known to cause peritonitis, as well as the history of infections in the patient. First-generation cephalosporins, such as cefazolin, or vancomycin are recommended for empirical coverage of Gram-positive organisms. Appropriate coverage for Gram-negative organisms includes third- or fourth-generation cephalosporins, such as ceftazidime or cefepime, or aminoglycosides. Alternatives for gram-negative coverage include oral fluoroquinolones and aztreonam. An example of an appropriate empiric treatment for peritonitis includes cefazolin in combination with ceftazidime, cefepime, or an aminoglycoside. If the patient has a β-lactam allergy, vancomycin in combination with an aminoglycoside or aztreonam is an alternative empirical treatment.[38] It should be noted that aminoglycosides can decrease residual renal function in patients receiving PD.

The preferred route of administration is intraperitoneal (IP) rather than IV to achieve maximum concentrations at the site of infection. Antibiotics can be administered IP intermittently as a single large dose in one exchange per day or continuously as multiple smaller doses with each exchange. Intermittent administration requires at least 6 hours of dwell time in the peritoneal cavity to allow for adequate systemic absorption and provides adequate levels to cover the 24-hour period. However, continuous administration is better suited for PD modalities that require more frequent exchanges (less than 6-hour dwell time). See the ISPD guidelines for dosing recommendations for IP antibiotics in CAPD and APD patients.[38] The dose of the antibiotics should be increased by 25% for patients with residual kidney function who are able to produce more than 100 mL urine output per day.

Once the organism has been identified and sensitivities are known, drug selection should be adjusted to reflect the susceptibilities of the organism. Streptococcal, staphylococcal, and enterococcal species sensitive to β-lactam antibiotics should be treated with continuous IP dosing to increase efficacy and minimize resistance.[38] Peritonitis caused by *S. aureus* or *P. aeruginosa* are often associated with catheter-related infections, which are difficult to treat and often require removal of the catheter. Two antibiotics are required for treatment of *P. aeruginosa* peritonitis.[38] If multiple organisms are cultured, treatment should cover all the organisms, including anaerobic organisms, and the patient should be evaluated for other intra-abdominal pathologies.[38]

Peritonitis caused by fungal organisms is associated with mortality in 25% of patients,[38] which can be reduced by removing the catheter after fungal organisms are identified. If a fungal organism is identified, empirical treatment should include IP amphotericin B and flucytosine,[38] but alternative agents can be used based on susceptibilities. Although IP amphotericin administration is associated with chemical irritation and pain, penetration of amphotericin into the peritoneal cavity is poor with IV administration. Fluconazole, voriconazole, or caspofungin may be suitable alternatives, depending on culture results.

Catheter-Related Infections Catheter-related infections generally occur at the exit site or the portion of the catheter that is tunneled in the SC tissue. Previous infections increase the risk and incidence of catheter-related infections.

Pathophysiology. The major pathologic organisms responsible for causing catheter-related infections are *S. aureus* and *P. aeruginosa*. These organisms also cause the most serious catheter-related infections. *S. epidermidis* is found in less than 20% of catheter-related infections.[39]

Exit-site infections present with purulent drainage at the site. Erythema may or may not be present with an exit-site infection. Tunnel infections are generally extensions of exit-site infections and rarely occur alone. Symptoms of a tunnel infection may include tenderness, edema, and erythema over the tunnel pathway but are often asymptomatic. Ultrasound can be used to detect tunnel infections in asymptomatic patients. Exit-site infections caused by *S. aureus* and *P. aeruginosa* often spread to tunnel infections and are the most common causes of catheter-infection–related peritonitis.

JCPP Patient Care Process: Chronic Kidney Disease

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements.
- Review the medical history, laboratory tests, and physical assessment.
- Speak with the patient and review records to identify socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Identify risk factors that increase the risk for CKD (Table 27–3).
- Determine whether the patient has any concomitant diseases that may hasten the progression of CKD or increase the risk of CVD.
- Identify medications the patient is taking that may cause nephrotoxicity or require adjustment for renal dysfunction.
- Review relevant laboratory tests to determine if patient is experiencing complications of CKD.
- Calculate GFR to determine the staging of CKD (Tables 27–1 and 27–2).
- Determine if the patient is experiencing signs and symptoms associated with CKD, or complications CKD (Figures 27–3 and 27–4).

Develop a Care Plan:

- Determine if pharmacotherapy is indicated for proteinuria or other concomitant disease states.
- Select appropriate medical treatments to control complications of CKD, including anemia (Figure 27–2, Tables 27–5 and 27–6); mineral and bone diseases (Figure 27–3, Tables 27–6 and 27–7); and electrolyte imbalances.
- Select medications and doses that are appropriately adjusted for the level of kidney function.

Implement the Care Plan:

- Educate the patient about changes in drug therapy.
- Address patient's concerns about CKD and its management.
- Educate the patient on dietary and lifestyle changes to treat complications of CKD.
- Stress the importance of adherence with the treatments for CKD and associated complications including lifestyle modifications and medications.
- Recommend a therapeutic regimen that is easy for the patient to accomplish.

Follow-up: Monitor and Evaluate:

- Follow-up at regular intervals to assess effectiveness and safety of therapy.
- Review physical exam and lab tests to assess changes in clinical status.

Treatment. Exit-site infections may be treated immediately with empiric coverage, or treatment may be delayed until cultures return. Empiric treatment of catheter-related infections should cover *S. aureus* with a first-generation cephalosporin or penicillinase-resistant penicillin. Coverage for MRSA or *P. aeruginosa* should also be included if the patient has a history of infections with either organism. Vancomycin or clindamycin are used for empiric coverage of MRSA, while oral fluoroquinolones are used as first-line agents to treat *P. aeruginosa*.[39]

Cultures and sensitivity testing are particularly important in tailoring antibiotic therapy for catheter-related infections to ensure eradication of the organism and prevent recurrence or related peritonitis. Treatment of catheter-related infections should be continued until the exit site appears normal with no erythema or drainage. Generally, at least 2 weeks of therapy or longer are required to ensure complete eradication of the organism and prevent future recurrence, which is common with *S. aureus* and *P. aeruginosa*. Infections that do not resolve may require replacement of the PD catheter. Catheter-related infections that present in conjunction with or progress to peritonitis with the same organism require removal of the PD catheter until the peritonitis is resolved.[39]

Prophylaxis of Peritonitis and Catheter-Related Infections. Prevention of peritonitis and catheter-related infections starts when the catheter is placed. The exit site should be properly cared for until it is well healed before it can be used for PD. Patients should receive proper instructions for care of the catheter during this time period, which can last up to 2 weeks. Patients should also be instructed on the proper techniques to use for dialysate exchanges to minimize the risk of infections during exchanges, which is the most common cause of peritonitis.

Topical antibiotics, including mupirocin, gentamicin, or ciprofloxacin cream or ointment should be applied daily around the exit site to prevent catheter-related infections.[39] Intranasal *S. aureus* increases the risk of *S. aureus* exit-site infections, tunnel infections, peritonitis, and subsequent catheter loss.[39]

Outcome Evaluation. Clinical improvement should be seen within 48 hours of initiating treatment for peritonitis or catheter-related infections. Perform daily inspections of peritoneal fluid or the exit site to determine clinical improvement. Peritoneal fluid should become clear with improvement of peritonitis and erythema, and discharge should remit with improvement of catheter-related infections. If no improvement is seen within 48 hours, obtain additional cultures and cell counts to determine the appropriate alterations in therapy.

Abbreviations Introduced in This Chapter

ACEI	Angiotensin-converting enzyme inhibitor
AGE	Advanced glycation end-product
AKI	Acute kidney injury
APD	Automated peritoneal dialysis
ARB	Angiotensin receptor blocker
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
BUN	Blood urea nitrogen
CAPD	Continuous ambulatory peritoneal dialysis
CCPB	Calcium-containing phosphate binder
CCPD	Continuous cycling peritoneal dialysis
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
CKD-MBD	Chronic kidney disease mineral and bone disease
CVD	Cardiovascular disease
DKD	Diabetic kidney disease
DM	Diabetes mellitus
ECG	Electrocardiogram
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agent
GFR	Glomerular filtration rate
HbA1c	Hemoglobin$_{\text{a1c}}$
Hct	Hematocrit
HD	Hemodialysis
HDL-C	High-density lipoprotein cholesterol
Hgb	Hemoglobin
IP	Intraperitoneal
iPTH	Intact parathyroid hormone
ISPD	International Society of Peritoneal Dialysis
KDIGO	Kidney Disease: Improving Global Outcomes
LDL-C	Low-density lipoprotein cholesterol
LVH	Left ventricular hypertrophy
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease (study)
MRSA	Methicillin-resistant *Staphylococcus aureus*
NIPD	Nightly intermittent peritoneal dialysis
NKF	National Kidney Foundation
NTPD	Nocturnal tidal peritoneal dialysis
PD	Peritoneal dialysis
PTH	Parathyroid hormone
RBC	Red blood cell
ROD	Renal osteodystrophy
RRT	Renal replacement therapy
SC	Subcutaneous
SCr	Serum creatinine
sHPT	Secondary hyperparathyroidism
SPS	Sodium polystyrene sulfonate
TIBC	Total iron binding capacity
TSat	Transferrin saturation
USRDS	United States Renal Data Service

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28 Fluids and Electrolytes

Mark A. Malesker and Lee E. Morrow

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Estimate the volumes of various body fluid compartments.
2. Calculate the daily maintenance fluid requirement for patients given their weight, and gender.
3. Differentiate among currently available fluids for volume resuscitation.
4. Identify the electrolytes primarily found in the extracellular and intracellular fluid compartments.
5. Describe the unique relationship between serum sodium concentration and total body water (TBW).
6. Review the etiology, clinical presentation, and management for disorders of sodium, potassium, calcium, phosphorus, and magnesium.

BODY FLUID COMPARTMENTS

A thorough understanding of the fundamentals of fluid and electrolyte homeostasis is essential, given the frequency with which clinical disturbances are seen and the profound effects these disturbances can have on various aspects of patient care. However, the interplay of body fluids, serum electrolytes, and clinical monitoring is complex, and a thorough command of these issues is a challenging task even for advanced practitioners.[1] Clinicians must be familiar with the key concepts of body compartment volumes, calculation of daily fluid requirements, and the various types of fluid available for replacement. The management of disorders of sodium, potassium, calcium, phosphorus, and magnesium integrates these concepts with issues of dose recognition and patient safety.

The most fundamental concept to grasp is an assessment of total body water (TBW), which is directly related to body weight. KEY CONCEPT TBW constitutes approximately 50% of lean body weight in healthy females and 60% of lean body weight in males. For clinical purposes, most clinicians generalize that TBW accounts for 60% of lean body weight in adults, regardless of gender. The percentage of TBW decreases as body fat increases and/or with age (75%–85% of body weight is water for newborns). Unless the patient is obese (body weight > 120% of ideal body weight [IBW]), clinicians typically use a patient's actual body weight when calculating TBW.[2] In obese patients, it is customary to estimate TBW using lean body weight or IBW as calculated by the Devine–Devine method: males' lean body weight = 50 kg + (2.3 kg/in. × [height in inches − 60]) and females' lean body weight = 45.5 kg + (2.3 kg/in. × [height in inches − 60]).[3–5] Note that 1 kg is equivalent to 2.2 lb, 1 in. is equivalent to 2.54 cm, and 1 L of water weighs 1 kg (2.2 lb).

The intracellular fluid (ICF) represents the water contained within cells and is rich in electrolytes such as potassium, magnesium, phosphates, and proteins. KEY CONCEPT The ICF is approximately two-thirds of TBW regardless of gender. For a 70-kg person, this would mean that the TBW is 42 L and the ICF is approximately 28 L. Note that ICF represents approximately 40% of total body weight.

The extracellular fluid (ECF) is the fluid outside the cell and is rich in sodium, chloride, and bicarbonate. KEY CONCEPT The ECF is approximately one-third of TBW (14 L in a 70-kg person) and is subdivided into two compartments: the interstitial fluid and the intravascular fluid. The interstitial fluid represents the fluid occupying the spaces between cells and is about 25% of TBW (10.5 L in a 70-kg person). The intravascular fluid (also known as plasma) represents the fluid within the blood vessels and is about 8% of TBW (3.4 L in a 70-kg person). Because the exact percentages are cumbersome to recall, many clinicians accept that the ECF represents roughly 20% of body weight (regardless of gender) with 15% in the interstitial space and 5% in the intravascular space.[6] Note that serum electrolytes are routinely measured from the ECF.

The transcellular fluid includes the viscous components of the peritoneum, pleural space, and pericardium, as well as the cerebrospinal fluid, joint space fluid, and the GI digestive juices. Although the transcellular fluid normally accounts for about 1% of TBW, this amount can increase significantly during various illnesses favoring fluid collection in one of these spaces (eg, pleural effusions or ascites in the peritoneum). The accumulation of fluid in the transcellular space is often referred to as "third spacing." To review the calculations of the body fluid compartments in a representative patient, see Patient Encounter 1.

Fluid balance is assessed by several means each of which has its limitations. Blood pressure (BP) measurements estimate fluid status relative to the amount of blood volume pumped by the heart but are affected by cardiac function and vascular pliability. Patients with significant volume deficiency may appear hypotensive, but this is a late finding that may require greater than

Patient Encounter 1: Body Fluid Compartments

Calculate the TBW, ICF, and ECF in a 78-kg male.

20% of TBW to be lost. Patients with significant volume excess may appear edematous; however, third spacing may hide this finding until late in the course as well. The physical examination can indicate the presence of fluid deficits (dry mucous membranes) and fluid excess (peripheral edema, coarse breath sounds). Data suggest that dynamic assessments of volume status (pulse pressure variability, ultrasound-derived vena cava diameter variations, passive leg raising) are more accurate than either the bedside clinical exam or passive measurements of volume status (arterial catheter, central venous catheter, pulmonary artery catheter).

To maintain fluid balance, the total amount of fluid gained throughout the day (input, or "ins") must equal the total amount of fluid lost (output, or "outs"). Although most forms of the body's input and output can be measured, several cannot. For a normal adult on an average diet, ingested fluids are easily measured and average 1400 mL/day. Other fluid inputs, such as those from ingested foods and the water by-product of oxidation, are not directly measurable. Fluid outputs such as urinary and stool losses are also easily measured and referred to as sensible losses. Other sources of fluid loss, such as evaporation of fluid through the skin and/or lungs, are not readily measured and are called insensible losses. Table 28–1 shows the estimated ins and outs (I&Os) for a healthy 68-kg (150-lb) man.[6] The measurable I&Os are routinely measured in hospitalized patients and are used to estimate total fluid balance for each 24-hour period. It is important to realize that in hospitalized patients, multiple other forms of fluid loss must be considered. These include losses from enteric suctioning (most commonly, nasogastric [NG] tubes), from surgical drains (eg, chest tubes, nephrostomy tubes, and pancreatic drains), via fistulous tracts, and enhanced evaporative losses (burns and fever).

TBW depletion (often referred to as "dehydration") is typically a gradual, chronic problem. Because TBW depletion represents a loss of hypotonic fluid (proportionally more water is lost than sodium) from all body compartments, a primary disturbance of **osmolality** is usually seen. The signs and symptoms of TBW depletion include CNS disturbances (mental status changes, seizures, and coma), excessive thirst, dry mucous membranes, decreased skin turgor, elevated serum sodium, increased plasma osmolality, concentrated urine, and acute weight loss. Common causes of TBW depletion include insufficient oral intake, excessive insensible losses, diabetes insipidus, excessive osmotic diuresis, and impaired renal concentrating mechanisms. Elderly long-term care residents are frequently admitted to the acute care hospital with TBW depletion secondary to lack of adequate oral intake, often with concurrent excessive insensible losses.

Table 28–1

Approximate I&Os for a Healthy 68-kg (150-lb) Man

Input	mL/day	Output	mL/day
Ingested fluid[a]	1400	Urine[a]	1500
Fluid in food	850	Skin losses	500
Water of oxidation	350	Respiratory tract losses	400
		Stool	200
Total	2600	Total	2600

[a]Readily quantifiable.

Table 28–2

Useful Calculations for the Estimation of Patient Maintenance Fluid Requirements

Neonate (1–10 kg) = 100 mL/kg
Child (10–20 kg) = 1000 mL + 50 mL for each kilogram greater than 10
Adult (> 20 kg) = 1500 mL + 20 mL for each kilogram greater than 20

The volume of fluid required to correct TBW depletion equals the basal fluid requirement plus ongoing exceptional losses plus the fluid deficit. Basal daily fluid requirements are calculated using the formulas in Table 28–2. For an adult, this represents 1500 mL/day for the first 20 kg of body weight plus 20 mL/day for each additional kilogram. The volume of replacement fluids required for a given patient (the fluid deficit) can be estimated by the acute weight change in the patient (1 kg = 1 L of fluid). Because the precise weight change is not typically known, it is often calculated as follows: fluid deficit = normal TBW − present TBW. Normal TBW is estimated based on the patient's weight using the formulas in Table 28–2, and the present TBW is estimated based on the patient's current body weight. The choice of fluids used for replacement is guided by the presence of concurrent electrolyte abnormalities and acid-base status. The adequacy of replacement is guided by each patient's objective response to fluid replacement (improved skin turgor, adequate urine output, normalization of heart rate, BP, etc.).

Once TBW has been restored, the volume of "maintenance" fluid equals the basal fluid requirement plus ongoing exceptional losses. If the pathophysiologic process leading to TBW depletion has not been identified and corrected (or accounted for in the calculation of maintenance fluid requirements), TBW depletion will quickly recur. To review the concepts involved in the calculation of replacement fluids for a representative patient, see Patient Encounter 2.

Compared with TBW depletion, ECF depletion tends to occur acutely. In this setting, rapid and aggressive fluid replacement is required to maintain adequate organ perfusion. Because ECF depletion is generally due to the loss of isotonic fluid (proportional losses of sodium and water), major disturbances of plasma osmolality are not common. ECF depletion manifests clinically as signs and symptoms associated with decreased tissue perfusion: dizziness, orthostasis, tachycardia, decreased urine output, increased hematocrit, decreased central venous pressure, and/or hypovolemic shock. Common causes of ECF depletion include external fluid losses (burns, hemorrhage, diuresis, GI losses, and adrenal insufficiency) and third spacing of fluids (septic shock, anaphylactic shock, or abdominal ascites).

In clinical practice, the most encountered problem is depletion of TBW and ECF. Accordingly, the fluid resuscitation strategy should address both compartments. As these compartments are repleted, serum electrolytes must be monitored closely as discussed in subsequent sections of this chapter.

Patient Encounter 2: Fluid Requirements

Calculate the daily fluid requirement for a 73-kg adult female.

THERAPEUTIC FLUIDS

Crystalloids

KEY CONCEPT Therapeutic IV fluids include crystalloid solutions and colloidal solutions. Crystalloids are composed of water and electrolytes, all of which pass freely through semipermeable membranes and remain in the intravascular space for shorter periods of time. As such, these solutions are very useful for correcting electrolyte imbalances but result in smaller hemodynamic changes for a given unit of volume.

Crystalloids can be classified further according to their tonicity. Isotonic solutions (ie, normal saline or 0.9% sodium chloride [NaCl]) have a tonicity equal to that of the ICF (approximately 310 mEq/L [mmol/L]) and do not shift the distribution of water between the ECF and the ICF. Because hypertonic solutions (ie, hypertonic saline or 3% NaCl) have greater tonicity than the ICF (> 376 mEq/L [mmol/L]), they draw water from the ICF into the ECF. In contrast, hypotonic solutions (ie, 0.45% NaCl) have less tonicity than the ICF (< 250 mEq/L [mmol/L]) leading to osmotic pressure gradient that favors shifts of water from the ECF into the ICF. The tonicity, electrolyte content, and glucose content of selected fluids are shown in Table 28–3.

The tonicity of crystalloid solutions is directly related to their sodium concentration. The most used crystalloids include normal saline, dextrose/half-normal saline, hypertonic saline, and lactated Ringer's solution. Excessive administration of any fluid replacement therapy, regardless of tonicity, can lead to fluid overload and/or electrolyte changes, particularly in patients with cardiac or renal insufficiency. Glucose is often added to hypotonic crystalloids in amounts that result in isotonic fluids (D_5W, D5½NS, and D5¼NS). These solutions are often used as maintenance fluids to provide basal amounts of calories and water.

▶ *Normal Saline (0.9% NaCl or NS)*

Normal saline is an isotonic fluid composed of water, sodium, and chloride. It provides primarily ECF replacement and can be used for virtually any cause of TBW depletion. Common uses of normal saline include perioperative fluid administration; volume resuscitation of shock, sepsis, hemorrhage, or burn patients; fluid challenges in hypotensive or oliguric patients; and hyponatremia. Normal saline can also be used to treat metabolic alkalosis (also known as contraction alkalosis). Large volumes of normal saline can cause a hyperchloremic metabolic acidosis.

▶ *Half-Normal Saline (0.45% NaCl or ½ NS)*

Half-normal saline is a hypotonic fluid that provides free water in relative excess when compared with the sodium concentration. This crystalloid is typically used to treat patients who are hypertonic due to primary depletion of the ECF. Because half-normal saline is hypotonic, serum sodium must be closely monitored during administration.

▶ *5% Dextrose/Half-Normal Saline (D5 ½ NS)*

D5 ½ NS is a hypotonic fluid that is commonly used as a maintenance fluid. This crystalloid is typically used once fluids deficits have been corrected with normal saline or lactated Ringer's solution. Because half-normal saline is hypotonic, serum sodium must be closely monitored during administration.

▶ *Hypertonic Saline (3% NaCl)*

Hypertonic saline is obviously hypertonic and provides a significant sodium load to the intravascular space. This solution is used very infrequently given the potential to cause significant shifts in the water balance between the ECF and the ICF. It is typically used to treat patients with severe hyponatremia who have symptoms attributable to low serum sodium. Hypertonic saline

Table 28–3

Electrolyte and Dextrose Content of Selected Crystalloid Fluids

IV Solution	Osmolarity (mOsm or mmol)	Dextrose (g/L) mmol/L	Sodium (mEq/L) mmol/L	Potassium (mEq/L) mmol/L	Calcium (mEq/L) mmol/L	Chloride (mEq/L) mmol/L	Lactate (mEq/L) mmol/L
D5%	250	50 2.78					
D10%	505	100 5.55					
0.9% NaCl	308		154			154	
0.45% NaCl	154		77			77	
3% NaCl	1025		512			512	
D5% and 0.45% NaCl	405	50 2.78	77			77	
Ringer's injection	310		147	4	5 2.5	156	
Lactated Ringer's solution	274		130	4	3 1.5	109	28
Lactated Ringer's solution and D5%	525	50 2.78	130	4	3 1.5	109	28

D, dextrose; NaCl, sodium chloride.

in concentrations of 3% to 23.4% has been used to acutely lower intracranial pressure in the setting of traumatic brain injury and stroke. The literature is inconsistent for the optimal hypertonic concentration, dosing, timing of replacement, and goals for use in this population. This fluid is used for short periods in the intensive care setting where frequent serum sodium and neurologic checks can be very closely monitored.

▶ *Ringer's Lactate*

This isotonic volume expander contains sodium, potassium, chloride, and lactate in concentrations that approximate the fluid and electrolyte composition of the blood. Ringer's lactate (also known as "Lactated Ringers" or LR) provides ECF replacement and is most often used in the perioperative setting and for patients with lower GI fluid losses, burns, or dehydration. The lactate component of LR is metabolized into bicarbonate in the liver and works as a buffer to increase the pH. Accordingly, large volumes of LR may cause iatrogenic metabolic alkalosis. Because patients with significant liver disease are unable to metabolize lactate sufficiently, LR administration in this population may lead to accumulation of lactate with iatrogenic lactic acidosis.

▶ *5% Dextrose in Water (D_5W)*

D_5W solution is a combination of free water and dextrose that provides a modest amount of calories but no electrolytes. Although it is technically isotonic, it acts as a hypotonic solution in the body. It is commonly used to treat severe hypernatremia. D5W is also used in small volumes (100 mL) to dilute many IV medications or at a low infusion rate (10 to 15 mL/h) to "keep the vein open" (KVO) for IV medications.

Colloids

In contrast to crystalloids, colloids do not dissolve into a true solution and therefore do not pass readily across semipermeable membranes. As such, colloids effectively remain in the intravascular space and increase the oncotic pressure of the plasma. This effectively shifts fluid from the interstitial compartment to the intravascular compartment. In clinical practice, these theoretical benefits are generally short lived (given metabolism of colloidal proteins/sugars), and for most patients, there is little therapeutic advantage of colloids over crystalloids or vice versa. Examples of colloids include 5% albumin, 25% albumin, the dextrans, hetastarch, and fresh-frozen plasma (FFP). Because each of these agents contains a substance (proteins or complex sugars) that will ultimately be metabolized, the oncotic agent will be ultimately lost and only the remaining hypotonic fluid delivery agent will remain. As such, use of large volumes of colloidal agents is more likely to induce fluid overload compared with crystalloids. Although smaller volumes of colloids have equal efficacy as larger volumes of crystalloids, they generally must be infused more slowly. Often the net result is that the time to clinical benefit is the same regardless of which class of fluid is utilized. For example, 500 mL of normal saline is required to increase the systolic BP to the same degree as seen with approximately 250 mL of 5% albumin; however, the normal saline can be administered twice as fast.

▶ *Albumin*

Albumin is a protein derived from fractionating human plasma. Because albumin infusion is expensive and may be associated with adverse events, it should be used for acute volume expansion and *not* as a supplemental source of protein calories. Historically, albumin was used indiscriminately in the intensive care unit until anecdotal publications suggested that albumin might cause immunosuppression. However, the Saline Versus Albumin Fluid Evaluation (SAFE) trial found that the mortality for those who received albumin was the same as for those who received normal saline.[7] In 1818 patients with severe sepsis, albumin replacement with crystalloids as compared to crystalloids alone did not improve the rate of survival at 28 and 90 days.[8]

Based on limited availability, health systems and hospitals have had to define the appropriate albumin indications for their patients and ration albumin accordingly. Evidence-based indications for albumin include plasmapheresis/apheresis, large-volume paracentesis (> 4 L removed), hypotension in hemodialysis, and spontaneous bacterial peritonitis. Inappropriate uses of albumin include nutritional supplementation, pancreatitis, alteration of drug pharmacokinetics, or acute normovolemic hemodilution in surgery.

▶ *Hydroxyethyl Starch Solutions and Dextran*

While albumin is the most used colloid, the other available products are not without their own risks and benefits. Hydroxyethyl starch solutions (HES) include Hetastarch and Hextend. Hetastarch (various manufacturers) contains 6% starch and 0.9% NaCl. Hextend, Hospira, is a comparable plasma expander that contains 6% hetastarch in a lactated electrolyte solution. HES products have no oxygen-carrying capacity and are administered intravenously as plasma expanders. Limitations of these products include acquisition cost, hypersensitivity reactions, and bleeding. Dosing should be reduced in the presence of renal dysfunction. Clinical data linking HES solutions with an increased risk of mortality and renal injury requiring renal replacement therapy in critically ill patients prompted the FDA to issue a MedWatch safety communication in November 2013. FDA concluded these solutions should not be used in critically ill patients, including sepsis and those admitted to the intensive care unit, and a boxed warning to highlight the risk of mortality and severe renal injury is warranted. A list of recommendations for patients and health-care providers to consider before use of HES solutions can be found on the FDA website. (http://www.fda.gov/Safety/MedWatch/)

Low molecular weight dextran 40 (various manufacturers) is a polysaccharide plasma expander. Anaphylactic reactions and prolonged bleeding times have limited its use. Potential mechanisms of colloid solution-induced bleeding include platelet inhibition or possible dilution of clotting factors via infusion of a large-volume colloid solution.

Fluid Management Strategies

Classic indications for IV fluid include maintenance of BP, restoring the ICF volume, replacing ongoing renal or insensible losses when oral intake is inadequate, for medication delivery, and the need for glucose as a fuel for the brain.[9]

When determining the appropriate fluid to be utilized, it is important to first determine the type of fluid problem (TBW versus ECF depletion) and start therapy accordingly. For patients demonstrating signs of impaired tissue perfusion, the immediate therapeutic goal is to increase the intravascular volume and restore tissue perfusion. The historical standard therapy is normal saline given at 150 to 500 mL/hour (for adult patients) until perfusion is optimized. Although LR is a therapeutic alternative, lactic acidosis may arise with massive or prolonged infusions. LR has less chloride content versus normal saline (109 mEq/L [mmol/L] versus 154 mEq/L [mmol/L]) and has the advantage of use when large volumes of normal saline produce acidosis during fluid resuscitation. In severe cases, a colloid or blood transfusion may be indicated to increase oncotic pressure within the vascular space. Once euvolemia is achieved, patients may be switched to a more hypotonic maintenance solution (D5 ½ NS or 0.45% NaCl) at a rate that delivers estimated daily needs.

In two linked studies (SMART, SALT-ED) collectively studying over 29,000 patients, NS administration was associated with a significantly higher risk of metabolic acidosis and major adverse kidney events when compared to balanced crystalloid solutions. As a result, many clinicians have transitioned their practice to prioritize LR and Plasma-Lyte as first-line agents over NS for volume resuscitation and fluid maintenance.[10,11]

The clinical scenario and the severity of the volume abnormality dictate monitoring parameters during fluid replacement therapy. These may include the subjective sense of thirst, mental status, skin turgor, orthostatic vital signs, pulse rate, weight changes, blood chemistries, fluid input and output, central venous pressure, pulmonary capillary wedge pressure, and cardiac output. Fluid replacement requires particular caution in patient populations at risk of fluid overload, such as those with renal failure, cardiac failure, hepatic failure, or the elderly. Other complications of parenteral fluid therapy include IV site infiltration, infection, phlebitis, thrombophlebitis, and extravasation.

In summary, common settings for fluid resuscitation include hypovolemic patients (eg, sepsis or pneumonia), hypervolemic patients (eg, congestive heart failure [CHF], cirrhosis, or renal failure), euvolemic patients who are unable to take oral fluids in proportion to insensible losses (eg, the perioperative period), and patients with electrolyte abnormalities (see below).

ELECTROLYTES

Normally, the number of anions (negatively charged ions) and cations (positively charged ions) in each fluid compartment are equal. Cell membranes play the critical role of maintaining distinct ICF and ECF spaces, which are biochemically distinct. Serum electrolyte measurements reflect the stores of ECF electrolytes rather than that of ICF electrolytes. Table 28–4 lists the chief cations and anions along with their normal concentrations in the ECF and ICF. The principal cations are sodium, potassium, calcium, and magnesium; the key anions are chloride, bicarbonate, and phosphate. In the ECF, sodium is the most common cation and chloride is the most abundant anion; in the ICF, potassium is the primary cation and phosphate is the main anion. Normal serum electrolyte values are listed in Table 28–5.

Table 28–4

Normal Cation and Anion Concentrations in the ECF and ICF

	ECF		ICF	
Ion Species	**Plasma (mEq/L [mmol/L])**	**Interstitial Fluid (mEq/L [mmol/L])**	**Ion Species**	**mEq/L [mmol/L]**
Cations			Cations	
Na^+	142 [142]	144 [144]	K^+	135 [135]
K^+	4 [4]	4 [4]	Mg^{2+}	43 [21.5]
Ca^{2+}	5 [2.5]	2.5 [1.25]		
Mg^{2+}	3 [1.5]	1.5 [0.75]		
Total	154 [150]	152 [150]	Total	178 [156.5]
Anions			Anions	
Cl^-	103 [103]	114 [114]	PO_4^{2-}	90 [45]
HCO_3^-	27 [27]	30 [30]	Protein	70 [70]
PO_4^{2-}	2 [1]	2 [1]	SO_4^{2-}	18 [9]
SO_4^{2-}	1 [0.5]	1 [0.5]		
Organic acid	5 [5]	5 [5]		
Protein	16 [16]	0		
Total	154 [152.5]	152 [150.5]	Total	178 [124]

ECF, extracellular fluid; ICF, intracellular fluid.

Table 28–5

Normal Ranges for Serum Electrolyte Concentrations

Sodium	135–145 mEq/L (mmol/L)
Potassium	3.5–5.0 mEq/L (mmol/L)
Chloride	98–106 mEq/L (mmol/L)
Bicarbonate	21–30 mEq/L (mmol/L)
Magnesium	1.4–2.2 mEq/L or 0.7–1.1 mmol/L
Calcium:	
Total	4.4–5.2 mEq/L (9–10.5 mg/dL) or 2.2–2.6 mmol/L
Ionized	2.2–2.8 mEq/L (4.5–5.6 mg/dL) or 1.1–1.4 mmol/L
Phosphorus	3–4.5 mg/dL (1.0–1.5 mmol/L)

Osmolality is a measure of the number of osmotically active particles per unit of solution, independent of the weight or nature of the particle. Equimolar concentrations of all substances in the undissociated state exert the same osmotic pressure. Although the normal serum osmolality is 280 to 300 mOsm/kg (mmol/kg), multiple scenarios exist where this value becomes markedly abnormal. **KEY CONCEPT** The calculated serum osmolality helps determine deviations in TBW content. As such, it is often useful to calculate the serum osmolality as follows:

Serum **osmolality** (mOsm/kg)
= 2 (Na mEq/L) + (glucose [mg/dL])/18
+ (BUN [mg/dL])/2.8.

Serum osmolality using SI units (mmol/kg)
= 2 (Na mmol/L) + (glucose mmol/L)
+ (BUN mmol/L)

Because the body regulates water to maintain osmolality, deviations in serum osmolality are used to estimate TBW stores. Water moves freely across all cell membranes, making serum osmolality an accurate reflection of the osmolality within all body compartments. An increase in osmolality is equated with a loss of water greater than the loss of solute (TBW depletion). A decrease in serum osmolality is seen when water is retained in excess of solute (CHF or hepatic cirrhosis). The difference between the measured serum osmolality and the calculated serum osmolality, using the equation just stated, is referred to as the osmolar gap. Under normal circumstances the osmolar gap should be 10 mOsm/kg (mmol/kg) or less. An increased osmolar gap suggests the presence of a small osmotically active agent and is most commonly seen with the ingestion of alcohols (ethanol, methanol, ethylene glycol, or isopropyl alcohol) or medications such as mannitol or lorazepam. Patient Encounter 3 illustrates the utility of serum osmolality in a clinical setting.

Many of the electrolyte disturbances discussed in the remainder of this chapter represent medical emergencies that call for aggressive interventions including the use of concentrated electrolytes. It is very difficult to promptly reverse the effects of concentrated electrolytes when they are administered improperly, and these solutions are a frequent source of medical errors with significant potential for patient harm. **KEY CONCEPT** As such, The Joint Commission recommends that concentrated electrolyte

Patient Encounter 3: Calculate the Plasma Osmolality

A 42-year-old man reports drinking 750 ml of whiskey each day before lunch. He presents to the emergency department with complaints of dizziness, unsteadiness, and inability to walk by himself without assistance. Symptoms started two days ago and have been progressively worse. Patient endorses no food intake for five days. He was admitted with multiple electrolyte disorders. BP of 131/66 mm Hg was noted. The sodium is 126 mEq/L (mmol/L), potassium 2.1 mEq/L (mmol/L), chloride 64 mEq/L (mmol/L), bicarbonate 38 mEq/L (mmol/L), glucose 247 mg/dL (13.7 mmol/L), and BUN 7 mg/dL (2.5 mmol/L). The measured osmolality was 250 mOsm/kg (mmol/kg).

Calculate the osmolality.

Calculate the osmolar gap.

What is the likely cause of an increased gap in this patient?

solutions (KCl, potassium phosphate, NaCl > 0.9%, sodium bicarbonate 8.4%, and magnesium 50%) be removed from patient care areas. Hospitals should keep concentrated electrolytes in patient care areas only when patient safety necessitates their immediate use and precautions are used to prevent inadvertent administration. Examples include crash carts in intensive care units, emergency departments, and procedural areas. Collaborative cooperation among pharmacists, nurses, and physicians is essential.[12]

Sodium

The body's normal daily sodium requirement is 1.0 to 1.5 mEq/kg (mmol/kg) (80–130 mEq [mmol]) to maintain a normal serum sodium concentration of 135 to 145 mEq/L (mmol/L). Sodium is the predominant cation of the ECF and largely determines ECF volume. Sodium is also the primary factor in establishing the osmotic pressure relationship between the ICF and ECF. All body fluids are in osmotic equilibrium, and changes in serum sodium concentration are associated with shifts of water into and out of body fluid compartments. When sodium is added to the intravascular fluid compartment, fluid is pulled intravascularly from the interstitial fluid and the ICF until osmotic balance is restored. As such, a patient's measured sodium concentration should *not* be viewed as an index of sodium need because this parameter reflects the balance between total body sodium content and TBW. Disturbances in the sodium concentration most often represent disturbances of TBW. Sodium imbalances cannot be properly assessed without first assessing body fluid status.

KEY CONCEPT Hyponatremia is the most common electrolyte disorder in hospitalized patients and is defined as a serum sodium concentration below 135 mEq/L (mmol/L). Clinical signs and symptoms appear at concentrations below 120 mEq/L (mmol/L) and typically consist of irritability, mental slowing, unstable gait/falls fatigue, headache, and nausea. With profound hyponatremia (< 110 mEq/L [mmol/L]), confusion, seizures, stupor/coma, and respiratory arrest may be seen. Clinical practice guidelines regarding the diagnosis and treatment of hyponatremia have recently been published. Hyponatremia can be classified based upon serum sodium concentration, rate of development, symptom severity, serum osmolality, and volume status.[13] Because therapy is also influenced by volume status, hyponatremia is further defined as (a) hypertonic hyponatremia, (b) hypotonic hyponatremia with an increased ECF volume, (c) hypotonic hyponatremia with a normal ECF volume, and (d) hypotonic hyponatremia with a decreased ECF volume.[14]

Hypertonic hyponatremia is usually associated with significant hyperglycemia. Glucose is an osmotically active agent that leads to an increase in TBW with little change in total body sodium. For every 60 mg/dL (3.3 mmol/L) increase in serum glucose above 200 mg/dL (11.1 mmol/L), the sodium concentration is expected to decrease by approximately 1 mEq/L (mmol/L). Appropriate treatment of the hyperglycemia will return the serum sodium concentration to normal.[13]

Hypotonic hyponatremia with an increase in ECF (hypervolemic hyponatremia) is also known as dilutional hyponatremia. In this scenario, patients have an excess of total body sodium and TBW; however, the excess in TBW is greater than the excess in total body sodium. Common causes include CHF, hepatic cirrhosis, and nephrotic syndrome. Treatment includes sodium and fluid restriction in conjunction with treatment of the underlying disorder—for example, salt and water restrictions are used in the setting of CHF along with loop diuretics, angiotensin-converting enzyme inhibitors, and spironolactone.

In hypotonic hyponatremia with a normal ECF volume (euvolemic hyponatremia), patients have an excess of TBW with relatively normal sodium content. In essence, there is a presence of excess free water. This is most frequently seen in patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Common causes of SIADH include carcinomas (eg, lung or pancreas), pulmonary disorders (eg, pneumonias or tuberculosis), CNS disorders (eg, meningitis, stroke, tumor, or trauma), and medications (eg, sulfonylureas, antineoplastic agents, barbiturates, morphine, antipsychotics, tricyclic antidepressants, nonsteroidal anti-inflammatory agents, selective serotonin reuptake inhibitors, dopamine agonists, and general anesthetics). These medications stimulate the release of antidiuretic hormone (ADH) from the pituitary gland resulting in water retention and dilution of the body's sodium stores.

Short-term treatment of euvolemic hyponatremia includes fluid restriction, isotonic normal saline, hypertonic saline, or a vaptan (eg, conivaptan, tolvaptan). Initial treatment generally consists of fluid restriction alone. Hypertonic saline is used only when the sodium concentration is less than 110 mEq/L (mmol/L) and/or severe symptoms (eg, seizures) are present. Given the limitations associated with these treatment strategies (unpredictable therapeutic effects and side effects), the arginine vasopressin antagonist conivaptan (Vaprisol, Astellas Pharma) was developed for short-term treatment of euvolemic hyponatremia. While conivaptan can also be used to manage hypervolemic hyponatremia in hospitalized patients, it should not be used for hypovolemic hyponatremia. Conivaptan is dosed 20 mg IV over 30 minutes, followed by a 20-mg continuous infusion over 24 hours for up to 4 days.

Long-term treatment options for euvolemic hyponatremia include fluid restriction, demeclocycline, loop diuretics, saline, lithium, urea, and tolvaptan. Demeclocycline (available as generic) is dosed at 600 to 1200 mg/day, takes days before clinical effect is realized, and can cause nephrotoxicity. Lithium (various generics) also has a slow onset of action and is limited by CNS side effects, GI disturbances, and cardiotoxicity. Furosemide (various generics) or other loop diuretics allow relaxation of fluid restriction but can cause significant volume depletion and electrolyte disturbances, and it has the potential for ototoxicity. Ure-Na is a USP urea, marketed as a medical food to treat euvolemic and hypervolemic hyponatremia, including SIADH. Urea increases water loss in the urine, thus normalizing sodium levels. Ure-Na is available in 15 g pouches, and some patient may experience a mild GI upset. This product should be used only under medical supervision and close laboratory monitoring (www.ure-na.com). Tolvaptan (Samsca, Otsuka) is an oral alternative to IV conivaptan. This product is indicated for treatment of clinically significant hypervolemic and euvolemic hyponatremia (sodium < 125 mEq/L [mmol/L]) or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction. Patients with CHF, cirrhosis, and SIADH would be candidates for long-term use. Tolvaptan has a boxed warning for initiation of treatment in a hospital setting because of the need for close sodium monitoring. The initial dose is 15 mg orally daily and may be titrated up to a max of 60 mg. Concurrent use with potent CYP 3A4 inhibitors should be avoided: ketoconazole (available as generic), clarithromycin (available as generic), ritonavir (Norvir, Abbott), diltiazem (available as generic), verapamil (available as generic), fluconazole (available as generic), and grapefruit juice.

In hypotonic hyponatremia with a decreased ECF volume (hypovolemic hyponatremia), patients usually have a deficit of both total body sodium and TBW, but the sodium deficit exceeds the TBW deficit. Common causes include diuretic use, profuse sweating, wound drainage, burns, GI losses (vomiting or diarrhea), hypoadrenalism (low cortisol and low aldosterone), and renal tubular acidosis. Treatment includes the administration of sodium to correct the sodium deficit and water to correct the TBW deficit. The sodium deficit can be calculated with the following equation[2]:

$$\text{Sodium deficit (mEq or mmol)} = (\text{TBW [in liters]})(\text{desired Na}^+ \text{ concentration [mEq/L or mmol/L]} - \text{current Na}^+ \text{ concentration}).$$

Although both water and sodium are required in this instance, sodium needs to be provided in excess of water to fully correct this abnormality. As such, hypertonic saline (3% NaCl) is often used. One can estimate the change in serum sodium concentration after 1 L of 3% NaCl infusion using the following equation[14]:

$$\text{Change in serum Na}^+ \text{ (mEq/L or mmol/L)} = (\text{infusate Na}^+ - \text{serum Na}^+)/(\text{TBW} + 1).$$

In this formula, TBW is increased by 1 to account for the addition of the liter of 3% NaCl. Patient Encounters 4 and 5 illustrate the concepts of calculating and correcting the sodium deficit.

Depending on the severity of the hyponatremia and acuity of onset, 0.9%, 3%, or 5% NaCl can be utilized. Most patients can be adequately managed with normal saline rehydration, which is generally the safest agent. Hypertonic saline (3% or 5% NaCl) is generally reserved for patients with severe hyponatremia (< 120 mEq/L [mmol/L]) accompanied by coma, seizures, or high urinary sodium losses. In general, a sodium replacement strategy should target a correction of 6 to 8 mEq/L (mmol/L) in serum per day. To prevent overcorrection of severe hyponatremia, the administration of desmopressin 2 to 4 mcg IV or SC q 8 to 12 hours until the sodium is greater than 128 mEq/L (mmol/L) can prevent excessive urinary water losses.[15] Overly aggressive correction of symptomatic hyponatremia (> 12 mEq/L [mmol/L] per day) can result in central pontine myelinolysis.[16] Given the potential for irreversible neurologic damage if untreated or if improperly treated, acute hyponatremia is an urgent condition that should be promptly treated with careful attention to monitoring serial sodium values and adjusting therapeutic infusions accordingly.[17]

Hypernatremia is a serum sodium concentration greater than 145 mEq/L (mmol/L) and can occur in the absence of a sodium deficit (pure water loss) or in its presence (hypotonic fluid loss).[18] The signs and symptoms of hypernatremia manifest with a serum sodium concentration greater than 160 mEq/L (mmol/L) and are usually the same as those found in TBW depletion: thirst, mental slowing, and dry mucous membranes. Signs and symptoms become more profound as hypernatremia worsens, with the patient eventually demonstrating confusion, hallucinations, acute weight loss, decreased skin turgor, intracranial bleeding, and/or coma. Many coexisting disorders and medications may complicate the diagnosis.

The classic causes of hypernatremia are associated with TBW depletion. These include dehydration from loss of hypotonic fluid from the respiratory tract or skin, decreased water intake, osmotic diuresis (eg, mannitol, available as generic), and diabetes insipidus (eg, decreased ADH; phenytoin, available as generic; lithium, available as generic). Hypernatremia in hospitalized patients occurs secondary to inappropriate fluid management in patients at risk for increased free water losses and impaired thirst or restricted water intake.[19] Iatrogenic hypernatremia is occasionally caused by the administration of excessive hypertonic saline. Treatment of hypernatremia includes calculation of the TBW deficit followed by the administration of hypotonic fluids as previously described. The fluid volume should be replaced over 48 to 72 hours depending on the severity of symptoms and the degree of hypertonicity.[20] For asymptomatic patients, the rate of correction should not exceed 0.5 mEq/L/h (mmol/L/h). One rule of thumb is to reduce serum sodium by a maximum of 6 to 8 mEq (mmol) every 24 hours.[18] Excessively rapid correction of hypernatremia may lead to cerebral edema and death. Patient Encounters 6 and 7 reinforce the concepts of calculating TBW deficit and expected changes in serum sodium concentration with therapy.

Potassium

The body's normal daily potassium requirement is 0.5 to 1 mEq/kg (mmol/kg) or 40 to 80 mEq (mmol) to maintain a serum

Patient Encounter 5: Estimate the Anticipated Change in Serum Sodium

Estimate the anticipated change in serum sodium concentration after the infusion of 1 L of 3% NaCl in a 78-kg male with a serum sodium of 122 mEq/L (mmol/L).

Patient Encounter 4: Calculation of Serum Sodium Deficit

Calculate the sodium deficit for a 78-kg male with a serum sodium of 122 mEq/L (mmol/L).

Patient Encounter 6: Calculate Water Deficit

Calculate the water deficit in an 84-kg female with a serum sodium of 160 mEq/L (mmol/L). The daily goal is to correct the sodium 6 mEq/L (mmol/L).

Patient Encounter 7: Calculate the Anticipated Change in Serum Sodium

Calculate the anticipated change in serum sodium concentration after IV infusion of 1 L of 5% dextrose in a 82 kg male with a serum sodium of 156 mEq/L (mmol/L).

potassium concentration of 3.5 to 5 mEq/L (mmol/L). Potassium is the most abundant cation in the ICF, balancing the sodium contained in the ECF and maintaining electroneutrality of bodily fluids. Because most potassium is intracellular, serum potassium concentration is not a good measure of total body potassium; however, clinical manifestations of potassium disorders correlate well with serum potassium. The acid–base balance of the body affects serum potassium concentrations: hyperkalemia is routinely seen in patients with decreased pH (acidosis). Potassium regulation is primarily under the control of the kidneys with excess dietary potassium being excreted in the urine. Although mild abnormalities of serum potassium are considered a nuisance, severe hyperkalemia or hypokalemia can be life threatening.[21-23]

Hypokalemia (serum potassium < 3.5 mEq/L [mmol/L]) is a common clinical problem. While generally asymptomatic, signs and symptoms of hypokalemia include cramps, muscle weakness, polyuria, electrocardiogram (ECG) changes (flattened T waves and presence of U waves), and cardiac arrhythmias (bradycardia, heart block, atrial flutter, premature ventricular contractions, and ventricular fibrillation). Causes of hypokalemia include GI losses (vomiting, diarrhea, or NG tube suction), renal losses (high aldosterone and low magnesium), inadequate potassium intake (in IV fluids or oral), or alkalosis. Many medications can precipitate hypokalemia. β_2-agonists (eg, albuterol, available as generic) and insulin (multiple product formulations) lower potassium via cellular redistribution. The use of loop diuretics (furosemide, Lasix, also available as generic), thiazide diuretics (hydrochlorothiazide, available as generic), high-dose antibiotics (penicillin, available as generic), and corticosteroids (prednisone, available as generic) cause renal potassium wasting. In addition, amphotericin B (available as generic), cisplatin (available as generic), and foscarnet (available as generic) can also produce hypokalemia secondary to depletion of magnesium. Hypomagnesemia diminishes intracellular potassium concentration and produces potassium wasting. Given the potential for significant morbidity and mortality, serum potassium concentrations should be monitored closely for patients with known (or suspected) hypokalemia.[2,23,24] Hypokalemia is a risk factor for digitalis toxicity.

Potassium repletion should be guided by close monitoring of serial serum concentrations instead of using empirically chosen amounts. Of the five potassium salts available, potassium acetate (10.2 mEq/K$^+$/g [mmol/K$^+$/g]) and KCl (13.4 mEq/K$^+$/g [mmol/K$^+$/g]) are the most used forms. When hypokalemia occurs in the setting of alkalosis, KCl is the preferred agent; in acidosis, potassium should be provided in the form of acetate, citrate, bicarbonate, or gluconate salt. Table 28–6 outlines the potassium content of each potassium salt preparation, and Table 28–7 lists each of the oral potassium replacement products. Potassium acetate and chloride are available for IV infusions as premixed solutions. The usual dose of these agents is 10 to 20 mEq (mmol) diluted in 100 mL of normal saline.[2,24,25]

Table 28–6

Potassium Content in Various Potassium Salt Preparations

Potassium Salt	mEq/g (mmol/g)
Potassium gluconate[a]	4.3
Potassium citrate[a]	9.8
Potassium bicarbonate[a]	10.0
Potassium acetate[a]	10.2
Potassium chloride[b]	13.4

[a] Favored for hypokalemia and concurrent acidosis.

[b] Favored for hypokalemia and concurrent alkalosis.

Moderate hypokalemia is defined as a serum potassium of 2.5 to 3.5 mEq/L (mmol/L) without ECG changes. In this setting, potassium replacement can usually be given orally at a dose of 40 to 120 mEq/day (mmol/day). Anecdotally, oral potassium supplementation (see Table 28–7) is often more effective in repleting moderate hypokalemia. Oral potassium supplements should be administered with or after meals to minimize potential gastrointestinal irritation. For patients with an ongoing source of potassium loss, chronic replacement therapy should be considered. The potassium deficit is a rough approximation of the amount of potassium needed to be replaced and can be estimated as follows:

$$\begin{aligned}&\text{Potassium deficit (mEq/L or mmol/L)}\\&\quad = (4.0 - \text{current serum potassium}) \times 100\end{aligned}$$

Severe hypokalemia is defined as a serum potassium less than 2.5 mEq/L (mmol/L) or hypokalemia of any magnitude that is associated with ECG changes (eg, flattening of T wave or elevation of U wave) and cardiac arrhythmias. In these situations, IV replacement should be initiated urgently. **KEY CONCEPT** Potassium infusion at rates exceeding 10 mEq/h (mmol/h) requires cardiac monitoring given the potential for cardiac arrhythmias. Although the maximally concentrated solution for potassium replacement is 80 mEq/L (mmol/L), the maximum infusion rate is 40 mEq/h (mmol/h) and must be administered via a central line. For safety, most hospitals define 20 mEq/h (mmol/h) as the maximum infusion rate. Table 28–8 outlines current IV potassium replacement guidelines.

Caution must be exercised when repleting potassium with IV agents given possible vein irritation and/or thrombophlebitis.

Table 28–7

Oral Potassium Replacement Products

Product	Salt	Strength[a]
Extended/controlled-release tablets	Chloride	10 mEq (750 mg) 20 mEq (1500 mg)
Effervescent tablets	Chloride and bicarbonate	10 mEq 20 mEq 25 mEq
Liquid	Chloride	20 mEq/15 mL (10%) 40 mEq/15 mL (20%)
Powder packets	Chloride	20 mEq 25 mEq

[a] For potassium, 1 mEq = 1 mmol.

Table 28–8

Recommended Potassium Dosage/Infusion Rate

Clinical Scenario	Maximum Infusion Rate[a]	Maximum Concentration[a]
K^+ greater than 2.5 mEq/L *and* No ECG changes of hypokalemia	10 mEq/h	40 mEq/L
K^+ less than 2.5 mEq/L *or* ECG changes of hypokalemia	40 mEq/h	80 mEq/L

[a]For potassium, 1 mEq = 1 mmol.

The risk of these complications is minimized by using less concentrated solutions and by giving infusions via central access if possible. Administration of potassium in vehicles containing glucose is discouraged because glucose facilitates the intracellular movement of potassium. Posttherapy improvements in serum potassium may be transient, and continuous monitoring is required. Patients with low serum magnesium will have exaggerated potassium losses from the kidneys and GI tract leading to refractory hypokalemia. In this situation, the magnesium deficit must be corrected to successfully treat the concurrent potassium deficiency. In the hypokalemic patient with concurrent acidosis, potassium is often given as the acetate salt, given that acetate is metabolized to bicarbonate. In the patient with depleted phosphorus and potassium, therapy with potassium phosphate is the natural choice.[21,26,27]

Hyperkalemia is defined as a serum potassium concentration greater than 5 mEq/L (mmol/L). Manifestations of hyperkalemia include muscle weakness, paresthesias, hypotension, ECG changes (eg, peaked T waves, shortened QT intervals, and wide QRS complexes), cardiac arrhythmias, and a decreased pH. Causes of hyperkalemia fall into three broad categories: (a) increased potassium intake, (b) decreased potassium excretion, and (c) potassium release from the intracellular space.

Increased potassium intake results from excessive dietary potassium (salt substitutes), excess potassium in IV fluids, and other select medications (potassium-sparing diuretics, cyclosporine [available as generic], angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory agents, pentamidine [available as generic], unfractionated heparin, and low molecular weight heparins). Decreased potassium excretion results from acute renal failure, chronic renal failure, or Addison's disease. Excess potassium release from cells results from tissue breakdown (surgery, trauma, hemolysis, or rhabdomyolysis), blood transfusions, and metabolic acidosis.

In addition to discontinuing all potassium supplements, potassium-sparing medications, and potassium-rich salt substitutes, management of hyperkalemia addresses three concurrent strategies: (a) agents to antagonize the proarrhythmic effects of hyperkalemia, (b) agents to drive potassium into the intracellular space and acutely lower the serum potassium, and (c) agents that will definitively (but more gradually) lower the total body potassium content.[28] If the serum potassium concentration is greater than 7 mEq/L (mmol/L) and/or ECG changes are present, IV calcium is administered to stabilize the myocardium. Depending on the acuity of the situation, 1 g of calcium chloride (13.5 mEq or 6.75 mmol) is administered by direct injection or diluted in 50 mL of D_5W and delivered IV over 15 minutes. Clinical effects are seen within 1 to 2 minutes of infusion and persist for 10 to 30 minutes. Repeat doses may be administered, as necessary. Because most patients with clinically significant hyperkalemia receive multiple boluses of calcium directed by ECG findings, iatrogenic hypercalcemia is a potential complication of hyperkalemia treatment. As such, total calcium concentration is commonly checked with each potassium concentration measurement. Ionized calcium measurements should be obtained in patients who have comorbid conditions that would lead to inconsistency between total serum calcium and free calcium (abnormal albumin, protein, or immunoglobulin concentrations).

Dextrose and insulin (with or without sodium bicarbonate) are typically given at the time of calcium therapy to redistribute potassium into the intracellular space. Dextrose 50% (25 g in 50 mL) can be given by slow IV push over 5 minutes or dextrose 10% with 20 units of regular insulin can be given by continuous IV infusion over 1 to 2 hours. The onset of action for this combination is 30 minutes; the duration of clinical effects is 2 to 6 hours. High-dose inhaled β_2-agonists (eg, albuterol, available as generic) may also be used to acutely drive potassium into the intracellular space.

It is critically important to recognize that the treatments of hyperkalemia discussed thus far are transient, temporizing measures. They are intended to provide time to institute definitive therapy aimed at removing excess potassium from the body. Agents that increase potassium excretion from the body include sodium polystyrene sulfonate (Kayexalate, available as generic), sodium zirconium cyclosilicate (Lokelma, AstraZeneca), loop diuretics, and hemodialysis or hemofiltration (used only in patients with renal failure). Sodium polystyrene sulfonate can be given orally, via NG tube, or as a rectal retention enema and is dosed at 15 to 60 g in four divided doses per day. MedWatch issued a safety alert that cases of colonic necrosis and other serious GI-adverse events (bleeding, ischemic colitis, perforation) had been reported in association with sodium polystyrene sulfonate (Kayexalate) suspension. Most of these cases reported the concurrent use of sorbitol, yet intestinal necrosis is also reported among patients not taking concurrent sorbitol. Clinicians are advised not to use sodium polystyrene sulfonate to reduce potassium levels. Medication safety alerts are available at www.fda.gov/MedWatch. Patiromer(Veltassa, Relypsa), a nonabsorbed cation exchange polymer increases fecal potassium excretion and is utilized to manage hyperkalemia in nonemergent situations, primarily in outpatients. Sodium zirconium cyclosilicate (Lokelma) exchanges potassium for hydrogen in the intestine. A delayed onset of action has limited the acute use of this product for emergency situations.

Calcium

More than 99% of total body calcium is found in bone; the remaining less than 1% is in the ECF and ICF. Calcium plays a critical role in the transmission of nerve impulses, skeletal muscle contraction, myocardial contractions, maintenance of normal cellular permeability, and the formation of bones and teeth. There is a reciprocal relationship between the serum calcium concentration (normally 8.6 to 10.2 mg/dL [2.15 to 2.55 mmol/L]) and the serum phosphate concentration that is regulated by a complex interaction between parathyroid hormone, vitamin D, and calcitonin. About one-half of the serum calcium is bound to plasma proteins; the other half is free ionized calcium. Given that the serum calcium has significant protein binding, the serum calcium measurement must be corrected in patients who have low albumin concentrations (the major serum protein). The most used formula adds 0.8 mg/dL (0.2 mmol/L) of calcium for each gram of albumin deficiency as follows:

$$\text{Corrected [Ca mg/dL]} = \text{Measured [Ca mg/dL]} + [0.8 \times (4 - \text{measured albumin g/dL})]$$[29–31]

$$\text{Corrected [Ca mmol/L]} = \text{Measured [Ca mmol/L]} + [0.02 \times (40 - \text{measured albumin g/L})]$$

Clinical manifestations of hypocalcemia are seen with total serum concentrations less than 6.5 mg/dL (1.63 mmol/L) or an ionized calcium less than 1.12 mmol/L and include tetany, circumoral tingling, muscle spasms, hypoactive reflexes, anxiety, hallucinations, hypotension, myocardial infarction, seizures, lethargy, stupor, and **Trousseau's sign** or **Chvostek's sign**.[23,32] Ionized calcium concentrations are typically used to assess calcium status in the critically ill as these patients often have concurrent hypoalbuminemia.

Causes of hypocalcemia include hypoparathyroidism, hypomagnesemia, alcoholism, hyperphosphatemia, blood product infusion (due to chelation by the citrate buffers), chronic renal failure, vitamin D deficiency, acute pancreatitis, alkalosis, and hypoalbuminemia. In the setting of hypocalcemia, magnesium concentration should be checked and corrected if low. Given that hypocalcemia may be caused by hypomagnesemia, clinicians should be aware that the serum calcium concentrations may not normalize until serum magnesium is replaced. Medications that cause hypocalcemia include phosphate replacement products, loop diuretics, phenytoin (Dilantin, available as generic), phenobarbital (available as generic), corticosteroids, aminoglycoside antibiotics, and acetazolamide (available as generic).[30–32]

Oral calcium replacement products include calcium carbonate (Os-Cal, Glaxo Consumer, and various generics; Tums, Glaxo Consumer and various generics) and calcium citrate (Citracal, Mission Bayer and various generics). IV calcium replacement products include calcium gluconate and calcium chloride (both products available as generic). **KEY CONCEPT** Calcium gluconate is preferred for peripheral use because it is less irritating to the veins; it may also be given intramuscularly. Each 10 mL of a 10% calcium gluconate solution provides 90 mg (4.5 mEq or 2.25 mmol) of elemental calcium. **KEY CONCEPT** Calcium chloride is associated venous irritation and extravasation and is generally reserved for administration via central line. Each 10 mL of a 10% calcium chloride solution contains 270 mg (13.5 mEq or 6.75 mmol) of elemental calcium. IV calcium products are given as a slow push or added to 100 mL of 0.9% normal saline for slow infusion.[31,32] In addition to hypocalcemia, IV calcium may also be used for massive blood transfusions, calcium channel blocker overdose, and emergent hyperkalemia and hypermagnesemia.

For acute symptomatic hypocalcemia, 200 to 300 mg of elemental calcium is administered IV and repeated until symptoms are fully controlled. This is achieved by infusing 1 g of calcium chloride or 2 to 3 g of calcium gluconate at a rate no faster than 30 to 60 mg of elemental calcium per minute. More rapid administration is associated with hypotension, bradycardia, or cardiac asystole. Total calcium concentration is commonly monitored in critically ill patients. Under normal circumstances, about half of calcium is loosely bound to serum proteins while the other half is free. Total calcium concentration measures bound and free calcium. Ionized calcium measures free calcium only. Under usual circumstances, a normal calcium concentration implies a normal free ionized calcium concentration. Ionized calcium should be obtained in patients with comorbid conditions that would lead to inconsistency between total calcium and free serum calcium (abnormal albumin, protein, or immunoglobulin concentrations). For chronic asymptomatic hypocalcemia, oral calcium supplements are given at doses of 2 to 4 g/day of elemental calcium. Many patients with calcium deficiency have concurrent vitamin D deficiency that must also be corrected to restore calcium homeostasis.[2,32,33]

Hypercalcemia is defined as a calcium concentration greater than 10.2 mg/dL (2.55 mmol/L). It may be categorized as mild if total serum calcium is 10.3 to 12 mg/dL (2.58 to 3.00 mmol/L), moderate if total serum calcium is 12.1 to 13 mg/dL (3.03–3.25 mmol/L), or severe when serum concentration is greater than 13 mg/dL (3.25 mmol/L). Causes of hypercalcemia include hyperparathyroidism, malignancy, Paget's disease, Addison's disease, granulomatous diseases (eg, tuberculosis, sarcoidosis, or histoplasmosis), hyperthyroidism, immobilization, multiple bony fractures, acidosis, and milk-alkali syndrome. Multiple medications cause hypercalcemia and include thiazide diuretics, estrogens, lithium, tamoxifen, vitamin A, vitamin D, and calcium supplements.[2,32,34,35]

Because the severity of symptoms and the absolute serum concentration are poorly correlated in some patients, institution of therapy should be dictated by the clinical scenario. All patients with hypercalcemia should be treated with aggressive rehydration: normal saline at 200 to 300 mL/h is a routine initial fluid prescription. For patients with mild hypercalcemia, hydration alone may provide adequate therapy. The moderate and severe forms of hypercalcemia are more likely to have significant manifestations and require prompt initiation of additional therapy. These patients may present with anorexia, confusion, and/or cardiac manifestations (bradycardia and arrhythmias with ECG changes). Total calcium concentrations greater than 13 mg/dL (3.25 mmol/L) are particularly worrisome because these concentrations can unexpectedly precipitate acute renal failure, ventricular arrhythmias, and sudden death.

Once fluid administration has repleted the ECF, forced diuresis (with associated calcium loss) can be initiated with a loop diuretic. For this approach to be successful, normal kidney function is required. In renal failure patients, the alternative therapy is emergent hemodialysis. Other treatment options include bisphosphonates (zoledronic acid, pamidronate), hydrocortisone, calcitonin, and gallium. Given their efficacy and favorable side-effect profile, bisphosphonates are typically the agents of choice. **Table 28–9** outlines the treatment options for hypercalcemia including time to onset of effect, duration of effect, and efficacy.[2,32,33,34]

Phosphorus

Phosphorus is primarily found in the bone (80%–85%) and ICF (15%–20%): the remaining less than 1% is found in the ECF. Note that phosphorus is the major anion within the cells. Given this distribution, serum phosphate concentration does not accurately reflect total body phosphorus stores. Phosphorus is expressed in milligrams (mg) or millimoles (mmol), not as milliequivalents (mEq). Because phosphorus is the source of phosphate for adenosine triphosphate (ATP) and phospholipid synthesis, manifestations of phosphorus imbalance are variable.

Dietary intake, parathyroid hormone levels, and renal function are the major determinants of the serum phosphorus concentration, which is normally 2.7 to 4.5 mg/dL (0.87–1.45 mmol/L).[2,32,36,37,38] Hypophosphatemia is defined by a serum phosphorus concentration less than 2.5 mg/dL (0.81 mmol/L); severe

Table 28–9

Selected Treatment Options for the Management of Hypercalcemia

Therapy	Dose	Onset	Duration	Efficacy[a]
Normal saline	3–6 L/day	Hours	Hours	1–2 mg/dL (0.25–0.50 mmol/L)
Furosemide (Lasix, available as generic)	80–160 mg/day	Hours	Hours	1–2 mg/dL (0.25–0.50 mmol/L)
Hydrocortisone (available as generic)	200 mg/day	Hours	Days	Mild/unpredictable
Calcitonin (Miacalcin, Novartis)	4–8 units/kg	Hours	Hours	1–2 mg/dL (0.25–0.50 mmol/L)
Pamidronate (available as generic)	30–90 mg/week	Days	1–4 weeks	1–5 mg/dL(0.25–1.25 mmol/L)
Zoledronic acid (available as generic)	4–8 mg	Days	Weeks	1–5 mg/dL (0.25–1.25 mmol/L

[a] Expected decrease in serum Ca^{2+}.

hypophosphatemia occurs when the phosphorus concentration is less than 1 mg/dL (0.32 mmol/L). Hypophosphatemia can be caused by increased distribution to the ICF (hyperglycemia, insulin therapy, or malnourishment), decreased absorption (starvation, excessive use of phosphorus-binding antacids, vitamin D deficiency, diarrhea, or laxative abuse) or increased renal loss (diuretic use, diabetic ketoacidosis, alcohol abuse, hyperparathyroidism, or burns).[33,36] **KEY CONCEPT** Severe hypophosphatemia can result in impaired diaphragmatic contractility and acute respiratory failure. Medications that can cause hypophosphatemia include diuretics (acetazolamide [Diamox, available as generic], furosemide [Lasix, available as generic], hydrochlorothiazide [HydroDIURIL, available as generic]), sucralfate (Carafate, available as generic), corticosteroids, cisplatin (available as generic), antacids (aluminum carbonate, calcium carbonate, and magnesium oxide [antacids all available as generic]), foscarnet (available as generic), phenytoin (Dilantin, available as generic), phenobarbital (available as generic), and phosphate binders (sevelamer [Renvela, Genzyme Corp.], and calcium acetate [PhosLo, available as generic]).

Signs and symptoms of hypophosphatemia include paresthesias, muscle weakness, myalgias, bone pain, anorexia, nausea, vomiting, red blood cell breakdown (hemolysis), acute respiratory failure, seizures, and coma.[33,39] For mild hypophosphatemia, patients should be encouraged to eat a high-phosphorus diet including eggs, nuts, whole grains, meat, fish, poultry, and milk products. For moderate hypophosphatemia (1–2.5 mg/dL, 0.32–0.81 mmol/L), oral supplementation of 1.5 to 2 g/day (30–60 mmol/day) is usually adequate. Diarrhea may be a dose-limiting side effect with oral phosphate replacement products.

Injectable phosphate products are reserved for patients with severe hypophosphatemia or those in the intensive care unit.[40] The available agents are provided as sodium or potassium salts; however, unless concurrent hypokalemia is present, sodium phosphate is usually used. Empirically, for a mild serum phosphorus deficiency (2.3–3.0 mg/dL, 0.74–0.97 mmol/L), the corresponding IV phosphorus dose is 0.32 mmol/kg; for a moderate deficiency of serum phosphorus 1.6 to 2.2 mg/dL (0.52–0.71 mmol/L), the replacement dose is 0.64 mmol/kg; and the dose is 1 mmol/kg when the serum phosphorus is less than 1.5 mg/dL (0.48 mmol/L).[41] IV phosphorus preparations are usually infused over 4 to 12 hours. Table 28–10 compares the available phosphate replacement products.

Hyperphosphatemia is defined by a serum phosphorus concentration greater than 4.5 mg/dL (1.45 mmol/L). The manifestations of hyperphosphatemia are similar to findings of hypocalcemia (see earlier), and include paresthesias, ECG changes (prolonged QT interval and prolonged ST segment), and metastatic calcifications. Causes of hyperphosphatemia include impaired phosphorus excretion (hypoparathyroidism or renal failure), redistribution of phosphorus to the ECF (acid–base imbalance, rhabdomyolysis, muscle necrosis, or tumor lysis during chemotherapy), and increased phosphorus intake (various medications).[33] Medications that can cause hyperphosphatemia include enemas containing phosphorus (eg, Fleet, Fleet), laxatives containing phosphate or phosphorus, parenteral or oral supplements (eg, K-Phos Neutral, Beach), vitamin D supplements, and the bisphosphonates (eg, pamidronate, various manufacturers).[42]

Hyperphosphatemia is generally benign and rarely needs aggressive therapy. Dietary restriction of phosphate and protein is effective for most minor elevations. Phosphate binders such as aluminum-based antacids, calcium carbonate, calcium acetate (PhosLo, available as generic), sevelamer hydrochloride (Renagel, Genzyme), sevelamer carbonate (Renvela, Genzyme, Global), and lanthanum carbonate (Fosrenol, Shire) may be necessary for some patients (typically those with chronic renal failure).[43] Sucroferric oxyhydroxide (Velphoro, Fresenius Medical Care) is a

Table 28–10

Phosphate Replacement Products

Product	Route	mgPO$_4^-$	mmolPO$_4^-$	mEq (mmol) Na$^+$	mEq (mmmol) K$^+$
Potassium phosphate (KPO$_4$/mL), available as generic	IV	94	3	0	4.4
Sodium phosphate (NaPO$_4$/mL), available as generic	IV	94	3	4	0
Phos-NaK packets, Cypress	Oral	250	8	7.2	7
K-Phos Neutral tablets, Beach	Oral	250	8	13.1	1.4
K-Phos Original tablets, Beach	Oral	114	3.7	-	3.7

noncalcium based chewable phosphate binder administered with each meal. If patients exhibit findings of hypocalcemia (tetany), IV calcium should be administered empirically. Phosphate binders can reduce serum phosphate concentration by 1 to 2 mg/dL (0.32-0.65 mmol/L) in patients requiring dialysis. Interestingly, the clinical benefit of phosphate binders in end stage renal disease has not been demonstrated by randomized clinical trial data to date versus no treatment.[44]

Magnesium

The body's normal daily magnesium requirement is 300 to 350 mg/day to maintain a serum magnesium concentration of 1.5 to 2.4 mEq/L (0.75–1.20 mmol/L). Less than 1% of magnesium is found in the ECF. Magnesium is the second most abundant ICF cation and ECF serum concentrations are a relatively poor measure of total body stores. Magnesium catalyzes and/or activates more than 300 enzymes, provides neuromuscular stability, and is involved in myocardial contraction. Magnesium is generally not part of standard chemistry panels and therefore must be ordered separately.[2,32,42,45,46]

Hypomagnesemia is defined as a serum magnesium less than 1.5 mEq/L (0.75 mmol/L) and is most frequently seen in the intensive care and postoperative settings. Hypomagnesemia results from inadequate intake (alcoholism, dietary restriction, or inadequate magnesium in total parenteral nutrition [TPN]), inadequate absorption (steatorrhea, cancer, malabsorption syndromes, or excess calcium or phosphorus in the GI tract), excessive GI loss of magnesium (diarrhea, laxative abuse, NG tube suctioning, or acute pancreatitis), or excessive urinary loss of magnesium (primary hyperaldosteronism, certain medications, diabetic ketoacidosis, and renal disorders). Hypomagnesemia often occurs in the setting of hypokalemia and hypocalcemia. Clinicians should evaluate the serum magnesium concentration in these patients and correct if low. To evaluate magnesium status, both laboratory tests and clinical assessment is required. For calcium and potassium concentrations to normalize, magnesium supplementation is often required. Medications that potentially can cause hypomagnesemia include aminoglycoside antibiotics, amphotericin B (available as generic), cisplatin (available as generic), insulin, cyclosporine (available as generic), loop diuretics, and thiazide diuretics There is also a strong correlation between hypokalemia and hypomagnesemia.[33,35,42,47] Clinicians should be alerted that the long-term use of proton pump inhibitors may be associated with unexplained hypomagnesemia, with subsequent hypokalemia or hypocalcemia.

The findings of hypomagnesemia include muscle weakness, cramps, agitation, confusion, tremor, seizures, ECG changes (increased PR interval, prolonged QRS complex, peaked T waves, and increased QT interval), findings of hypocalcemia (see earlier), refractory hypokalemia (see earlier), metabolic alkalosis, and digoxin toxicity.[42,48,49]

Asymptomatic mild magnesium deficiencies (1.0–1.5 mEq/L) (0.50–0.75 mmol/L) can be managed with increased oral intake of magnesium-containing foods or with oral supplementation. Magnesium oxide (Mag-Ox various manufacturers) 400-mg tablets contain 241 mg (20 mEq or 10 mmol) of magnesium, and magnesium chloride hexahydrate tablets (Slow-Mag, various generics) contains 64 mg of elemental magnesium. Diarrhea is often a dose-limiting side effect of oral supplementation. Severely deficient patients (< 1.0 mEq/L [0.50 mmol/L]) and all deficient critically ill patients should be managed with IV magnesium sulfate. Ten milliliters of a 10% magnesium sulfate solution contains 1 g of magnesium, which is equivalent to 98 mg (8.12 mEq or 4.06 mmol) of elemental magnesium. IV magnesium supplementation may also be used in the setting of status asthmaticus, premature labor, and torsade de pointes. In May 2013, the FDA released a drug safety communication recommending against the prolonged use of magnesium sulfate to stop preterm labor due to bone changes in exposed babies. Administration of magnesium sulfate injection to pregnant women longer than 5 to 7 days may lead to low calcium levels and bone fractures in the developing baby or fetus. (http://www.fda.gov/Safety/MedWatch/) Magnesium concentrations need to be monitored closely in these patients. **KEY CONCEPT** Because magnesium concentration does not correlate well with total body magnesium stores, magnesium is often administered empirically to critically ill patients.[2,32]

The most common causes of hypermagnesemia are renal failure, often in conjunction with magnesium-containing medications (cathartics, antacids, or magnesium supplements), and lithium therapy (available as generic). Hypermagnesemia is defined as a serum magnesium concentration greater than 2.4 mEq/L (1.20 mmol/L). Mild hypermagnesemia is present if

Patient Encounter 8: Putting It All Together

MH, a 69-year-old man who resides in an independent living center is admitted to the hospital with a 3-day history of altered mental status. The patient was unable to give a history or review of systems. On physical examination, the vital signs revealed a BP of 100/60 mm Hg, pulse 113 beats per minute, respirations 16 per minute, and a temperature of 38.3°C (101°F). Rales and dullness to percussion were noted at the posterior right base. The cardiac examination was significant for tachycardia. No edema was present. Laboratory studies included sodium 159 mEq/L (mmol/L), potassium 4.6 mEq/L (mmol/L), chloride 119 mEq/L (mmol/L), bicarbonate 30 mEq/L (mmol/L), glucose 104 mg/dL (5.8 mmol/L), BUN 34 mg/dL (12.1 mmol/L), and creatinine 2.2 mg/dL (194 μmol/L). The CBC was within normal limits. Procalcitonin is pending. Chest x-ray indicated right lower lobe pneumonia. The patient is 5 ft 10 in. (178 cm) tall and currently weighs 72 kg (158 lb). His normal weight is 77 kg (170 lb).

What are the likely causes for the increased sodium concentration in this patient?

Calculate the TBW, ICF, and ECF for this patient.

Calculate DM's fluid deficit if one is present.

In the next 24 hours, the medical team wants to replace 50% of the fluid deficit plus an extra 240 mL to account for increased insensible losses in addition to the patient's maintenance needs. Using the equation (1500 mL + 20 mL for each kilogram > 20 kg), calculate the rate of fluid administration for the total fluids needed in this 24-hour period and over the next 48 hours.

Calculate MH's daily maintenance fluids.

Calculate MH's fluid administration rate for the first 24 hours (hospital day 1).

Calculate MH's fluids for the subsequent 48 hours (hospital days 2 and 3) if the goal is to replete the remaining fluid deficit during that time.

What type of fluid should be used to treat MH's fluid disorder?

Patient Care and Monitoring

Collect Information

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements.
- Review the medical history, laboratory data, and physical assessment findings.
- Identify lifestyle habits, preferences, health goals, and socioeconomic factors that cause risk of fluid imbalance and/or acute and chronic electrolyte disorders.

Assess the Information

- Determine if the patient is taking any substance that could alter fluid status or electrolyte balance.
- Based upon physical exam, review of systems, and laboratory data, determine whether the patient is experiencing signs or symptoms of fluid imbalance or an electrolyte disorder.
- Identify any significant adverse drug effects or interactions.

Develop a Care Plan

- Determine if fluid replacement and/or electrolyte supplementation is indicated.
- Choose replacement fluid and/or electrolyte doses that are optimal for the patient.

Implement the Care Plan

- Educate the patient about changes in drug therapy, medication administration, potential new effects, and how to manage and report adverse events that occur.
- Discuss importance of medication adherence and lifestyle changes to maintain fluid status and electrolyte balance.
- Determine if the patient has insurance coverage on whether recommended agents are included on the institution's formulary.

Follow-up: Monitor and Evaluate

- Follow up at appropriate intervals to assess effectiveness and safety of electrolyte replacement therapy.
- Review medication adherence.
- Review physical exam, laboratory tests, and results of other diagnostic tests to assess changes in clinical status.

the serum magnesium concentration is between 2.5 and 4 mEq/L (1.25–2.00 mmol/L) and manifests as nausea, vomiting, cutaneous vasodilation, and bradycardia. Moderate hypermagnesemia is present if the serum magnesium concentration is between 4 and 12 mEq/L (2 to 6 mmol/L) and may manifest with hyporeflexia, weakness, somnolence, hypotension, and ECG changes (increased QRS interval). Severe hypermagnesemia is present if the serum magnesium concentration is greater than 13 mEq/L (6.5 mmol/L) and can manifest as muscle paralysis, complete heart block, asystole, respiratory failure, refractory hypotension, and death.[2,50]

All patients with hypermagnesemia should have all magnesium supplements or magnesium-containing medications discontinued.[2,32] Iatrogenic hypermagnesemia has been observed after IV magnesium therapy for refractory asthma or preeclampsia. Mild hypermagnesemia and moderate hypermagnesemia without cardiac findings can be treated with normal saline infusion and furosemide therapy (assuming the patient has normal renal function). Moderate hypermagnesemia with cardiac irritability and severe hypermagnesemia require concurrent IV calcium gluconate to reverse the neuromuscular and cardiovascular effects. Calcium gluconate given at typical doses of 1 to 2 g IV will have transient effects and can be repeated as clinically indicated. Hemodialysis may be necessary for those with severely compromised renal function.

CONCLUSION

Because disturbances in fluid balance are routinely encountered in clinical medicine, it is essential to have a thorough understanding of body fluid compartments and the therapeutic use of fluids. Similarly, disturbances in serum sodium, potassium, calcium, phosphorus, and magnesium are ubiquitous and must be mastered by all clinicians. Dysregulation of fluid and/or electrolyte status has serious implications regarding the concepts of drug absorption, volumes of distribution, and toxicity. Similarly, many medications can disrupt fluid and/or electrolyte balance as an unintended consequence.

Abbreviations Introduced In This Chapter

ADH	Antidiuretic hormone
ASHP	American Society of Health-System Pharmacists
ATP	Adenosine triphosphate
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^+	Calcium
CHF	Congestive heart failure
Cl	Chloride
D5W	Dextrose 5% water
ECF	Extracellular fluid
ECG	Electrocardiogram
FFP	Fresh-frozen plasma
IBW	Ideal body weight
ICF	Intracellular fluid
I&Os	Ins and outs
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
K^+	Potassium
KPO^4	Potassium phosphate
KVO	Keep the vein open
LR	Lactated Ringer's (solution)
Mg^{++}	Magnesium
Na^+	Sodium
NaCl	Sodium chloride
NaPO4	Sodium phosphate
NG	Nasogastric
NS	Normal saline
SI	Standardized international units
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
TBW	Total body water
TPN	Total parenteral nutrition

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29

Acid–Base Disturbances

Lee E. Morrow and Mark A Malesker

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Compare and contrast the six primary acid–base disturbances within the human body.
2. Apply simple formulas in a systematic manner to determine the etiology of simple acid–base disturbances and the adequacy of compensation.
3. Integrate the supplemental concepts of the anion gap and the excess gap to further assess for complex acid–base disturbances.
4. Discuss the most common clinical causes for each primary acid–base abnormality.
5. Describe the potential clinical complications of altered acid–base homeostasis.
6. Propose an appropriate treatment plan for patients with deranged acid–base physiology.

INTRODUCTION

Given its reputation for complexity and the need to memorize innumerable formulas, acid–base analysis intimidates many health-care providers. In reality, acid–base disorders always obey well-defined biochemical and physiological principles. The pH determines a patient's acid–base status and an assessment of the serum bicarbonate (HCO_3^-) and arterial blood carbon dioxide ($PaCO_2$) values identifies the underlying process. Rigorous use of a systematic approach to arterial blood gases increases the likelihood that derangements in acid–base physiology are recognized and correctly interpreted. This chapter outlines a clinically useful approach to acid–base abnormalities and applies it in a series of increasingly complex clinical scenarios.

Disturbances of acid–base equilibrium occur in a wide variety of illnesses and are among the most frequently encountered disorders in critical care medicine. The importance of a thorough command of this content cannot be overstated given that acid–base disorders are remarkably common and may result in significant morbidity and mortality. Although severe derangements may affect virtually any organ system, the most serious clinical effects are cardiovascular (arrhythmias, impaired contractility), neurologic (coma, seizures), pulmonary (dyspnea, impaired oxygen delivery, respiratory fatigue, respiratory failure), and/or renal (hypokalemia). Changes in acid–base status also affect multiple aspects of drug disposition (clearance, protein binding) and pharmacodynamics.

PHYSIOLOGY OF ACID–BASE HOMEOSTASIS

Acid–base homeostasis is responsible for maintaining blood hydrogen ion concentration [H^+] near normal despite the daily acidic and/or alkaline loads derived from the intake and metabolism of foods. Acid–base status is traditionally represented in terms of pH, the negative logarithm of [H^+]. Because [H^+] is equal to 24 times the ratio of $PaCO_2$ to HCO_3^- (for $PaCO_2$ expressed in units of mm Hg), the pH can be altered by a change in either the bicarbonate concentration or the dissolved carbon dioxide. A critically important concept is that [H^+] depends only on the *ratio* of $PaCO_2$ to HCO_3^- and not the absolute amount of either. As such, a normal $PaCO_2$ or HCO_3^- alone does not guarantee that the pH will be normal. Conversely, a normal pH does not imply that either the $PaCO_2$ or HCO_3^- will be normal.[1]

KEY CONCEPT Acid–base homeostasis is tightly regulated by the complex, but predictable, interactions of the kidneys, the lungs, and various buffer systems. The kidneys control serum HCO_3^- concentration through the excretion or reabsorption of filtered HCO_3^-, the excretion of metabolic acids, and synthesis of new HCO_3^-. The lungs control arterial carbon dioxide (CO_2) concentrations through changes in the depth and/or rate of respiration. The net result is tight regulation of the blood pH by these three distinct mechanisms working in harmony: extracellular HCO_3^- and intracellular protein buffering systems; pulmonary regulation of $PaCO_2$, effectively allowing carbonic acid to be eliminated by the lungs as CO_2; and renal reclamation or excretion of HCO_3^- and excretion of acids such as ammonium.

Because kidneys excrete less than 1% of the estimated 13,000 mEq (mmol) of H^+ ions generated in an average day, renal failure can be present for prolonged periods before life-threatening imbalances occur. Conversely, cessation of breathing for minutes results in profound acid–base disturbances.[1]

The best way to assess a patient's acid–base status is to review the results of an arterial blood gas (ABG) specimen. ABG analyzers directly measure the pH and $PaCO_2$, while the HCO_3^- value is calculated using the Henderson-Hasselbalch equation. A more direct measure of serum HCO_3^- is obtained by measuring the total venous carbon dioxide (tCO_2). Because dissolved CO_2 is almost exclusively in the form of HCO_3^-, tCO_2 is essentially equivalent to the measured serum HCO_3^- concentration. This value (HCO_3^-) is routinely reported on basic chemistry panels. In the remainder of this chapter, the pH and $PaCO_2$ values should be assumed to come from an ABG while HCO_3^- values should be considered to be the measured serum concentration.

BASIC PATHOPHYSIOLOGY

Under normal circumstances, the arterial pH is tightly regulated between 7.35 and 7.45. **Acidemia** is an abnormally low arterial blood pH (< 7.35) while **acidosis** is a pathologic process that acidifies body fluids. Similarly, **alkalemia** is an abnormally high arterial blood pH (> 7.45) while **alkalosis** is a pathologic process that alkalinizes body fluids. As such, although a patient can simultaneously have acidosis *and* alkalosis, the end result will be acidemia *or* alkalemia.

Changes in the arterial pH are driven by changes in the $PaCO_2$ and/or the serum HCO_3^-. CO_2 is a volatile acid regulated by the depth and rate of respiration. Because CO_2 can be either "blown off" or "retained" by the respiratory system, it is referred to as being under respiratory control. KEY CONCEPT **Respiratory acidosis** and **alkalosis** result from primary disturbances in the arterial CO_2 concentration. Metabolic compensation for respiratory disturbances is a slow process, often requiring days for the serum HCO_3^- to reach steady state. KEY CONCEPT **Respiratory acidosis** is caused by respiratory insufficiency resulting in an increased arterial CO_2 concentration. The compensation for respiratory acidosis (if present for prolonged periods) is an increase in serum HCO_3^-. KEY CONCEPT **Respiratory alkalosis** is caused by hyperventilation resulting in a decreased arterial CO_2 concentration. The compensation for respiratory alkalosis (if present for prolonged periods) is a decrease in serum HCO_3^-.

A respiratory acid–base disorder is a pH disturbance caused by pathologic alterations of the respiratory system or its CNS control. Such an alteration may result in the accumulation of $PaCO_2$ beyond normal limits (> 45 mm Hg [6.0 kPa]), a situation termed *respiratory acidosis*, or it may result in the loss of $PaCO_2$ beyond normal limits (< 35 mm Hg or 4.7 kPa), a condition termed *respiratory alkalosis*. Variations in respiratory rate and/or depth allow the lungs to achieve changes in the $PaCO_2$ very quickly (within minutes).

HCO_3^- is a base regulated by renal metabolism via the enzyme carbonic anhydrase. As such, HCO_3^- is often referred to as being under metabolic control. KEY CONCEPT **Metabolic acidosis** and alkalosis result from primary disturbances in the serum HCO_3^- concentration. Respiratory compensation of metabolic disturbances begins within minutes and is complete within 12 hours. KEY CONCEPT **Metabolic acidosis** is characterized by a decrease in serum HCO_3^-. The anion gap is used to narrow the differential diagnosis because metabolic acidosis may be caused by addition of acids (increased anion gap) or loss of HCO_3^- (normal anion gap). The compensation for metabolic acidosis is an increase in ventilation with a decrease in arterial CO_2. KEY CONCEPT **Metabolic alkalosis** is characterized by an increase in serum HCO_3^-. This disorder requires loss of fluid that is low in HCO_3^- from the body or addition of HCO_3^- to the body. The compensation for metabolic alkalosis is a decrease in ventilation with an increase in arterial CO_2.

A metabolic acid–base disorder is a pH disturbance caused by derangement of the pathways responsible for maintaining a normal HCO_3^- concentration. This may result in a pathologic accumulation of HCO_3^- (> 26 mEq/L [mmol/L]), a condition termed *metabolic alkalosis*, or it may result in the loss of HCO_3^- beyond normal (< 22 mEq/L [mmol/L]), a condition termed *metabolic acidosis*. In contrast to the lungs' rapid effects on CO_2, the kidneys change the HCO_3^- very slowly (hours to days).

Respiratory and metabolic derangements can occur in isolation or in combination. If a patient has an isolated primary acid–base disorder that is not accompanied by another primary acid–base disorder, a simple (uncomplicated) disorder is present. The most common clinical disturbances are simple acid–base disorders. If two or three primary acid–base disorders are simultaneously present, the patient has a mixed (complicated) disorder. More complex clinical situations lead to mixed acid–base disturbances. Because CO_2 is a volatile acid, it can rapidly be changed by the respiratory system. If a respiratory acid–base disturbance is present for minutes to hours, it is considered an acute disorder, while if it is present for days or longer it is considered a chronic disorder. By definition, the metabolic machinery that regulates HCO_3^- results in slow changes, and all metabolic disorders are chronic.

Physiologic changes that follow the primary disorder and attempt to restore the blood pH to normal are referred to as compensatory changes. It should be stressed that compensation never normalizes the pH. Because all metabolic acid–base disorders are chronic and the normal respiratory system can quickly alter the $PaCO_2$, essentially all metabolic disorders are accompanied by some degree of respiratory compensation.[2,3] Similarly, chronic respiratory acid–base disorders are typically accompanied by attempts at metabolic compensation.[4,5] However, with acute respiratory acid–base disorders, there is insufficient time for the metabolic pathways to compensate significantly.[6] As such, acute respiratory derangements are essentially uncompensated.

The amount of compensation (metabolic or respiratory) can be reliably predicted based on the degree of derangement in the primary disorder. Table 29–1 outlines the simple acid–base disorders and provides formulas for calculating the expected compensatory responses.[7] Although it is not mandatory to memorize these formulas to interpret acid–base problems, they can be helpful tools. If the measured values differ markedly from the calculated values (the measured serum HCO_3^- is > 2 mEq/L [mmol/L] from the calculated value or the measured $PaCO_2$ is more than 4 mm Hg [0.5 kPa] from the calculated value), a second acid–base disorder is present as outlined in Table 29–2.

Table 29–1

The Six Simple Acid–Base Disorders

Type of Disorder	pH	$PaCO_2$[a]	HCO_3^-
1. Metabolic acidosis	↓	Decreased[b] $PaCO_2 = (1.5 \times HCO_3^-) + 8$	Decreased[c]
2. Metabolic alkalosis	↑	Increased[b] $PaCO_2 = (0.9 \times HCO_3^-) + 15$	Increased[c]
3. Acute respiratory acidosis	↓	Increased[c]	Approximately normal $\Delta HCO_3^- = 0.1 \times \Delta PaCO_2$[a]
4. Chronic respiratory acidosis	↓	Increased[c]	Increased[d] $\Delta HCO_3^- = 0.35 \times \Delta PaCO_2$[a]
5. Acute respiratory alkalosis	↑	Decreased[c]	Approximately normal $\Delta HCO_3^- = 0.2 \times \Delta PaCO_2$[a]
6. Chronic respiratory alkalosis	↑	Decreased[c]	Decreased[d] $\Delta HCO_3 = 0.4 \times \Delta PaCO_2$[a]

[a] $PaCO_2$ in mm Hg and is calculated from kPa by dividing by 0.133.

[b] Respiratory compensation: If inappropriate, see Table 29–2.

[c] Primary disorder.

[d] Metabolic compensation: If inappropriate, see Table 29–2.

Table 29–2

Diagnosis of Concurrent Acid–Base Disturbances When Compensation Is Inappropriate

Primary Acid–Base Disturbance	Assessment of Compensation	Concurrent Acid–Base Disturbance
Metabolic acidosis	PaCO$_2$ too low[a]	Respiratory alkalosis
	PaCO$_2$ too high[a]	Respiratory acidosis
Metabolic alkalosis	PaCO$_2$ too low[a]	Respiratory alkalosis
	PaCO$_2$ too high[a]	Respiratory acidosis
Respiratory acidosis	Hco$_3^-$ too low[b]	Metabolic acidosis
	Hco$_3^-$ too high[b]	Metabolic alkalosis
Respiratory alkalosis	HCO$_3^-$ too low[b]	Metabolic acidosis
	HCO$_3^-$ too high[b]	Metabolic alkalosis

[a] Measured PaCO$_2$ more than 4 mm Hg (0.5 kPa) from the calculated value.

[b] Measured HCO$^-_3$ more than 2 mEq/L (mmol/L) from the calculated value.

DIAGNOSIS

When given an ABG for interpretation, it is essential to use an approach that is focused and comprehensive.[8] An algorithm illustrating this concept is shown in Figure 29–1. Using this algorithm, Step 1 is to identify all abnormalities in the pH, PaCO$_2$, and/or HCO$_3^-$ and then decide which abnormal values are primary and which are compensatory. This is best done by initially looking at the pH. Whichever side of 7.40 the pH is on, the process that caused it to shift to that side is the primary abnormality. If the arterial pH is lower than 7.40 (acidemia), an elevated PaCO$_2$ (> 45 mm Hg [6.0 kPa], **respiratory acidosis**) or a lowered HCO$_3^-$ (< 22 mEq/L [mmol/L], **metabolic acidosis**) would be the primary abnormality. If the arterial pH is higher than 7.40 (alkalemia), a decreased PaCO$_2$ (< 35 or 4.7 kPa, **respiratory alkalosis**) or an increased HCO$_3^-$ (> 25 mEq/L [mmol/L], **metabolic alkalosis**) would be the primary abnormality. Once the primary disorder is established, step 2 is to apply the formulas from Table 29–1 to assess whether the observed compensation is appropriate for the primary disorder and to look for concurrent processes.[7]

An alternative to a diagnostic algorithm is use of a graphic nomogram.[9] These nomograms are plots of the pH, PaCO$_2$, and HCO$_3^-$ that allow the user to rapidly determine whether arterial blood gas values are consistent with one of the six simple primary acid–base disturbances. Although nomograms are commonly used to identify acid–base disturbances in clinical practice, only individuals who fully comprehend the fundamental concepts of acid–base assessment should use these tools. Also, appreciate that

Patient Encounter 1

A 23-year-old heroin addict is brought to the emergency department after friends found her unconscious with a needle in her arm. Her initial ABG has a pH of 7.12 with a PaCO$_2$ of 75 mm Hg (10.0 kPa), and the serum HCO$_3$ is 27 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

Patient Encounter 2

A 79-year-old man with advanced emphysema presents to the emergency department with superficial facial burns after the cigarette he was smoking ignited the supplemental oxygen he was using. His admission ABG shows a pH of 7.33, a PaCO$_2$ of 75 mm Hg (10.0 kPa), and an HCO$_3^-$ of 36 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

Patient Encounter 3

A 61-year-old woman presented to the ER with chest pain, palpitations, and a sense of impending doom. After an extensive workup is negative, her symptoms are attributed to a panic attack. Her ABG shows a pH of 7.55, a PaCO$_2$ of 19 mm Hg (2.5 kPa), and an HCO$_3^-$ of 20 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

Patient Encounter 4

An 18-year-old man presents to his university's student health clinic for evaluation of dyspnea and peripheral edema. He has a reduced left ventricular ejection fraction due to congenital cardiomyopathy and is prescribed daily furosemide therapy to maintain euvolemia. However, he has been intermittently noncompliant since moving into his dormitory. An ABG shows the following: pH of 7.49, a PaCO$_2$ of 43 mm Hg (5.7 kPa), and an HCO$_3^-$ of 31 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

Patient Encounter 5

A 50-year-old woman who is being admitted to the hospital for orthopedic surgery after suffering fractures to her left femur, pelvis, and ribs in a skiing accident. Although she has no comorbid illnesses and does not take any medications chronically, she has been taking acetazolamide for altitude sickness prophylaxis for the past 5 days. Her ABG in the ER shows a pH of 7.26, a PaCO$_2$ of 26 mm Hg (3.5 kPa), and an HCO$_3^-$ of 12 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

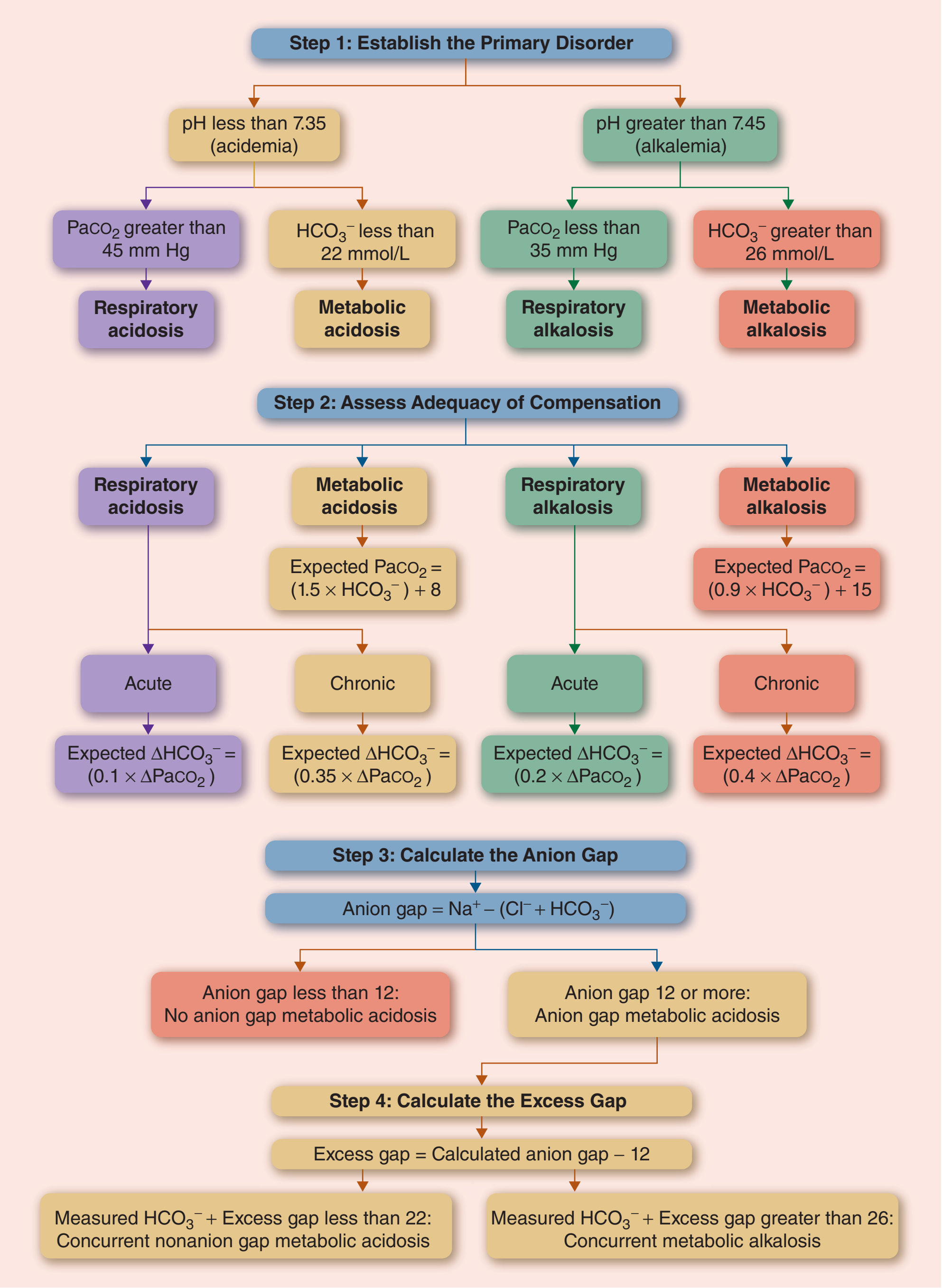
Step 1: Establish the Primary Disorder
pH less than 7.35 (acidemia)
pH greater than 7.45 (alkalemia)
Paco$_2$ greater than 45 mm Hg
HCO_3^- less than 22 mmol/L
Paco$_2$ less than 35 mm Hg
HCO_3^- greater than 26 mmol/L
Respiratory acidosis
Metabolic acidosis
Respiratory alkalosis
Metabolic alkalosis
Step 2: Assess Adequacy of Compensation
Respiratory acidosis
Metabolic acidosis
Respiratory alkalosis
Metabolic alkalosis
Expected Paco$_2$ = (1.5 × HCO_3^-) + 8
Expected Paco$_2$ = (0.9 × HCO_3^-) + 15
Acute
Chronic
Acute
Chronic
Expected ΔHCO_3^- = (0.1 × ΔPaco$_2$)
Expected ΔHCO_3^- = (0.35 × ΔPaco$_2$)
Expected ΔHCO_3^- = (0.2 × ΔPaco$_2$)
Expected ΔHCO_3^- = (0.4 × ΔPaco$_2$)
Step 3: Calculate the Anion Gap
Anion gap = $Na^+ - (Cl^- + HCO_3^-)$
Anion gap less than 12: No anion gap metabolic acidosis
Anion gap 12 or more: Anion gap metabolic acidosis
Step 4: Calculate the Excess Gap
Excess gap = Calculated anion gap – 12
Measured HCO_3^- + Excess gap less than 22: Concurrent nonanion gap metabolic acidosis
Measured HCO_3^- + Excess gap greater than 26: Concurrent metabolic alkalosis

FIGURE 29–1. An algorithmic approach to acid–base disorders. Normal values: pH 7.35 to 7.45, $PaCO_2$ 35 to 45 mm Hg (4.7 to 6.0 kPa), HCO_3^- 22 to 26 mEq/L (mmol/L), anion gap less than 12 mEq/L (mmol/L). Note that $PaCO_2$ should be in units of mm Hg to use the equations in the figure. To convert $PaCO_2$ in units of kPa to mm Hg, divide by 0.133. (Cl^-, chloride ion; HCO_3^-, bicarbonate; Na^+, sodium ion; $PaCO_2$, partial pressure of arterial carbon dioxide.)

nomograms have limited utility when dealing with complex acid–base derangements.

Acid–base disturbances are always manifestations of underlying disorders. It is useful to specifically define the primary acid–base abnormality because each disorder is caused by a limited number of disease processes. Establishing the specific disease process responsible for the observed acid–base disorder is clinically important because treatment of a given disorder will only be accomplished by correcting the underlying disease process.

ADVANCED PATHOPHYSIOLOGY

The concepts in this section are used to further expand on steps 3 and 4 of the diagnostic algorithm shown in Figure 29–1. Under normal circumstances, the serum is in the isoelectric state. This means that the positively charged entities reported in a standard chemistry panel (cations: sodium [Na+] and potassium [K+]) should be exactly balanced by the negatively charged entities (anions: chloride [Cl^-] and bicarbonate [HCO_3^-]). However, this relationship is consistently incorrect because the measured cations are higher than the measured anions by 10 to 12 mEq/L (mmol/L). This discrepancy results from the presence of unmeasured anions (eg, circulating proteins, phosphates, and sulfates). This apparent difference in charges, the serum **anion gap**, is calculated as follows:

$$\text{Anion gap} = \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-).$$

Because the serum K+ content is relatively small and is very tightly regulated, it is generally omitted from the calculation.[10]

It is important to realize that the serum HCO_3^- concentration may be affected by the presence of unmeasured endogenous acids (lactic acid or ketoacids). HCO_3^- will attempt to buffer these acids, resulting in a 1 mEq (mmol) loss of serum HCO_3^- for each 1 mEq (mmol) of acid titrated. Because the cation side of the equation is not affected by this transaction, the loss of serum HCO_3^- results in an increase in the calculated anion gap. Identification of an increased anion gap is very important because a limited number of clinical scenarios lead to this unique acid–base disorder. A mnemonic to recall the differential diagnosis for an anion gap acidosis is shown in Table 29–3. The concept of the increased anion gap is applied later in Patient Encounters 6 through 10.

Step 3 in Figure 29–1 suggests that any time an ABG is analyzed, it is wise to concurrently inspect the serum chemistry values and calculate the anion gap. The body does not generate an anion gap to compensate for a primary disorder. As such, if the calculated anion gap exceeds 12 mEq/L (mmol/L), there is a primary metabolic acidosis regardless of the pH or the serum HCO_3^- concentration. The anion gap may be artificially lowered by decreased serum albumin, multiple myeloma, lithium intoxication, or a profound increase in the serum potassium, calcium, or magnesium.[11] Of these etiologies, hypoalbuminemia is the most clinically relevant as albumin accounts for approximately 75% of the unmeasured anions in the normal anion gap.[12] The anion gap is reduced by 2.5 mEq/L (mmol/L) for each 1 g/dL (10 g/L) the albumin is reduced below normal (4.0 g/dL [40 g/L]).

Step 4 in Figure 29–1 shows how calculation of the anion gap also facilitates determination of the **excess gap** or the degree to which the calculated anion gap exceeds the normal anion gap. The excess gap is calculated as follows:

$$\begin{aligned}\text{Excess gap} &= \text{calculated anion gap} - \text{normal anion gap}\\ &= [\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)] - 12.\end{aligned}$$

The excess gap represents the amount of HCO_3^- that has been lost due to buffering unmeasured cations. The excess gap can be added back to the measured HCO_3^- to determine what the patient's HCO_3^- would be if these endogenous acids were not present. This is a very valuable tool that can be used in narrowing the differential diagnosis of certain acid–base disorders as well as in uncovering occult or mixed acid–base disorders.

Table 29–3

Mnemonics for the Differential Diagnoses of Metabolic Acidosis

Elevated Anion Gap[a]	Normal Anion Gap[a]
M—Methanol, metformin	**U**—Ureteral diversion
U—Uremia	**S**—Saline infusion
D—Diabetic (or alcoholic) ketoacidosis	**E**—Exogenous acid
P—Paraldehyde, phenformin	**D**—Diarrhea
I—Isoniazid, iron	**C**—Carbonic anhydrase inhibitors
L—Lactic acidosis	**A**—Adrenal insufficiency
E—Ethylene glycol, ethanol	**R**—Renal tubular acidosis
S—Salicylates	

[a] Anion gap = serum sodium concentration − (serum chloride concentration + serum bicarbonate concentration). Under normal circumstances, the anion gap should be 10 mEq/L (mmol/L) or less.

In summary, the approach to assessment of acid–base status involves four key steps as outlined in Figure 29–1: step 1 = initial inspection of the pH, PaCO_2, and HCO_3^-; step 2 = assessment of the adequacy of compensation; step 3 = calculation of the anion gap; and step 4 = calculation of the excess gap.

ETIOLOGY AND TREATMENT

KEY CONCEPT Arterial blood gases, serum electrolytes, physical examination findings, the clinical history, and the patient's recent medications must be reviewed to establish the etiology of a given acid–base disturbance. Tables 29–3 to 29–7 outline the most commonly encountered causes for each of the primary acid–base disorders. The therapeutic approach to each of these acid–base derangements should emphasize a search for the cause, as opposed to immediate attempts to normalize the pH.

KEY CONCEPT It is critical to treat the underlying causative process to effectively resolve most observed acid–base disorders. However, supportive treatment of the pH and electrolytes is often needed until the underlying disease state is improved.[13,14]

All patients with significant disturbances in their acid–base status require continuous cardiovascular and hemodynamic monitoring. Because frequent assessment of the patient's response to treatment is critical, an arterial line is often placed to minimize patient discomfort with serial ABG collections. If the anion gap was initially abnormal, serial blood chemistries should be followed to ensure that the anion gap resolves with treatment. Specific treatment decisions depend on the underlying pathophysiologic state (eg, dialysis for renal failure, insulin for diabetic ketoacidosis, or improving tissue perfusion and oxygenation for lactic acidosis).

Metabolic Acidosis

Metabolic acidosis is characterized by a reduced arterial pH, a primary decrease in the HCO_3^- concentration, and a compensatory reduction in the PaCO_2. The etiologies of metabolic acidosis are divided into those that lead to an increase in the anion gap and those associated with a normal anion gap and are listed in Table 29–4. Although there are numerous mnemonics to recall the differential diagnosis of the metabolic acidosis, two simple ones are shown in Table 29–3. High anion gap metabolic acidosis is most frequently caused by lactic acidosis, ketoacidosis, and/or renal failure. Although there is considerable variation, the largest anion gaps are caused by ketoacidosis, lactic acidosis, and methanol or ethylene glycol ingestion.[15]

Symptoms of metabolic acidosis are attributable to changes in cardiovascular, musculoskeletal, neurologic, or pulmonary functioning. Respiratory compensation requires marked increases in minute ventilation and may lead to dyspnea, respiratory fatigue, and respiratory failure. Acidemia predisposes to ventricular arrhythmias and reduces cardiac contractility, each of which can result in pulmonary edema and/or systemic hypotension.[16] Neurologic symptoms range from lethargy to coma and are usually proportional to the severity of the pH derangement. Chronic metabolic acidosis leads to a variety of musculoskeletal problems including impaired growth, rickets, osteomalacia, or osteopenia. These changes are believed to be caused by the release of calcium and phosphate during bone buffering of excess H^+ ions.

Table 29–4

Common Causes of Metabolic Acidosis

Elevated Anion Gap[a]	Normal Anion Gap[a]
Intoxications	Bowel fistula
Methanol	Diarrhea
Ethylene glycol	Dilutional acidosis
Salicylates	Drugs
Paraldehyde	Acetazolamide[b]
Isoniazid	Ammonium chloride[b]
Ketoacidosis	Amphotericin B[b]
Diabetic	Arginine hydrochloride[c]
Ethanol	Cholestyramine[b]
Starvation	Hydrochloric acid[b]
Lactic acidosis	Lithium[b]
Carbon monoxide poisoning	Parenteral nutrition[b]
Drugs	Topiramate[b]
IV lorazepam (due to vehicle)[c]	Zonisamide[b]
Metformin[b]	Lead poisoning
Nitroprusside (due to cyanide accumulation)[b]	Renal tubular acidosis
Nucleoside reverse transcriptase inhibitors[b]	Surgical drains
Propofol[c]	Ureteral diversion
Seizures	Villous adenomas (some)
Severe hypoxemia	
Shock	
Renal failure	

[a] Anion gap = serum sodium concentration – (serum chloride concentration + serum bicarbonate concentration). Under normal circumstances, the anion gap should be 10 mEq/L (mmol/L) or less.

[b] May be observed with therapeutic doses or overdoses.

[c] Typically observed with overdoses or prolonged, high-dose infusions (the so-called propofol infusion syndrome).

As previously discussed, in anion gap metabolic acidosis, the isoelectric state is maintained because unmeasured anions are present. With a *normal* anion gap metabolic acidosis, the isoelectric state is maintained by an increase in the measured chloride. Because of this, normal anion gap metabolic acidosis is often referred to as hyperchloremic acidosis.

In patients with a normal anion gap metabolic acidosis, it is often helpful to calculate the urine anion gap (UAG).[17] The UAG is calculated from a spot urine collection as follows:

$$\text{UAG} = (\text{Urine Na}^+ + \text{Urine K}^+) - \text{Urine Cl}^-.$$

Patient Encounter 6

A 31-year-old man is admitted to the intensive care unit after ingesting an unknown quantity of aspirin tablets in a suicide attempt. His admission labs are as follows: pH of 7.50, $PaCO_2$ of 20 mm Hg (2.7 kPa), HCO_3^- of 16 mEq/L (mmol/L), sodium concentration of 140 mEq/L (mmol/L), and chloride level of 103 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

Patient Encounter 7

A 68-year-old woman is brought to the emergency room by her family for increasing confusion. They report that she has had the stomach flu with frequent bouts of emesis over the past 5 days. Given her poor oral intake, frequent vomiting, and weakness, she skipped her last three hemodialysis sessions. Her labs show: pH of 7.40, $PaCO_2$ of 40 mm Hg (5.3 kPa), HCO_3^- of 24 mEq/L (mmol/L), sodium concentration of 145 mEq/L (mmol/L), and chloride level of 100 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

Patient Encounter 8

A frail, 74-year-old man with metastatic colon cancer is brought to the ER from the Hospice House. His family says his condition has worsened dramatically since transfer there from the hospital, and they would like him to be readmitted to resume full cares. They are upset that he has had multiple bouts of feculent emesis from a bowel obstruction since Hospice was started. They are also frustrated that his mental status has steadily worsened. He is an insulin-dependent diabetic, but glucose checks and insulin administration were stopped upon transfer to Hospice. They insisted on transfer to the hospital when they noticed his breathing was very slow and shallow this morning. The blood work drawn in the ER shows a pH of 7.10, a $PaCO_2$ of 50 mm Hg (6.7 kPa), an HCO_3^- of 15 mEq/L (mmol/L), a sodium concentration of 145 mEq/L (mmol/L), and a chloride level of 100 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

Patient Encounter 9

A belligerent, intoxicated 18-year-old man is brought to the ER by police after he was found urinating on a police car as part of a fraternity pledging ritual. Shortly after admission he vomits a large volume of emesis that reeks of beer. He immediately develops coughing, some stridorous upper airway sounds, and complains of shortness of breath. Auscultation of his lungs demonstrates coarse rhonchi throughout. He is urgently transferred to the ICU where he is intubated and started on mechanical ventilation for rapidly progressive hypoxemia. His ABG immediately postintubation shows: pH of 7.50, $PaCO_2$ of 20 mm Hg (2.7 kPa), HCO_3^- of 15 mEq/L (mmol/L), sodium concentration of 145 mEq/L (mmol/L), and chloride level of 100 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

The normal UAG ranges from 0 to 5 mEq/L (mmol/L) and represents the presence of unmeasured urinary anions. In metabolic acidosis, the excretion of NH_4^+ and concurrent Cl^- should increase markedly if renal acidification capacity is intact. This results in UAG values from −20 to −50 mEq/L (mmol/L). This occurs because the urinary Cl^- concentration now markedly exceeds the urinary Na^+ and K^+ concentrations. Diagnoses consistent with an excessively negative UAG include proximal (type 2) renal tubular acidosis, diarrhea, or administration of acetazolamide or hydrochloric acid (HCl). Excessively positive values of the UAG suggest a distal (type 1) renal tubular acidosis.

To effectively treat metabolic acidosis, the *causative process* must be identified and treated.[18] The precise role of adjunctive therapy with sodium bicarbonate ($NaHCO_3$) is not universally agreed upon. However, most practitioners accept that $NaHCO_3$ is indicated when renal dysfunction precludes adequate regeneration of HCO_3^- or when severe acidemia (pH < 7.15) is present.[19] The metabolic acidosis seen with lactic acidosis and ketoacidosis generally resolves with therapy targeted at the underlying cause, and $NaHCO_3$ may be unnecessary regardless of the pH. The metabolic acidosis of renal failure, renal tubular acidosis, or intoxication with ethylene glycol, methanol, or salicylates is much more likely to require $NaHCO_3$ therapy.

If $NaHCO_3$ is used, the plasma HCO_3^- should not be corrected entirely. Instead, aim at increasing HCO_3^- above an absolute value of 10 mEq/L (mmol/L). The total HCO_3^- deficit can be calculated from the current bicarbonate concentration ($HCO_3^-{}_{\text{curr}}$), the desired bicarbonate concentration ($HCO_3^-{}_{\text{post}}$), and the body weight (in kilograms) as follows:

$$\begin{aligned} HCO_3^- \text{ deficit} &= [(2.4/HCO_3^-{}_{\text{curr}}) + 0.4] \times \text{weight} \\ &\quad \times (HCO_3^-{}_{\text{curr}} - HCO_3^-{}_{\text{post}}). \end{aligned}$$

No more than half of the calculated HCO_3^- deficit should be given initially to avoid volume overload, hypernatremia, hyperosmolarity, overshoot alkalemia, hypocalcemia, and/or hypokalemia. The calculated HCO_3^- deficit reflects only the present situation and does not account for ongoing H+ production and HCO_3^- loss. When giving HCO_3^- therapy, serial blood gases are needed to monitor therapy.

Historically, another option for patients with severe acidemia has been tromethamine (tris-hydroxymethyl aminomethane or THAM).[20] This inert amino alcohol buffers acids and CO_2 through its amine ($-NH_2$) moiety:

$$\text{THAM} - NH_2 + H^+ = \text{THAM} - NH_3^+$$
$$\text{THAM} - NH_2 + H_2O + CO_2 = \text{THAM} - NH_3^+ + HCO_3^-$$

Protonated THAM (with Cl^- or HCO_3^-) is excreted in the urine at a rate that is slightly higher than creatinine clearance. As such, THAM augments the buffering capacity of the blood without generating excess CO_2. THAM is less effective in patients with renal failure, and toxicities may include hyperkalemia, hypoglycemia, and possible respiratory depression. THAM is particularly useful in patients with volume overload because it does not contain sodium.

THAM is often administered as an empiric dose of 18 g (150 mEq [mmol]) in 500 mL water via slow IV infusion. Additional infusions are given as dictated by the severity and progression of acidosis. Unfortunately, the only US manufacturer of THAM discontinued its production in 2016, and no future production is anticipated.

Chronic metabolic acidosis can successfully be managed using potassium citrate/citric acid (Polycitra-K, Cytra-K) or sodium citrate/citric acid (Bicitra, Oracit).

Table 29–5

Common Causes of Metabolic Alkalosis

Urine Cl^- < 10 mEq/L (mmol/L)	Urine Cl^- > 10 mEq/L (mmol/L)
Alkali administration	Drugs[a]
IV bicarbonate therapy	Corticosteroid therapy
Oral alkali therapy	Diuretics
Parenteral nutrition with acetate	Hypokalemia
“Contraction alkalosis” postdiuretic use	Mineralocorticoid excess
Decreased chloride intake	Hyperaldosteronism
Loss of gastric acid	Bartter’s syndrome
Vomiting	Cushing’s syndrome
Nasogastric suction	
Posthypercapnia	
Villous adenomas (some)	

[a] May be observed with therapeutic doses or overdoses.

Metabolic Alkalosis

Metabolic alkalosis is characterized by an increased arterial pH, a primary increase in the HCO_3^- concentration, and a compensatory increase in the $PaCO_2$. Patients will always hypoventilate to compensate for metabolic alkalosis—even if it results in profound hypoxemia. For a metabolic alkalosis to persist, there must concurrently be a process that elevates serum HCO_3^- concentration (gastric or renal loss of acids) and another that impairs renal HCO_3^- excretion (hypovolemia, hypokalemia, or mineralocorticoid excess). The etiologies of metabolic alkalosis are listed in Table 29–5.

Patients with metabolic alkalosis rarely have symptoms attributable to alkalemia. Rather, complaints are usually related to volume depletion (muscle cramps, positional dizziness, weakness) or to hypokalemia (muscle weakness, polyuria, polydipsia).

To effectively treat metabolic alkalosis, the *causative process* must be identified and treated. The major causes of metabolic alkalosis are often readily apparent after carefully reviewing the patient’s history and medication list. In hospitalized patients, always look for administration of compounds such as citrate in blood products and acetate in parenteral nutrition that can raise the HCO_3^- concentration. If the etiology of the metabolic alkalosis is still unclear, measurement of the urinary chloride may be useful. Some processes leading to metabolic alkalosis (eg, vomiting, nasogastric suction losses, factitious diarrhea) will have low urinary Cl^- concentrations (< 25 mEq/L [mmol/L]) and are likely to respond to administration of saline. Other causes (eg, diuretics, hypokalemia, and mineralocorticoid excess) will have higher urinary Cl^- concentrations (> 40 mEq/L [mmol/L]) and are less likely to correct with saline infusion.

In general, contributing factors such as diuretics, naso-gastric suction, and corticosteroids should be discontinued if possible. Any fluid deficits should be treated with IV normal saline. Again, patients with metabolic alkalosis and high urine Cl^- (while relatively uncommon) are generally resistant to saline loading. Potassium supplementation should always be given if it is also deficient.

In patients with mild or moderate alkalosis who require ongoing diuresis but have rising HCO_3^- concentrations, the carbonic anhydrase inhibitor acetazolamide can be used to reduce the HCO_3^- concentration. Acetazolamide is typically dosed at 250 mg every 6 to 12 hours as needed to maintain the pH in a clinically acceptable range. This agent results in gradual changes in the serum HCO_3^- and is not used to acutely correct a patient’s acid–base status. If alkalosis is profound and potentially life threatening (due to seizures or ventricular tachyarrhythmias), hemodialysis or transient HCl infusion can be considered. The hydrogen ion deficit (in mEq or mmol) can be estimated from the current serum bicarbonate concentration ($HCO_3^-{}_{curr}$), the desired bicarbonate concentration ($HCO_3^-{}_{post}$), and the body weight (in kg) as follows:

$$H^+ \text{ deficit} = 0.4 \times \text{weight} \times (HCO_3^-{}_{curr} - HCO_3^-{}_{post}).$$

After estimating the H^+ deficit, 0.1 to 0.2 N hydrochloric acid (HCl) is infused at 20 to 50 mEq/h (mmol/h) into a central vein. Arterial pH must be monitored at least hourly and the infusion stopped as soon as clinically feasible. Ammonium chloride and arginine hydrochloride, agents that result in the formation of HCl, are not commonly prescribed because they may lead to significant toxicity. Ammonium chloride may cause accumulation of ammonia leading to encephalopathy while arginine hydrochloride can induce life-threatening hyperkalemia through unclear mechanisms.

Respiratory Acidosis

Respiratory acidosis is characterized by a reduced arterial pH, a primary increase in the arterial $PaCO_2$ and, when present for sufficient time, a compensatory rise in the HCO_3^- concentration. Because increased CO_2 is a potent respiratory stimulus, respiratory acidosis represents ventilatory failure or impaired central control of ventilation as opposed to an increase in CO_2 production. As such, most patients will have hypoxemia in addition to hypercapnia. The most common etiologies of respiratory acidosis are listed in Table 29–6.

Table 29–6

Common Causes of Respiratory Acidosis

- CNS disease
  - Brainstem lesions
  - Central sleep apnea
  - Infection
  - Intracranial hypertension
  - Trauma
  - Tumor
  - Vascular
- Drugs[a]
  - Aminoglycosides
  - Anesthetics
  - β-Blockers
  - Botulism toxin
  - Hypnotics
  - Narcotics
  - Neuromuscular blocking agents
  - Organophosphates
  - Sedatives
- Neuromuscular disease
  - Guillain-Barré syndrome
  - Muscular dystrophy
  - Myasthenia gravis
  - Polymyositis
- Pulmonary disease
  - Lower airway obstruction
  - Foreign body
  - Status asthmaticus
  - Chronic obstructive pulmonary disease
- Pneumonia
- Pneumonitis
- Pulmonary edema
- Restrictive lung disease
  - Ascites
  - Chest wall disorder
  - Fibrothorax
  - Kyphoscoliosis
  - Obesity
  - Pleural effusion
  - Pneumoconiosis
  - Pneumothorax
  - Progressive systemic sclerosis
  - Pulmonary fibrosis
  - Spinal arthritis
- Smoke inhalation
- Upper airway obstruction
  - Foreign body
  - Laryngospasm
  - Obstructive sleep apnea
- Others
  - Abdominal distention
  - Altered metabolic rate
  - Congestive heart failure
  - Hypokalemia
  - Hypothyroidism
  - Inadequate mechanical ventilation

[a] May be observed with therapeutic doses or overdoses.

Severe, acute respiratory acidosis produces a variety of neurologic abnormalities. Initially these include headache, blurred vision, restlessness, and anxiety. These may progress to tremors, asterixis, somnolence, and/or delirium. If untreated, terminal manifestations include peripheral vasodilation leading to hypotension and cardiac arrhythmias. Chronic respiratory acidosis is typically associated with cor pulmonale and peripheral edema.

To effectively treat respiratory acidosis, the *causative process* must be identified and treated. If a cause is identified, specific therapy should be started. This may include naloxone for opiate-induced hypoventilation or bronchodilator therapy for acute bronchospasm. Because respiratory acidosis represents ventilatory failure, an increase in alveolar ventilation is required. This can often be achieved by controlling the underlying disease (eg, bronchodilators and corticosteroids in asthma) and/or physically augmenting ventilation.

Although their precise role and mechanisms of action are unclear, agents such as medroxyprogesterone, theophylline, and doxapram stimulate respiration and have been used to treat mild-to-moderate respiratory acidosis. Of these, only doxapram is approved by the FDA for this indication. Doxapram is administered IV, typically 0.5 to 1 mg/kg repeated every five minutes to a maximum dose of 3 g per 24 hours. Patients given doxapram require monitoring of their blood pressure, pulse, and deep tendon reflexes as this drug can cause cardiac excitation and spasticity. Moderate or severe respiratory acidosis requires assisted ventilation. This can be provided to spontaneously breathing patients via bilevel positive airway pressure (BiPAP) delivered via a tight-fitting mask or by intubation followed by mechanical ventilation. In mechanically ventilated patients, respiratory acidosis is treated by increasing the minute ventilation. This is achieved by increasing the respiratory rate and/or tidal volume.

As with the treatment of metabolic acidosis, the role of $NaHCO_3$ therapy is not well defined for respiratory acidosis. Realize that administration of $NaHCO_3$ can paradoxically result in increased CO_2 generation ($HCO_3^- + H^+ \rightarrow H_2O + CO_2$) and worsened acidemia. Careful monitoring of the pH is required if $NaHCO_3$ therapy is started for this indication. The use of tromethamine in respiratory acidosis (see Metabolic Acidosis section earlier) has unproven safety and benefit.

The goals of therapy in patients with chronic respiratory acidosis are to maintain oxygenation and improve alveolar ventilation if possible. Because of the presence of metabolic compensation, it is usually not necessary to treat the pH, even in patients with severe hypercapnia. Although the specific treatment varies with the underlying disease, excessive oxygen and sedatives should be avoided because they can worsen CO_2 retention.

Respiratory Alkalosis

Respiratory alkalosis is characterized by an increased arterial pH, a primary decrease in the arterial $PaCO_2$ and, when present for sufficient time, a compensatory fall in the HCO_3^- concentration. Respiratory alkalosis represents hyperventilation and is remarkably common. The most common etiologies of respiratory alkalosis are listed in Table 29–7 and range from benign (anxiety) to life threatening (pulmonary embolism). Some causes of hyperventilation and respiratory acidosis are remarkably common (hypoxemia or anemia).

The symptoms produced by respiratory alkalosis result from increased irritability of the central and peripheral nervous systems. These include light-headedness, altered consciousness,

Table 29–7

Common Causes of Respiratory Alkalosis

- CNS disease
  - Infection
  - Trauma
  - Tumor
  - Vascular
- Drug or toxin induced[a]
  - Catecholamines
  - Doxapram
  - Methylphenidate
  - Methylxanthines
  - Nicotine
  - Progesterone
  - Salicylates
- Psychiatric disease
  - Anxiety
  - Hyperventilation
  - Hysteria
  - Panic disorder
- Pulmonary disease
  - Early restrictive lung disease
  - Infection
  - Pneumothorax
  - Pulmonary edema
  - Pulmonary embolism
- Tissue hypoxia
  - Burn injury
  - Excessive mechanical ventilation
  - Fever
  - Hepatic failure
  - Hypoxemia
  - Pain
  - Postmetabolic acidosis
  - Pregnancy
  - Severe anemia
  - Thyrotoxicosis

[a] May be observed with therapeutic doses or overdoses.

distal extremity paresthesias, circumoral paresthesia, cramps, carpopedal spasms, and syncope. Various supraventricular and ventricular cardiac arrhythmias may occur in extreme cases, particularly in critically ill patients. An additional finding in many patients with severe respiratory alkalosis is hypophosphatemia, reflecting a shift of phosphate from the extracellular space into the cells. Chronic respiratory alkalosis is generally asymptomatic.

It is imperative to identify serious causes of respiratory alkalosis and institute effective treatment. In spontaneously breathing patients, respiratory alkalosis is typically only mild or moderate in severity and no specific therapy is indicated. Severe alkalosis generally represents respiratory alkalosis imposed on metabolic alkalosis and may improve with sedation or rebreathing maneuvers (rebreathing mask, paper bag). Patients receiving mechanical ventilation are treated with reduced minute ventilation achieved by decreasing the respiratory rate and/or tidal volume. If the alkalosis persists in the ventilated patient, high-level sedation or paralysis is effective.

SUMMARY

Acid–base disturbances are common clinical problems that are not difficult to analyze if approached in a consistent manner. The pH, $PaCO_2$, and HCO_3^- should be inspected to identify all abnormal values. This should lead to an assessment of which deviations represent the primary abnormality and which represent compensatory changes. The serum electrolytes should always be used to calculate the anion gap. In cases in which the anion gap is increased, the excess anion gap should be added back to the measured HCO_3^-. The anion gap and the excess gap are useful tools that can identify hidden disorders. This rigorous assessment of the patient's acid–base status, incorporated with the available clinical data, increases the likelihood that the clinician will successfully determine the cause of each identified disorder. Although supportive therapy is often required for profound acid–base disturbances, definitive therapy must target the underlying process that has led to the observed derangements.

Patient Care Process

Collect Information

- Every patient with a suspected acid–base disturbance should have an arterial blood gas and a serum chemistry panel drawn concurrently.
- Review each patient's history, physical examination, and current medication list for clues regarding potential causes of the observed acid–base disorder.

Assess the Information

- The results of the arterial blood gas and serum chemistry should be reviewed using a systematic approach to ensure proper interpretation.
- What is/are the primary disorder(s)?
- Has compensation occurred?
- Is the anion gap excessively large?
- If the anion gap is abnormal, does calculation of the excess gap identify another acid–base disorder?

Develop a Care Plan

- Because all acid–base abnormalities result from underlying disease processes, an explanation for each acid-base disorder is necessary.
- Definitive therapy for acid-base disturbances requires treatment of the underlying illness that has disrupted the pH equilibrium.

Implement the Care Plan

- The severity of the acid-base disorder(s) dictates the proper site of care.
- Medications causing and/or contributing to the observed acid-base disorder should be withheld.

Follow-up: Monitor and Evaluate

- Continuous cardiovascular and hemodynamic monitoring should be used for significant pH disturbances because the most serious sequelae of acid–base disorders include electrolyte abnormalities, cardiac dysrhythmias, and hypotension.
- Serial arterial blood gases and serum chemistries should be compared because every patient's acid–base status is continuously changing based on the underlying disease state and any therapy initiated.

LIST OF ABBREVIATIONS

ABG	Arterial blood gas
BiPAP	Bilevel positive airway pressure
Cl^-	Chloride ion
CO2	Carbon dioxide
Δ(delta)	Change
ER	Emergency room
H^+	Hydrogen ion
HCl	Hydrochloric acid
HCO_3^-	Bicarbonate
$HCO_{3\ curr}^-$	Current bicarbonate
$HCO_{3\ post}^-$	Posttherapy bicarbonate
Hg	Mercury
K^+	Potassium ion

Na^+	Sodium ion
$NaHCO_3$	Sodium bicarbonate
NH_2	Terminal amine group
NH_4^+	Ammonium
pH	Logarithm of the hydrogen ion concentration
$PaCO_2$	Partial pressure of arterial carbon dioxide
tCO_2	Total venous carbon dioxide
THAM	Tromethamine
UAG	Urine anion gap

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30

Alzheimer Disease

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the epidemiology of Alzheimer disease (AD) and its effects on society.
2. Describe the pathophysiology, including genetic and environmental factors that may be associated with AD.
3. Detail the clinical presentation of the typical patient with AD.
4. Describe the clinical course of the disease and typical patient outcomes.
5. Explain how nonpharmacologic therapy is combined with pharmacologic therapy for patients with AD.
6. Recognize and recommend treatment options for disease-specific symptoms as well as behavioral/noncognitive symptoms associated with AD.
7. Educate patients and/or caregivers about the expected outcomes for patients with AD and provide contact information for support/advocacy agencies.

INTRODUCTION

KEY CONCEPT Alzheimer disease (AD) is characterized by progressive cognitive decline, including memory loss, disorientation, and impaired judgment and learning. There is no single symptom unique to AD; therefore, diagnosis typically relies on a thorough patient history. The exact pathophysiologic mechanism underlying AD is not entirely known, although certain genetic and environmental factors may be associated with the disease. There is no cure for AD; however, drug treatment can slow symptom progression.

Family members of AD patients can be profoundly affected by the increased dependence of their loved ones as the disease progresses. Advocacy organizations, such as the Alzheimer's Association, can provide early education and social support for both the patient and family. The Alzheimer's Association has developed a list of common warning signs, which include memory loss, difficulty completing familiar tasks, disorientation, problems with word finding, misplacing things, impaired judgment, social withdrawal, and changes in mood.[1]

EPIDEMIOLOGY AND ETIOLOGY

AD is the most common type of dementia, affecting an estimated 5.8 million Americans in 2020.[2] Eighty percent are of age 75 or older. Additional classifications of dementia include dementia of the Alzheimer type, vascular dementia, and dementia due to human immunodeficiency virus (HIV) disease, head trauma, Parkinson disease, Huntington disease, Pick disease, or Creutzfeldt–Jakob disease.[3] This chapter addresses only Alzheimer-type dementia.

The prevalence of AD increases with age. Three percent of people aged 65 to 74, 17% of people aged 75 to 84, and 32% of people aged 85 and older have AD.[2] It is projected that by 2050, the number of people aged 65 and older with AD is projected to reach 13.8 million.[2] The severity of AD also correlates with increasing age and is classified as mild, moderate, or severe. Other risk factors for AD include family history, female gender, and vascular risk factors such as diabetes, hypertension, heart disease, and current smoking.[4] It is unknown how factors such as the environment contribute and interact with the genetic predisposition for AD.

The mean survival time of persons with AD is approximately 4 to 8 years from symptom onset. However, age at diagnosis, severity of AD, and other medical conditions affect survival time.[5] Although AD does not directly cause death, it is associated with an increase in risk factors that often contribute to death, such as senility, sepsis, stroke, pneumonia, dehydration, and decubitus ulcers.[5]

The etiology of AD is unknown; however, genetic factors may contribute to errors in protein synthesis resulting in the formation of abnormal proteins, which contribute to pathogenesis.[6] Early onset (AD prior to age 60) accounts for approximately 1% of all AD. This type is usually familial and follows an autosomal dominant pattern in approximately 50% of cases. Mutations in three genes, presenilin 1 on chromosome 14, amyloid precursor protein (APP) on chromosome 21, and presenilin 2 on chromosome 1 lead to an increase in the accumulation of amyloid beta (Aβ) in the brain, resulting in oxidative stress, neuronal destruction, and the clinical syndrome of AD.[7,8]

In late-onset AD, genetic susceptibility is more sporadic, and it may be more dependent on environmental factors.[6] The apolipoprotein E (apo E) gene on chromosome 19 has been identified as a strong risk factor for late-onset AD. Of the three variants of apo E, carriers of two or more of the apo E4 allele have an earlier onset of AD (~6 years earlier) compared with noncarriers.[6] Only 50% of AD patients have the apo E4 allele, thus indicating it is only a susceptibility marker.

PATHOPHYSIOLOGY

KEY CONCEPT Pathologic hallmarks of the disease in the brain include neurofibrillary tangles (NFTs) (made up of abnormally phosphorylated tau [τ] protein) and neuritic plaques (primarily composed of insoluble forms of Aβ). Accumulation of these toxic forms results in neurodegeneration. In early stages of the disease, neurodegeneration of areas responsible for cholinergic transmission results in a cholinergic deficit. As the disease progresses, widespread neurodegeneration causes an imbalance in all neurotransmitter systems. These are primarily located in brain regions involved in learning, memory, and emotional behaviors such as the hippocampus within the medial temporal lobe of the cerebral cortex, basal forebrain, and amygdala.[9]

Tangles

NFTs interfere with neuronal function, and their presence has been correlated with the severity of dementia.[10] Unfortunately, NFTs are insoluble even after cell death, and they cannot be removed once established; thus, prevention is the key. The neurons that provide most of the cholinergic innervation to the cortex are prominently affected.[11]

Plaques

The Aβ protein is present in neuritic plaques in a nontoxic, soluble form in human brains. In AD, conformational changes occur that render it insoluble and cause it to deposit into amorphous diffuse plaques associated with dystrophic neuritis.[12] Over time, these deposits become compacted into plaques, and the Aβ protein becomes fibrillary and neurotoxic. Inflammation occurs secondary to clusters of astrocytes and microglia surrounding these plaques.

Acetylcholine

In AD, the plaques and tangles damage acetylcholine (Ach) pathways, leading to a shortage of Ach and learning and memory impairment.[13] The basis of current pharmacologic treatment of AD has been to improve cholinergic neurotransmission in the brain. Blocking acetylcholinesterase, the enzyme that degrades Ach in the synaptic cleft, leads to an increased level of Ach with a goal of stabilizing neurotransmission.[13] This process is flawed as cholinergic cell loss appears to be a secondary consequence of AD pathology and not the disease-producing event. Cholinergic neurons are only one of the many neuronal pathways affected in AD.

Glutamate

Glutamate is the primary excitatory neurotransmitter in the central nervous system; it is involved in memory, learning, and neuronal plasticity. It affects cognition through facilitation of connections with cholinergic neurons in the cerebral cortex and basal forebrain.[14] In AD, one type of glutamate receptor, *N*-methyl-D-aspartate (NMDA), is less prevalent than normal. There also appears to be overactivation of unregulated glutamate signaling. This results in a rise in calcium ions that induce secondary cascades, which lead to neuronal death and an increased production of APP.[13] The increased production of APP is associated with higher rates of plaque development and hyperphosphorylation of τ protein.[14] Current treatment of AD includes selective inhibition of NMDA receptor–mediated excitotoxicity.

Cholesterol

Increased cholesterol concentrations have also been associated with AD. Cholesterol increases β-amyloid protein synthesis, which can lead to plaque formation.[13] Also, the apo E4 allele is thought to be involved in cholesterol metabolism and is associated with higher cholesterol levels.[13]

Clinical Presentation and Diagnosis of Alzheimer Disease

General

The diagnosis of AD is primarily made by medical and psychiatric history, neurological examination, formal memory testing, interview of caregivers and family members, and laboratory and imaging data.

Signs and Symptoms

- Cognitive, which occur gradually: memory loss, problems with language, disorientation to time and place, poor or decreased judgment, problems with learning and abstract thinking, misplacing things
- Noncognitive: Changes in mood, behavior, personality, or loss of initiative
- Functional: Difficulty performing familiar tasks

Tests

- Neuropsychological tests such as the Folstein Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA)
- MRI, PET scan, or CT to measure changes in brain size and volume in the medial temporal lobe/hippocampus and rule out stroke, brain tumor, or cerebral edema

Laboratory Tests

- Tests to exclude possible causes of dementia: depression screen, vitamin B_{12} and folate levels, thyroid function tests (thyroid-stimulating hormone and free triiodothyronine and thyroxine), complete blood count, and chemistry panel[17]
- Other diagnostic tests to consider for differential diagnosis: erythrocyte sedimentation rate, urinalysis, toxicology, chest X-ray, heavy metal screen, HIV testing, and cerebrospinal fluid (CSF) examination

Cerebrovascular Pathologies

Cerebrovascular pathologies are common pathologies with age-related cognitive decline along with AD pathologies. Although criteria are still being evaluated to understand the levels of cerebrovascular pathologies that contribute to cognitive impairment, epidemiological studies have found that the presence of vascular and metabolic risk factors during midlife is most strongly associated with the risk of cognitive impairment and dementia.[15] Studies have found that antihypertensive treatment can be beneficial in reducing the risk of dementia.[16] Longitudinal studies are needed to study the evolution of cerebrovascular pathologies in those at higher risk of cardiovascular disease starting at midlife.

CLINICAL PRESENTATION AND DIAGNOSIS

KEY CONCEPT The diagnosis of AD is established following an extensive history and physical examination and by ruling out other potential causes of dementia. Molecular imaging with positron emission tomography (PET) tracers can help identify patients with high levels of amyloid protein (ie, florbetapir, flutemetamol, and florbetaben) and tau neurofibrillary tangles (ie, flortaucipir).[17]

Table 30–1

DSM-5 Diagnostic Criteria for Major Neurocognitive Disorders

- A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition) is based on:
  1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function and
  2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment
- B. Cognitive deficits interfere with independence in everyday activities
- C. Cognitive deficits do not occur exclusively in the context of delirium
- D. Cognitive deficits are not better explained by another mental disorder

Data from American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed, Washington, DC: American Psychiatric Association; 2013:602–603, with permission.

Further research is needed to improve brain imaging, CSF, and other AD biomarkers for routine clinical diagnostic use. The clinical presentation and diagnosis of AD are based on history, signs and symptoms, and laboratory and/or imaging tests.

AD is a progressive disease that, over time, affects multiple areas of cognition. The American Psychiatric Association has published criteria for AD in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*). See Tables 30–1, 30–2, and 30–3 for full criteria.[3]

Clinical Course and Typical Patient Outcomes

AD has a gradual onset and is slowly progressive, with episodic memory, executive function, visuospatial function, and

Table 30–2

DSM-5 Diagnostic Criteria for Mild Neurocognitive Disorder

- A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition) is based on:
  1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function and
  2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing, or in its absence, another quantified clinical assessment
- B. Cognitive deficits do not interfere with the capacity for independence in everyday activities
- C. Cognitive deficits do not occur exclusively in the context of delirium
- D. Cognitive deficits are not better explained by another mental disorder

Data from American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed, Washington, DC: American Psychiatric Association; 2013:605; with permission.

Table 30–3

DSM-5 Diagnostic Criteria for Major or Mild Neurocognitive Disorder Due to Alzheimer Disease

- A. Criteria are met for major or mild neurocognitive disorder
- B. Insidious onset and gradual progression of impairment in one or more cognitive domains (for major neurocognitive disorder, at least two domains must be impaired)
- C. Criteria are met for either probable or possible Alzheimer disease as follows:
  For Major Neurocognitive Disorder:
  Probable Alzheimer disease: diagnosed if either of the following is present; otherwise possible Alzheimer disease should be diagnosed.
  1. Evidence of a causative Alzheimer disease genetic mutation from family history or genetic testing
  2. All three of the following are present:
     - a. Clear evidence of decline in memory and learning and at least one other cognitive domain
     - b. Steadily progressive gradual decline in cognition, without extended plateaus
     - c. No evidence of mixed etiology

  For Mild Neurocognitive Disorder:
  Probable Alzheimer disease: diagnosed if there is evidence of a causative Alzheimer disease genetic mutation from either genetic testing or family history
  Possible Alzheimer disease: diagnosed if there is no evidence of a causative Alzheimer disease genetic mutation from either genetic testing or family history, and all three of the following are present:
  1. Clear evidence of decline in memory and learning
  2. Steadily progressive, gradual decline in cognition, without extended plateaus
  3. No evidence of mixed etiology
- D. Disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systematic disorder

Data from American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatric Association; 2013:611; with permission.

Patient Encounter Part 1

A man presents at the clinic with his 75-year-old mother complaining that his mother's memory is worsening. He complains that his mother is continuing to forget things, including paying the bills and emptying the cat's litter box. Three months ago, she was started on donepezil 5 mg, which was titrated to 10 mg. Her son organizes a weekly pillbox and helps administer the medications. The son asks if there is anything else his mother could take to help her memory.

What education points about Alzheimer disease would you provide to the son?

Where would you recommend the son find more information about Alzheimer disease?

How would you address the son's question regarding the pharmacologic management of his mother's Alzheimer disease?

word-finding difficulties being affected early in the disease course. Impairment in motor, behavioral, and sensory functioning occurs later in the illness. During the final stages, patients are not aware of the events occurring around them and are dependent on others.

TREATMENT

Desired Outcomes

KEY CONCEPT Treatment is focused on delaying disease progression and preservation of functioning as long as possible. Secondary goals include treating psychiatric and behavioral symptoms that may occur during the course of the disease.

General Approach to Treatment

KEY CONCEPT The current gold standard of treatment for cognitive symptoms includes pharmacologic management with an acetylcholinesterase (AChE) inhibitor and/or an NMDA antagonist. There are four agents approved for the treatment of AD, but none are curative or known to directly reverse the disease process; donepezil, rivastigmine, galantamine, and memantine.

Treatment of AD includes education, communication, and planning with the patient's family/caregiver. Treatment options, legal and financial decisions, and course of the illness should be discussed with the patient and family members. The clinician's emphasis should be on helping to maintain a therapeutic living environment while minimizing the burden of care resulting from the disease.

Nonpharmacologic Therapy

The life of a patient with AD must become progressively more simple and structured as the disease progresses, and the caregiver must learn to keep requests and demands on the patient simple. Basic principles in the treatment of patients with AD are shown in Table 30–4.

Pharmacologic Therapy

▶ *Conventional Pharmacologic Treatment for Cognitive Symptoms*

AChE Inhibitors (Donepezil, Rivastigmine, and Galantamine)

Guidelines recommend the use of AChE inhibitors as a valuable treatment for AD.[18] The few head-to-head studies comparing the AChE inhibitors conclude that there are no major differences in clinical outcomes. The selection of one AChE inhibitor over another should be based on differences in mechanisms of action, adverse reactions, titration schedules, potential drug interactions, and patient and caregiver preference.[10,18] AChE inhibitors provide only a modest benefit that should be communicated to the patient and caregiver. Doses of AChE should be titrated to limit adverse effects but high enough to achieve maximum potential benefit.

Table 30–4

Basic Principles in the Management of Patients with AD

- Use a gentle, calm approach to the patient
- Provide reassurance when needed
- Empathy with the patient's concerns
- Use distraction and redirection
- Maintain daily routines
- Provide a safe environment
- Provide daytime activities
- Avoid overstimulation
- Use familiar decorative items in the living area
- Bring abrupt declines in function and the appearance of new symptoms to professional attention

AD, Alzheimer disease.

Data From: Rabins PV, Rovner BW, Rummans T, Schneider LS, Tariot PN. American Psychiatric Association Guideline Watch (October 2014): Practice Guideline for the Treatment of Patients with Alzheimer's Disease and Other Dementias. Washington, DC: American Psychiatric Press; 2014.

Table 30–5

Treatment Algorithm for Cognitive Symptoms of AD

1. Patient diagnosed with AD
2. Assess all comorbid medical disorders and medication therapies that may affect cognition
3. Rule out comorbid depression
4. Evaluate for pharmacotherapy based on illness stage
   a. Mild AD: Acetylcholinesterase inhibitor
   b. Moderate-to-severe AD: Acetylcholinesterase inhibitor, memantine, or combination acetylcholinesterase inhibitor and memantine
5. Deteriorating Mini-Mental State Examination (MMSE) score > 2–4 points after 1 year: Change to a different acetylcholinesterase inhibitor
6. Stable MMSE: Continue regimen
7. Treat behavioral/noncognitive symptoms associated with AD as they arise

AD, Alzheimer disease.

Data From: Rabins PV, Rovner BW, Rummans T, Schneider LS, Tariot PN. American Psychiatric Association Guideline Watch (October 2014): Practice Guideline for the Treatment of Patients with Alzheimer's Disease and Other Dementias. Washington, DC: American Psychiatric Press; 2014.

Treatment should begin as early as possible after diagnosis.[10,18] Table 30–5 provides a recommended treatment algorithm. Patients should be switched to another AChE inhibitor from their initial AChE inhibitor if they show an initial lack of efficacy, initially respond but then lose clinical benefit, or experience safety/tolerability issues. This switch should not be attempted until the patient has been on a maximally tolerated dose for 3 to 6 months. The switch should also be based on realistic expectations of the patient and/or caregiver.[10,18] Mixed recommendations exist regarding AChE inhibitor discontinuation. There is some data to suggest continuation versus stopping treatment in moderate-to-severe dementia, but the long-term adverse effects of AChE inhibitor therapy need to be considered as well (ie, anorexia, weight loss, falls, hip fractures, syncope, bradycardia, increased use of cardiac pacemakers).[19] Beneficial effects of AChE inhibitor therapy can be found if a patient's dementia appears to be progressing slowly and should be continued as long as the patient or caregiver is willing to continue, adherence to the treatment is maintained, there are no comorbidities to offset the medication, adverse effects are monitored, and the patient has not progressed to a severely impaired stage.[20] Abrupt discontinuation should be avoided as this can worsen cognitive impairment.

Donepezil Donepezil is a piperidine AChE inhibitor that reversibly and noncompetitively inhibits centrally active acetylcholinesterase.[21] A dose of 10 mg/day has demonstrated efficacy in patients with either mild-to-moderate or moderate-to-severe forms of AD, while the 23-mg dose is also approved for patients with moderate-to-severe disease. The 23-mg dose showed a small improvement in cognitive symptoms compared to the

Table 30–6

Dosing Strategies for Cognitive Agents

	Donepezil (Aricept)	Rivastigmine (Exelon)	Galantamine (Razadyne)	Memantine (Namenda, Namenda XR)	Memantine +Donepezil (Namzaric)
Starting dose	5 mg daily in the evening	Oral: 1.5 mg twice daily Patch: 4.6 mg/24 hour applied daily	IR: 4 mg twice daily ER: 8 mg daily in the morning	IR: 5 mg daily ER: 7 mg daily	7 mg/10 mg (if patient is stabilized on donepezil and not currently on memantine); 28 mg/10 mg (if patient is stabilized on memantine and donepezil)
Maintenance dose	5–23 mg daily	Oral: 3–6 mg twice daily Patch: 9.5 mg/24 hour applied daily	IR: 8–12 mg twice daily ER: 16–24 mg daily	IR: 10 mg twice daily ER: 28 mg daily	28 mg/10 mg daily
Time between dose adjustments	4–6 weeks between 5 and 10 mg increment; 3 months between 10 and 23 mg increment	Oral: 2 weeks Patch: 4 weeks	4 weeks	1 week	1 week
Dosage adjustments for renal or hepatic impairment	None	Moderate-to-severe renal impairment, mild-to-moderate hepatic impairment, or low body weight (< 50 kg): consider a maximum dose of 4.6 mg/24 hour (not studied in hepatic impairment)	Do not exceed 16 mg for moderately impaired hepatic or renal function; do not administer in severe renal or hepatic impairment	Severe renal impairment: target maintenance dose of 5 mg twice daily or 14 mg daily	Severe renal impairment: 14 mg/10 mg daily

IR: immediate release; ER: extended release

Aricept [package insert]. Woodcliff Lake, NJ: Eisai; 2018.

Exelon [package insert]. East Hanover, NJ: Novartis; 2018.

Razadyne ER/Razadyne [package insert]. Titusville, NJ: Ortho-McNeil Neurologics; 2020.

Namenda [package insert]. Madison, NJ: Allergan USA, Inc.; 2018.

Namenda XR [package insert]. Madison, NJ: Allergan USA, Inc.; 2019.

Namzaric [package insert]. Madison, NJ: Allergan USA, Inc.; 2019.

10 mg/day dose; however, there was no improvement in the overall functioning, and there was a higher incidence of adverse effects.[22] Table 30–6 describes dosing strategies for all of the approved agents for AD. The most frequent adverse effects are mild-to-moderate gastrointestinal symptoms.[21,23–27] Others include headache, dizziness, syncope, bradycardia, and muscle weakness. Table 30–7 compares their major side effects and monitoring parameters.[21,23–27]

Only a small number of drug interactions have been reported with donepezil. Monitoring for increased peripheral side effects is advised when adding a cytochrome P450 (CYP) 2D6 or 3A3/4 inhibitor to donepezil treatment. Also, inducers of CYP2D6 and 3A4 could increase the elimination rate of donepezil.[21]

Rivastigmine Rivastigmine, approved for the treatment of mild-to-moderate AD, has a central activity for both acetylcholinesterase and butyrylcholinesterase, which could potentially lead to broader efficacy.[23]

Rivastigmine is available as an oral formulation and a patch. If the patient is taking less than 6 mg/day orally, the 4.6 mg/24-hour patch is recommended if switching from oral form to the patch. If the patient is taking 6 to 12 mg/day orally, the 9.5 mg/24-hour patch is recommended. The first patch should be applied on the day following the last oral dose.[23]

Cholinergic side effects are common, but they are usually well tolerated if the recommended dosing schedule is followed. If side effects cause intolerance, several doses can be held, and then dosing can be restarted at the same or next lower dose. Drugs that induce or inhibit CYP450 metabolism are not expected to alter rivastigmine metabolism.[23]

Galantamine Galantamine, approved for the treatment of mild-to-moderate AD, is an AChE inhibitor, which elevates Ach in the cerebral cortex.[24] It also modulates the nicotinic Ach receptors to increase Ach release from surviving presynaptic nerve terminals. Galantamine may also increase glutamate and serotonin levels, but whether this brings additional benefit is unknown.

CYP3A4 and 2D6 are the major metabolizing enzymes, and pharmacokinetic studies with inhibitors of these enzymes have shown increased galantamine concentrations or reductions in clearance. Similar to donepezil, if inhibitors are given concurrently with galantamine, increased cholinergic side effects should be monitored.[24]

NMDA Receptor Antagonist Memantine is a noncompetitive antagonist of the NMDA type of glutamate receptors that are located throughout the brain. NMDA receptors regulate activity

Table 30–7

Adverse Effects for Currently Approved Medications for Alzheimer Disease[a]

Adverse Event	Donepezil 5–10 mg/day (%) (n = 747)	Donepezil 23 mg/day (%) (n = 963)	Rivastigmine 6–12 mg/day (%) (n = 1189)	Galantamine IR 16–24 mg/day (%) (n = 2932)	Memantine IR 5–20 mg/day (%) (n = 940)	Memantine XR 28 mg/day (%) (n = 341)
Nausea	11	12	47	25	NR	NR
Vomiting	5	9	31	13	3	2
Diarrhea	10	8	19	9	NR	5
Headache	10	4	17	8	6	6
Dizziness	8	5	21	9	7	5
Muscle cramps	6	NR	NR	NR	NR	NR
Insomnia	9	3	9	2	NR	NR
Fatigue	5	2	9	4	2	3
Anorexia	4	5	17	4	NR	NR
Depression	3	NR	6	4	NR	3
Abnormal dreams	3	NR	NR	NR	NR	NR
Weight decrease	3	5	3	NR	NR	NR
Abdominal pain	NR	NR	13	3	NR	2
Rhinitis	NR	NR	NR	NR	NR	NR

[a] Caution is urged in making comparisons between drugs based on these data because different clinical trials often collect adverse event data using different methodologies.

NR, not reported.

Aricept [package insert]. Woodcliff Lake, NJ: Eisai; 2018.

Exelon [package insert]. East Hanover, NJ: Novartis; 2018.

Razadyne ER/Razadyne [package insert]. Titusville, NJ: Ortho-McNeil Neurologics; 2020.

Namenda [package insert]. Madison, NJ: Allergan USA, Inc.; 2018.

Namenda XR [package insert]. Madison, NJ: Allergan USA, Inc.; 2019.

Namzaric [package insert]. Madison, NJ: Allergan USA, Inc.; 2019.

throughout the brain by controlling the amount of calcium that enters the nerve cell, a process essential for establishing an environment required for information storage. Overstimulation of the NMDA receptor by excessive glutamate allows too much calcium into the cell, disrupting information processing. Blocking NMDA receptors with memantine may protect neurons from the effects of excessive glutamate without disrupting normal neurotransmission.[25]

Memantine is approved to treat moderate-to-severe AD. It can be given as monotherapy or in combination with AChE inhibitors. Only the modest benefit can be anticipated with the utilization of memantine. Memantine is not indicated for mild AD, and current evidence does not support its use in mild AD.[28] Adverse reactions associated with memantine include constipation, confusion, dizziness, headache, coughing, and hypertension. Closer monitoring should be done if memantine is given concurrently with an AChE inhibitor.

In vitro studies have shown that memantine produces minimal inhibition of CYP450 enzymes 1A2, 2A6, 2C9, 2D6, 2E1, and 3A4, and that no pharmacokinetic interactions with drugs metabolized by these enzymes should be expected.[25,26]

Future Therapies **KEY CONCEPT** Future therapies for AD may include disease-modifying therapies. Current investigations into future therapies for the treatment of AD include the following:

- Targeting of the etiologic pathologies of AD: neurofibrillary tangles and senile plagques.[29,30]
- Fortifying transcortical networks and enhancing interneuronal connections in order to enhance cognitive function.[31]
- Early identification of the at-risk population and subsequent treatment in the preclinical stage.[32]

▶ *Nonconventional Pharmacologic Treatment*

Nonconventional treatments have historically been used as adjunctive treatments of AD. Vitamin E was previously recommended because of its antioxidant properties, but a meta-analysis suggested that greater than 400 IU/day should be avoided due to an increased all-cause mortality.[33] There is insufficient data supporting efficacy for nonsteroidal anti-inflammatory drugs (NSAIDs); gastritis, GI bleeds, and increased cardiovascular events are associated with their use.[34] Statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors) should be reserved for those who have other indications for their use.[35] Until Ginkgo biloba has a more standardized manufacturing process and its long-term safety and efficacy are established, it should be recommended with caution.[36]

The medical food caprylidene (AC-1202, Axona) is a medium chain triglyceride approved for the dietary management of metabolic processes associated with mild-to-moderate AD.[37] Reduced neuronal metabolism of glucose has been associated with AD, and ketone bodies can potentially be used as an alternative energy source for AD patients.[37] Caprylidene is converted by the liver into the ketone body β-hydroxybutyrate (BHB). BHB crosses the blood–brain barrier and can be utilized by neurons as a potential energy source to generate adenosine triphosphate (ATP) and increase pools of Ach.[38] Tramiprosate (homotaurine) demonstrated early promise in the treatment of AD, but phase III trials were disappointing. Homotaurine is naturally occurring in seaweed and is thought to interfere with amyloid plaque formation and subsequent degeneration of neuronal cells.[39]

With the growing body of evidence that brain vascular disease plays a role in the progression of dementia, guidelines support monitoring blood pressure, glucose, cholesterol, and homocysteine, and initiating appropriate interventions.[16] Adherence to the Mediterranean Diet or Dietary Approaches to Stop Hypertension diet may reduce the risk of cognitive impairment or decline.[40] Additionally, physical activity is an important component of vascular brain health and has been shown in some short-term studies to be associated with a reduced risk of cognitive impairment as well.[40]

Patient Encounter Part 2

The patient returns to the clinic in 6 months. She has been on donepezil 10 mg daily and memantine 10 mg twice daily. Her memory symptoms have slowed in their decline, but recently she has been agitated at bedtime and talking to her deceased sister. The son is particularly concerned about the symptoms and wants to know what he could do to help. The patient's record is as follows:

PMH: Diabetes mellitus since age 51 (well controlled until last year when she became confused about when to take her medication); hypertension (treated for 23 years, well controlled, has been hypotensive on a few occasions recently during physicals); osteopenia (last bone mineral density test 12 months ago [T-score = −1.2] on therapy); hypercholesterolemia (last cholesterol panel 12 months ago showed well-controlled levels in normal range, on therapy)

FH: Father died of myocardial infarction at age 76; mother died of breast cancer at age 79

SH: Lives with wheelchair-bound husband; son lives across street and checks in daily; denies drinking alcohol or smoking

Meds: Metformin 500 mg orally twice daily; insulin glargine 18 units subcutaneously at bedtime; hydrochlorothiazide 25 mg orally once daily in the morning; lisinopril 20 mg orally once daily in the morning; calcium carbonate and vitamin D 600 mg/200 international units orally twice daily with lunch and dinner; atorvastatin 10 mg orally once daily with dinner; donepezil 10 mg orally daily and memantine 10 mg orally twice daily

ROS: (+) Weight loss of 6.3 kg (14 lb) since last visit; (−) N/V/D, change in appetite, heartburn, chest pain, or shortness of breath

PE:

VS: BP 111/72 mm Hg supine, P 79 beats/min, RR 16 breaths/min, T 37°C (98.6°F)

Gen: Poorly groomed, thin woman looks as stated age

Neuro: Folstein Mini-Mental State Examination score 20/30 (suggestive of moderate dementia) and MoCA score 18/30 (suggestive of moderate dementia); disoriented to month, date, and day of week, clinic name and floor; poor registration with impaired attention and short-term memory; good language skills but problems with commands

CT Scan: Mild-to-moderate generalized cerebral atrophy

What do you recommend with regard to her current donepezil and memantine treatment?

What nonpharmacologic and pharmacologic interventions could be recommended for the agitation and psychosis?

Treatment of Behavioral Symptoms

KEY CONCEPT Treatment of behavioral symptoms should not only begin with nonpharmacologic treatments but may also include antipsychotic agents and/or antidepressants. Nonpharmacologic recommendations for treatment include the following[41]:

- Music
- Videotapes of family members
- Audiotapes of the voices of caregivers
- Walking and light exercise
- Sensory stimulation and relaxation

Clinical trials have reported a modest benefit in managing behavioral symptoms with AChE inhibitors and memantine, although the long-term benefits have not been demonstrated to date. Antipsychotics are also frequently used for neuropsychiatric symptoms associated with AD. A meta-analysis concluded that only 17% to 18% of dementia patients demonstrated treatment response to atypical antipsychotics.[42] A double-blind, placebo-controlled trial of olanzapine, quetiapine, or risperidone for the treatment of psychosis, aggression, or agitation in patients with AD showed that adverse effects outweigh the benefits of atypical antipsychotics.[43]

In April 2005, the US Food and Drug Administration (FDA) issued a statement requiring black box warnings on all antipsychotics stating that elderly people with dementia-related psychosis treated with an antipsychotic are at an increased risk of death compared with those treated with placebo.[44] Fifteen of 17 trials investigating olanzapine, aripiprazole, quetiapine, or risperidone in elderly demented patients with behavioral disorders showed an increase in mortality compared with the placebo-treated groups (1.6–1.7 times increased risk of death). Causes for these deaths were heart-related events (heart failure and sudden death) and infections (mostly pneumonia).[44] Readers are referred to Chapter 38 for additional information on antipsychotics.

Antipsychotics are not approved for the treatment of elderly patients with dementia-related psychosis. Therefore, it is important to individually assess and balance the risk versus benefit of antipsychotic use in this population. Both the American Society of Consultant Pharmacists and the American Psychiatric Association have published statements regarding the use of antipsychotics to treat agitation and psychosis in dementia.[45,46]

Depressive symptoms occur in as many as 50% of patients with AD and can be difficult to differentiate from symptoms of dementia. Symptoms of depression should be documented for several weeks prior to initiating therapy for depression with AD.[7] The selective serotonin reuptake inhibitors are most commonly used based on their side-effect profile and evidence of efficacy.[7] Indications for the use of antidepressants include depression characterized by poor appetite, insomnia, hopelessness, anhedonia, withdrawal, suicidal thoughts, and agitation.[7] Readers are referred to Chapter 39 for more information on antidepressants.

Other miscellaneous therapies for AD include benzodiazepines for anxiety, agitation, and aggression. However, their routine use is not advised because of the increase in falls.[7] Mood stabilizer anticonvulsants, carbamazepine, valproic acid, or gabapentin may be used as alternatives, but the current evidence is conflicting.[47] Buspirone has shown benefit in treating agitation and aggression in a limited number of patients with minimal adverse effects.[48] In open-label and controlled studies, selegiline decreased anxiety, depression, and agitation, although monoamine oxidase inhibitors are not typically well tolerated.[49] Finally, trazodone has been shown to decrease insomnia, agitation, and dysphoria, and it has been used to treat sundowning in AD patients.

Patient Encounter Part 3

The patient returns to the clinic for follow-up 6 months later. Her son states her memory has progressed significantly. Her current MoCA score is now 14/30. The addition of risperidone 0.5 mg at bedtime helped with her agitation, but she has significant symptoms that appear late in the afternoon on most days, especially if they have visitors to the house. Recently, she went outside and wandered off the property resulting in a brief police search to find and return her home. Her son would like to know if there are any other choices to help treat his mom.

What changes to the patient's current medications would you recommend?

GENOMICS

KEY CONCEPT At this time, there are no specific recommendations regarding the choice of medications or dosing regimens for the current treatments for AD based on genotype or other biomarkers.

OUTCOME EVALUATION

- The success of therapy is measured by the degree to which the care plan decreases the pretreatment rate of cognitive deterioration, preserves the patients' functioning, and treats psychiatric and behavioral symptoms. The primary outcome measure is thus subjective information from the patient and the caregiver, although the MMSE or MoCA can be a helpful tool. There are no physical examinations or laboratory parameters to evaluate the success of therapy.
- Develop a plan to assess the effectiveness of the AChE inhibitor in slowing the deterioration of cognitive functioning after an appropriate interval (every 3–6 months).
- Assess improvement in quality-of-life measures such as ability to function independently and for slowing of memory deterioration (every 3–6 months).
- Evaluate functional performance, mood, and behaviors.
- Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions at appropriate intervals (soon after drug initiation or change and every 3–6 months).

CONCLUSION

AD is a progressive deterioration of cognitive abilities, often accompanied by behavioral disturbances and personality changes in the later stages of the disease. In an effort to help prepare patients and their caregivers for the inevitable, the Alzheimer's Association has developed 10 quick tips on "Living with Alzheimer's disease," and they can also provide many resources for patients and caregivers. Access the association at:

Alzheimer's Association

Contact Center: 1-800-272-3900

Patient Care Process

Collect Information:

- Assess the type, frequency, and duration of cognitive and noncognitive symptoms.
- Review any available diagnostic data from the medical and psychiatric history, including interviews from family, neuropsychologic testing, CT, PET, and MRI, and other labs (ie, vitamin deficiencies, thyroid function tests, complete blood counts, and chemistry panel).
- Obtain a thorough history of prescription, nonprescription, and natural drug product use.
- Identify allergies to medications and other substances.

Assess the Information:

- Determine whether the patient has any other disease state (ie, depression) or is taking any medication that could contribute to cognitive changes in the elderly.
- Document current cognitive and noncognitive symptoms present in the patient.
- Assess the current pharmacotherapy regimen for appropriateness, effectiveness, adverse effects, drug interactions, appropriate dosing, and medication adherence (see Table 30–7).

Develop a Care Plan:

- Select an appropriate AChE inhibitor to avoid drug–drug interactions and adverse effects and in consideration of cost and patient preference (see Tables 30–6 and 30–7).
- Develop a plan to monitor cognitive response to treatment over time.
- Select appropriate medications for behavior symptoms if lifestyle modifications do not achieve goals.

Implement the Care Plan:

- Provide patients and caregivers information about lifestyle modification and refer them to support when needed.
- Be a resource and give continuous support to the patients and caregivers throughout the long course of the disease.
- Educate patients and caregivers on what to expect from pharmacotherapy.

Follow-up: Monitor and Evaluate:

- Follow up at needed intervals to assess effectiveness and safety of therapy. Review medical history and physical examination findings, lab tests, and results of other diagnostic tests.
- Monitor pharmacotherapy initiation (see Table 30–6) and regularly evaluate the patient for the presence of adverse drug reactions, drug allergies, drug–drug and drug–disease interactions, and adherence.
- If symptoms progress, consider stopping/switching the AChE inhibitor. Switch if there is initial lack of efficacy, loss of clinical benefit, or if poor tolerability develops. Discontinue if there is poor adherence, persistent adverse effects, or development to severe stage of the illness.
- Continue to offer support to the patient and caregiver.

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Abbreviations Introduced in This Chapter

Ach	Acetylcholine
Aβ	Amyloid beta
AChE	Acetylcholinesterase
AD	Alzheimer disease
apo E	Apolipoprotein E
APP	Amyloid precursor protein
BHB	β-Hydroxybutyrate
CSF	Cerebrospinal fluid
CYP	Cytochrome P450
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition
HIV	Human immunodeficiency virus
MMSE	Mini-Mental State Examination
NMDA	*N*-Methyl-D-aspartate
NFTs	Neurofibrillary tangles
NSAID	Nonsteroidal anti-inflammatory drug
τ	Tau protein

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31

Multiple Sclerosis

Sarah Rajkovic and Jacquelyn L. Bainbridge

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Identify risk factors for multiple sclerosis (MS).
2. Distinguish between phenotypes of MS based on patient presentation and disease course.
3. Compare and contrast choice of disease-modifying therapies (DMT) for a given patient.
4. Determine appropriate symptomatic treatment options for a given patient.
5. Develop a monitoring plan for a patient initiated on a specific DMT.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) characterized by myelin destruction and axonal damage. *Multiple* describes the numerous CNS lesions that accrue over time, and *sclerosis* refers to the demyelination of lesions, also called plaques.

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

MS is the most common progressive neurologic disease, affecting approximately 2.3 million people worldwide.[1] Diagnosis usually occurs between 20 and 50 years of age, impacting at least twice as many women as men.[1] People of northern European ancestry are more likely to develop MS and the geographical risk increases with increasing distance (north or south) from the equator.[2]

Etiology

The cause of MS is unknown, but may be due to a combination of genetic, environmental, immunologic, or infectious factors. Genetic risks may explain up to 35% of cases.[2] Environmental theories involve infectious exposures (eg, Epstein–Barr Virus), decreased patient or maternal vitamin D serum concentrations, tobacco use, residence at high latitude, and childhood obesity.[2,3]

PATHOPHYSIOLOGY

While the causative agent of MS is unclear, the result is the development of an autoimmune disorder with areas of CNS inflammation and degeneration.

Inflammation

An unknown antigen presented by the major histocompatibility complex (MHC) class II molecules causes T cells to become autoreactive (Figure 31–1). Autoreactive T cells enter lymphatic tissues to expand. Upon a signal involving sphingosine-1-phosphate, T cells reenter the circulation.[4] Once activated, T cells cause blood–brain barrier breakdown and enter the CNS. These T cells come into contact with antigen-presenting cells (APCs) and proliferate and differentiate. Th1 cells secrete cytokines that enhance macrophage and microglial cells that attack myelin.[4]

B cells cross damaged sections of the blood–brain barrier where autoreactive T cells trigger B cells to form myelin autoantibodies. These inflammatory processes are the likely cause of relapses.[4]

Degeneration

Axonal injury and transection disrupts normal nerve signaling. Growing evidence suggests cytotoxic T cells cause axonal injury early in disease.[4] Axonal loss is likely responsible for MS progression.[4]

CLINICAL PRESENTATION AND DIAGNOSIS

Diagnosis

Clinically isolated syndrome (CIS) is a focal demyelinating event in the CNS, often optic neuritis or myelopathy, in a patient not known to have MS.[5] CIS has approximately 60% rate of conversion to clinically definite MS over 4 years.[6] This clinically definite MS (CDMS) diagnosis is made when dissemination in time and space is demonstrated. Diagnosis requires 1 year of disease progression and two of the following: dissemination in space on MRI of the brain, dissemination in space on MRI of the spinal cord, or positive cerebrospinal fluid (CSF).[7] The use of MRI is critical in the diagnosis of MS as they can help identify T2-hyperintensive lesions in four areas of the CNS, which include cortical, juxtacortical, infratentorial, and spinal cord.[8] An example of MRI findings of patients with MS can be seen in Figure 31–2.

KEY CONCEPT The 2017 McDonald criteria is used to evaluate for the presence of dissemination in time by more than one clinical attack and dissemination in space by the presence of lesions at a different or multiple site(s) in the CNS, such as multiple areas in the brain or spinal cord.[7] Evidence from magnetic resonance imaging (MRI) and/or oligoclonal immunoglobulin G bands can help fulfill these time and space criteria and facilitate earlier diagnosis and treatment (Figure 31–3).[7] **KEY CONCEPT** MS is classified into relapsing and progressive disease (Figure 31–4).

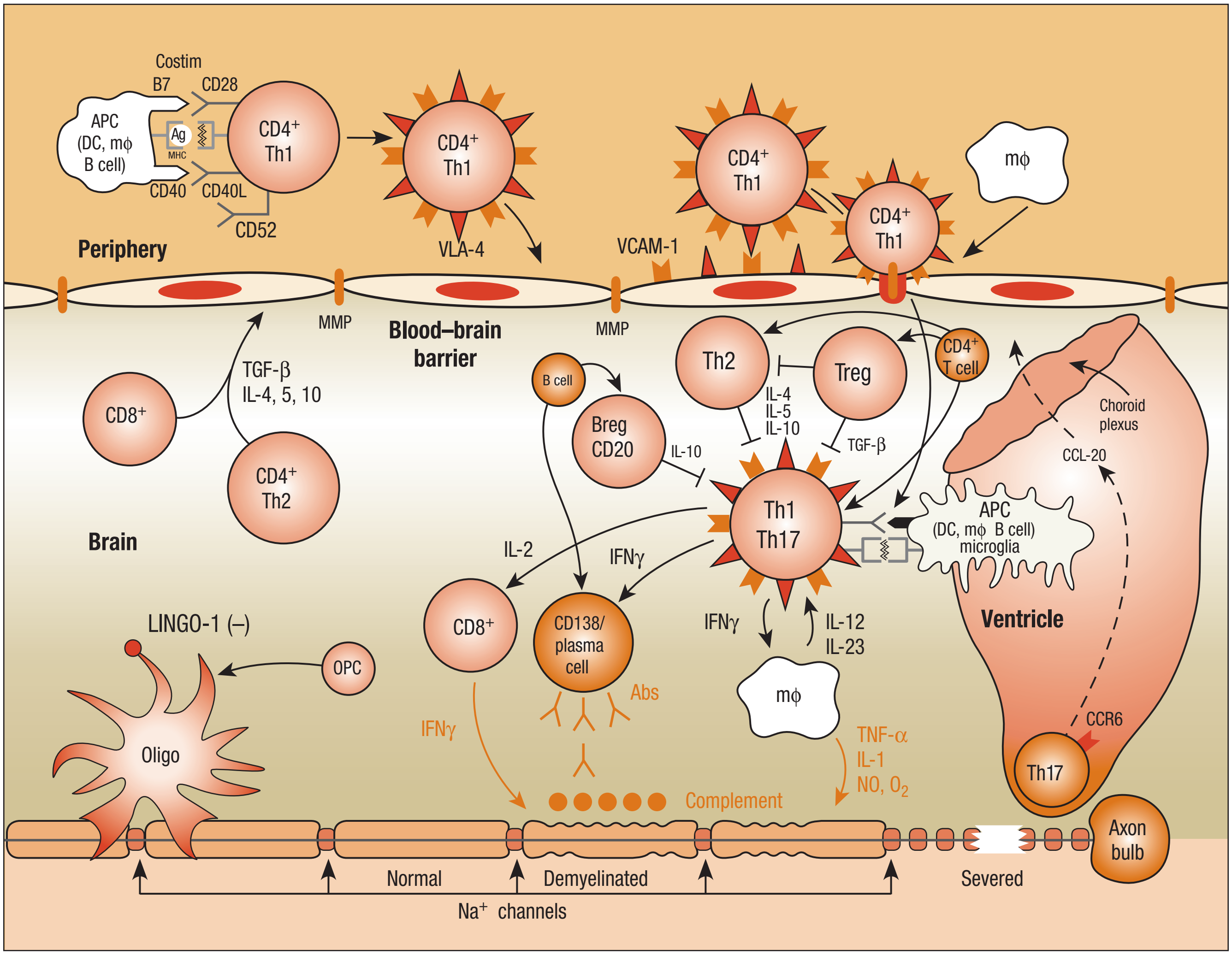

Costim
B7
CD28
APC
(DC, mϕ
B cell)
Ag
MHC
CD4+
Th1
CD40
CD40L
CD52
Periphery
CD4+
Th1
VLA-4
VCAM-1
CD4+
Th1
CD4+
Th1
mϕ
MMP
Blood–brain
barrier
MMP
TGF-β
IL-4, 5, 10
CD8+
CD4+
Th2
Brain
B cell
Breg
CD20
Th2
Treg
CD4+
T cell
IL-4
IL-5
IL-10
TGF-β
IL-10
Th1
Th17
APC
(DC, mϕ B cell)
microglia
Choroid
plexus
CCL-20
Ventricle
IL-2
IFNγ
CD8+
CD138/
plasma
cell
IFNγ
IL-12
IL-23
mϕ
LINGO-1 (–)
OPC
Oligo
IFNγ
Abs
TNF-α
IL-1
NO, O2
Complement
CCR6
Th17
Axon
bulb
Normal
Demyelinated
Severed
Na+ channels

FIGURE 31–1. Autoimmune theory of the pathogenesis of multiple sclerosis (MS). In MS, the immunogenic cells tend to be more myelin reactive, and these T cells produce cytokines mimicking a Th1-mediated proinflammatory reaction. T-helper cells (CD4$^+$) appear to be key initiators of myelin destruction in MS. These autoreactive CD4$^+$ cells, especially of the T-helper cell type 1 (Th1) subtype, are activated in the periphery, perhaps following a viral infection. The activation of T and B cells requires two signals. The first signal is the interaction between MHC and APC (macrophage, dendritic cell, and B cell). The second signal consists of the binding between B7 on the APC and CD28 on the T cell for T-cell activation. Similarly, CD40 expressed on APCs and CD40L expressed on T cells interact to signal the proliferation of B cells within the blood–brain barrier following the entry to T cells. The T cells in the periphery express adhesion molecules on their surfaces that allow them to attach and roll along the endothelial cells that constitute the blood–brain barrier. The activated T cells also produce MMP that help to create openings in the blood–brain barrier, allowing entry of the activated T cells past the blood–brain barrier and into the CNS. Once inside the CNS, the T cells produce proinflammatory cytokines, especially interleukins (ILs) 1, 2, 12, 17, and 23, tumor necrosis factor-α (TNF-α), and interferon-γ (INF-γ), which further create openings in the blood–brain barrier, allowing entry of B cells, complement, macrophages, and antibodies. The T cells also interact within the CNS with the resident microglia, astrocytes, and macrophages, further enhancing the production of proinflammatory cytokines and other potential mediators of CNS damage, including reactive oxygen intermediates and nitric oxide. The role of modulating, or downregulating, cytokines such as IL-4, IL-5, IL-10, and transforming growth factor-β (TGF-β) also has been described. These cytokines are the products of CD4$^+$, CD8$^+$, and Th1-cells. New pathogenic mechanisms involve, but are not limited to, receptor-ligand–mediated T-cell entry via choroid plexus (CCR6-CCL20 axis), coupling of key receptor-ligands for inhibition of myelination/demyelination (LINGO-1/NOGO66/p75 or TROY complex, Jagged-Notch signaling). (Ag, antigens; APC, antigen-presenting cell; DC, dendrite cell; IgG, immunoglobulin G; MΦ, macrophage; Na^+, sodium ion; MMP, matrix metalloproteinases; MHC, major histocompatibility complex; OPC, oligodendrocyte precursor cell; VLA, very late antigen; VCAM, vascular cell adhesion molecule.) (From Bainbridge JL, Miravalle A, Wong PS. Multiple sclerosis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017, with permission.)

Relapsing-remitting MS (RRMS) is the most common type of MS, affecting about 85% of patients, where patients will experience periods of relapse (exacerbation) followed by periods of remission. It is important to note that even during remission, there is still neuronal damage occurring even without symptoms present. Patients with RRMS can eventually move to a more progressive form of MS, called secondary progressive MS (SPMS).

Clinical Presentation of MS[10,11]

MS symptoms depend on the location of lesions within the CNS and thus can be nonspecific. Myelin increases the speed of nerve impulse transmission; demyelination slows the speed. No impulses can be transmitted if the axon is transected. The primary symptoms of MS are caused by this delay or cessation of impulses. The secondary symptoms of MS result as a complication from the primary symptoms.

Primary Symptoms	Frequency of Occurrence (%)	Related Secondary Symptoms
Urinary incontinence or retention	70	Decubitus ulcers Urinary tract infections
Spasticity	70–80	Falls, care difficulties, pain, gait problems
Optic neuritis	70	Falls, care difficulties
Bowel incontinence or constipation	39–73	Decubitus ulcers Pain
Depression	50	Suicide
Anxiety	36	
Cognitive deficits	43–70	Decline in work or social performance, care difficulties
Fatigue	92	Effects on employment and social roles
Uhthoff phenomenon	80	
Sexual dysfunction		
Erectile dysfunction	50–90	
Female sexual dysfunction	40–85	
Tremor	80	Inability to perform activities of daily living
Pain	86	
Trigeminal neuralgia	15	
Lhermitte sign	4–5	
Dysesthetic pain	14–29	
Impaired gait	64	Inability to perform activities of daily living

Progressive forms of MS are more difficult to diagnose because there are often no overt clinical attacks, rather, patients continue to decline in the Expanded Disability Status Scale (EDSS). For patients who present initially with a progressive onset, this is called primary progressive MS (PPMS). Progressive MS can further be categorized as active versus not active and progressing versus not progressing, which assists in guiding therapy decisions. MS is the most common cause of young adult disability (impaired walking, fine motor movements, sight, cognitive dysfunction, mood disorders, pain) and reduces life expectancy by 10 to 12 years. Early diagnosis and treatment (within first 5 years) is an important clinical consideration to prevent disease progression and disability in order to maintain the quality of life across the patient life span.[9]

TREATMENT

Desired Outcomes and General Approach to Treatment

The goal of treatment is preventing permanent neurologic damage and disability progression. There are three approaches to treatment. **KEY CONCEPT** First, treat acute relapses with corticosteroids to reduce inflammation and speed recovery. **KEY CONCEPT** Second, early initiation of disease-modifying therapies (DMT) decreases the number of annual relapses, prevents permanent neurologic damage, and prevents progression of disability. **KEY CONCEPT** Third, symptomatic treatments can be added to treat common primary symptoms such as pain and spasticity, depression, cognitive dysfunction, and urinary symptoms.

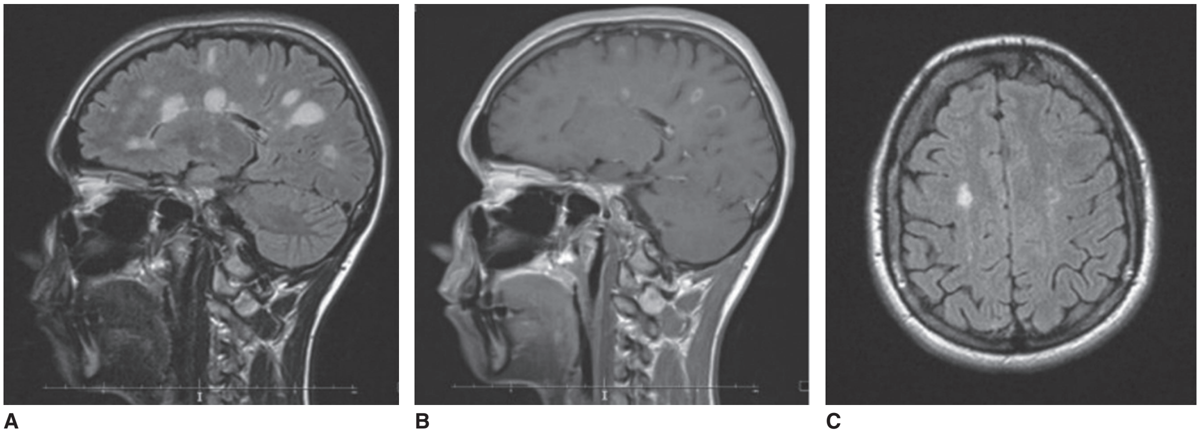


FIGURE 31–2. MRI findings of various white matter lesions, including: (1a) T-2 hyperintense lesions; (1b) gadolinium-enhanced lesions; and (1c) subcortical FLAIR-hyperintense white matter lesions.[8]

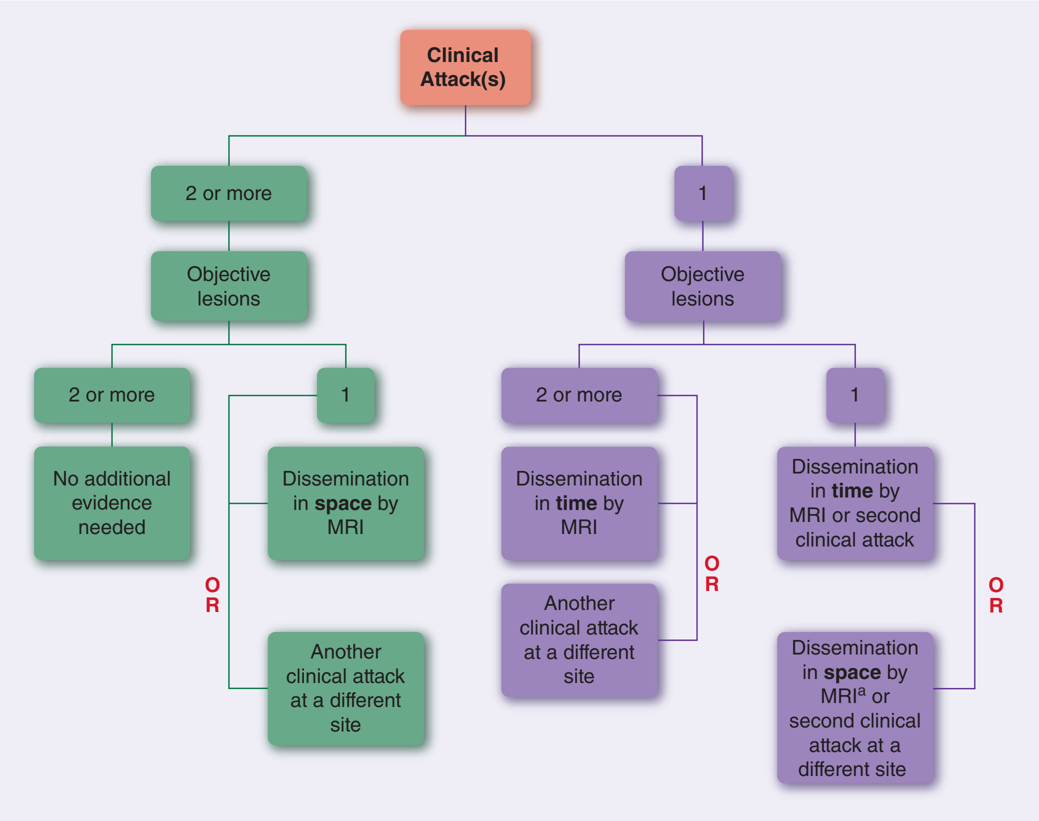

Clinical Attack(s)
2 or more
1
Objective lesions
Objective lesions
2 or more
1
2 or more
1
No additional evidence needed
Dissemination in **space** by MRI
OR
Another clinical attack at a different site
Dissemination in **time** by MRI
OR
Another clinical attack at a different site
Dissemination in **time** by MRI or second clinical attack
OR
Dissemination in **space** by MRI[a] or second clinical attack at a different site

FIGURE 31–3. The 2017 McDonald Criteria for the Diagnosis of MS.[9] An attack is defined as a patient-reported or objectively observed event typical of an acute inflammatory demyelinating event in the CNS with a duration of at least 24 hours in the absence of fever or infection. MRI evidence of dissemination over time is a new T2-weighted lesion after the initial clinical event or the simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time.[a] Dissemination in space by MRI evidence of one or more T2-weighted lesions in at least two of the following areas: periventricular, juxtacortical, infratentorial, spinal cord.

Pharmacologic Treatment

▶ *Treatment of Acute Relapses with Corticosteroids*

Pharmacology and Mechanism of Action Corticosteroids prevent inflammatory cytokine activation, inhibit T- and B-cell activation, and prevent immune cells from entering the CNS.[12] Corticosteroids hasten functional recovery.[12] Equivalence of IV and oral dosage forms has been demonstrated.[13]

Adverse Effects The most common adverse effects are taste change, flushing, gastrointestinal upset, insomnia, and mood disturbance.[14] Since patients are only on this regimen for a few days, adverse effects are usually mild and tolerated well.

Dosing and Administration Methylprednisolone is given 1000 mg/day IV or orally as one daily dose for 3 to 5 days.[13] Oral prednisone 1250 mg/day provides an equivalent dose. Recovery

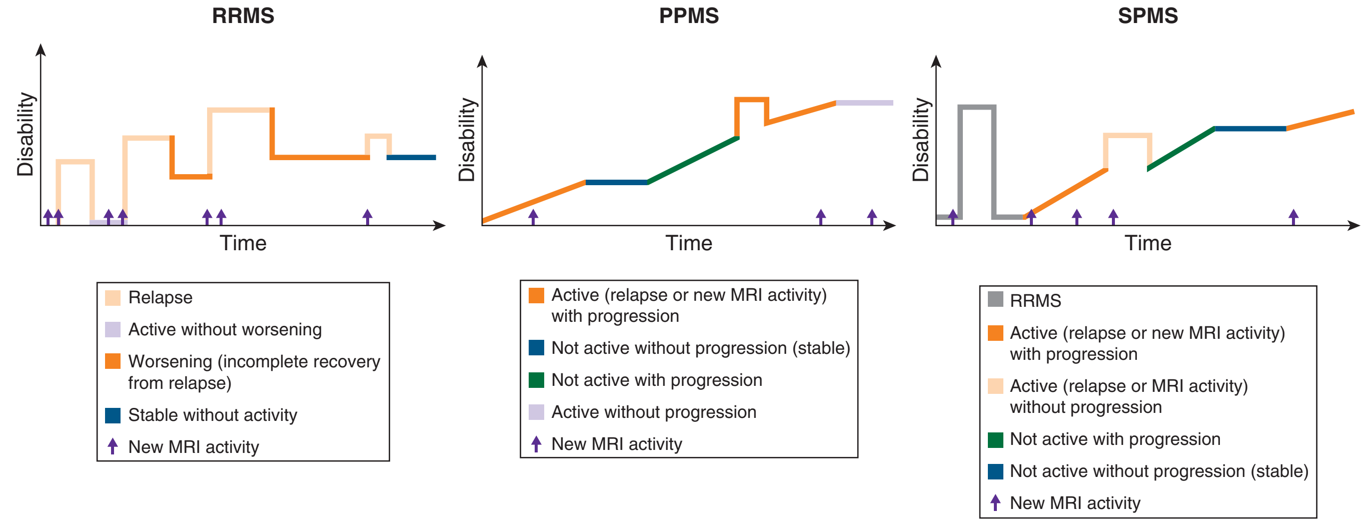


FIGURE 31–4. Clinical phenotypic patterns of MS disease course over time.[7]

Patient Encounter, Part 1

A 26-year-old Caucasian woman with a history of migraines presents to her primary care physician with complaints of decreased sensation and tingling in both of her hands that developed over several hours. She describes the tingling as “pins and needles” that did not resolve with movement. Over the last 2 to 3 years, she has had periodic changes in her visual acuity that resolve spontaneously over weeks and are not related to her typical migraine episodes. She also reports recently quitting her part-time summer job as a dog walker due to frequent loss of balance leading to multiple falls.

What information is suggestive of multiple sclerosis (MS)?

What risk factors does she have for MS?

What additional information or testing would assist in making the diagnosis of MS?

What treatment could be provided to her for the current acute event?

is equivalent with or without a subsequent oral corticosteroid taper.[15]

▶ Outcome Evaluation

- Monitor for symptom improvement
- Educate regarding adverse effects

Disease-Modifying Therapies

Agents indicated for MS are shown in Table 31–1. These DMTs can reduce annualized relapse rates (ARRs) from 30% to 70%.[16–43] Almost all agents are indicated for relapsing forms of MS to include RRMS and active SPMS, and some may be used for the treatment of CIS. **KEY CONCEPT** There is no consensus on the best medication for initial therapy due to the diverse clinical presentation, so treatment must be individualized to each patient. Figure 31–5 suggests a treatment approach.

▶ β-Interferons

Pharmacology and Mechanism of Action β-Interferons decrease T cell activation, thereby decreasing cytokine secretion, which prevents upregulation of adhesion molecules on activated T cells, limits T cells’ access to the CNS, and suppresses matrix metalloproteinases (MMPs), thereby maintaining the integrity of the blood–brain barrier. β-Interferons also decrease microglial proliferation, which helps to preserve myelin, promotes formation of Th2 cells rather than Th1 cells, decreases inflammation, and increases neural growth factor production. All of these mechanisms assist in CNS repair.[16]

Efficacy in Patients with Relapsing-Remitting MS (RRMS) β-Interferons reduce relapses by about one-third versus placebo.[16] CIS treatment with β-interferons resulted in fewer patients converting to CDMS compared with placebo.[16]

Efficacy in Patients with Secondary Progressive MS Who Experience Relapses β-Interferons reduce the risk of relapses but do not slow progression.[17] Treatment is most effective if clinical relapses or MRI inflammatory activity are present.[17]

Adverse Effects Adverse effects are common with β-interferons (Table 31–1). Flu-like symptoms (fever, fatigue, muscle aches, malaise, and chills) begin a few hours postinjection and dissipate within 24 hours.[18] Injection site reactions range from redness to necrosis. There are preventive and treatment measures for these reactions (Table 31–2). Because of conflicting data, it is difficult to determine if β-interferons cause depression; however, providers should monitor and assess for depression because patients with MS do commonly develop depression during the course of the disease (Table 31–3).[18] In a patient who presents with depression, another DMT should be selected to avoid worsening the patient’s condition. Antibodies to beta-interferons can reduce therapeutic effects of these DMT.[16] Neutralizing antibodies develop 6 to 18 months after initiation, can form against any β-interferon, and are cross-reactive.[16,18] There are no standardized recommendations for neutralizing antibody testing.[16]

▶ Glatiramer Acetate

Pharmacology and Mechanism of Action Glatiramer acetate binds to MHC class II, blocking the activation of T cells and activating Th2 cells, preventing inflammation. Activated Th2 cells secrete brain-derived neurotrophic factor, which may be neuroprotective.[20]

Efficacy Glatiramer acetate reduces relapses by 28% compared with placebo but does not prevent sustained progression of RRMS.[21] It is used in CIS to prevent conversion to CDMS.[20]

Adverse Effects Patients report experiencing injection site reactions, including lipoatrophy (see Table 31–2). Icing the injection site pre- and postinjection and/or topical anesthetics mitigate these reactions. A postinjection reaction may yield a systemic effect (flushing, chest tightness, palpitations, anxiety, and shortness of breath). If this occurs, it is self-limited to approximately 15 minutes, close in time to the injection, and recurrence is infrequent. Doses may be reduced by 75% for the week following the reaction, then increased by 25% per week to the full dose.[18]

▶ Teriflunomide

Pharmacology and Mechanism of Action Teriflunomide has a cytostatic effect on rapidly dividing B and T cells by inhibiting *de novo* pyrimidine synthesis and inhibits T-cell activation, entry to the CNS, and secretion of proinflammatory cytokines.[22]

Pharmacokinetics Half-life of oral teriflunomide is 2 weeks, taking about 3 months to achieve steady-state concentrations. An accelerated elimination process with cholestyramine or activated charcoal is available if needed (such as detection of a serious infection or liver injury). Teriflunomide inhibits CYP2C8 and induces CYP1A2 and CYP2C9 enzymes.

Efficacy Teriflunomide reduces relapse rate and progression of disease for relapsing forms of MS.[21] It also prevents CIS from converting to clinically definite MS.[23]

Adverse Effects Teriflunomide is fairly well tolerated, however requires a medication guide due to rare, but serious, adverse effects, including hepatotoxicity, skin reactions, peripheral neuropathy, infections, and teratogenicity.[22]

▶ Fumaric Acid Derivatives

Pharmacology and Mechanism of Action Dimethyl fumarate and diroximel fumarate are prodrugs that undergo metabolism to the same active metabolite, monomethyl fumarate.[24] As of May 2020, monomethyl fumarate is also available and does not require metabolism to the active metabolite. These drugs shift cytokine production from a proinflammatory state to an anti-inflammatory state, prevent macrophage entry into the CNS by an unknown mechanism, and stabilize transcription factor nuclear (erythroid-derived 2)-related factor which may reduce oxidative stress.[25]

Table 31–1

Disease-Modifying Therapies

Drug	Indications	Dose	Route	Frequency	Selected Adverse Effects	Black Box Warnings
Interferons						
Interferon β-1a (Avonex)	CIS RRMS	Initial 7.5 mcg for 1 week, then 15 mcg for 1 week, then 22.5 mg for 1 week, then 30 mcg	IM	Weekly	Flu-like symptoms 61% Anemia 8% Neutralizing antibody formation 2%–18.9%	None
Interferon β-1a (Rebif)	CIS RRMS	22 mcg or 44 mcg Initial 20% increase over 4 weeks to final dose	SQ	Three times/ week	Flu-like symptoms 28% Injection site reactions 66% Leukopenia 22% AST/ALT elevation 17%–27% Neutralizing antibody formation 16.5%–35.4%	None
Interferon β-1b (Betaseron, Extavia)	CIS RRMS	Initial 0.0625 mg, increase over 6 weeks to 0.25 mg	SQ	Every other day	Flu-like symptoms 60%–76% Injection site reactions 50%–85% Asthenia 49% Menstrual disorder 17% Leukopenia 10%–16% AST/ALT elevation 4%–19% Neutralizing antibody formation 27.3%–53.3%	None
Peginterferon β-1a (Plegridy)	RRMS	Initial 63 mcg, 94 mcg day 15, 125 mcg day 29	SQ	Every 2 weeks	Injection site reactions 62% Flu-like symptoms 47% Neutralizing antibody formation < 1%	None
Other Agents						
Glatiramer acetate (Copaxone, Glatopa)	CIS	20 mg	SQ	Daily	Injection site reaction 90% Chest reaction 15% Alopecia 61% Menstrual disorders 61% Urinary tract infection 32% Leukopenia 19% GGT elevation 15% Injection site atrophy 2%	None
	RRMS	40 mg (Copaxone only)	SQ	Three times/ week		
Cladribine (Mavenclad)	Relapsing forms of MS Active SPMS	Course 1: 1.75 mg/kg divided into two cycles given 23–27 days apart Course 2: 1.75 mg/kg divided into two cycles given 23–27 days apart	PO	Course 1: once Course 2: once at least 43 weeks after completing course 1	Upper respiratory tract infection 38% Headache 25% Lymphopenia 24% Nausea 10% Arthralgia/arthritis 7% Insomnia 6%	Malignancies Teratogenicity
Teriflunomide (Aubagio)	Relapsing forms of MS CIS	7 or 14 mg	PO	Daily	AST elevation 12%–14% Alopecia 10%–13% Diarrhea 15%–18% Decreased white blood cell and platelet counts 10%–15%	Hepatotoxicity Teratogenicity
Fumarates						
Dimethyl fumarate (Tecfidera)	Relapsing forms of MS CIS	Initial 120 mg for 1 week, then 240 mg	PO	Twice daily	Flushing 30% Gastrointestinal effects 25% Leucopenia/lymphopenia 4%–10% Influenza viral infections 13% Diarrhea 12% Cough 10% Bradycardia 4%	None
Diroximel fumarate (Vumerity)	Relapsing forms of MS CIS	Initial 231 mg for 1 week, then 462 mg	PO	Twice daily	Flushing 40% Gastrointestinal effects 18% Pruritis 8% Rash 8% Erythema 5% AST elevation 4%	None

(*Continued*)

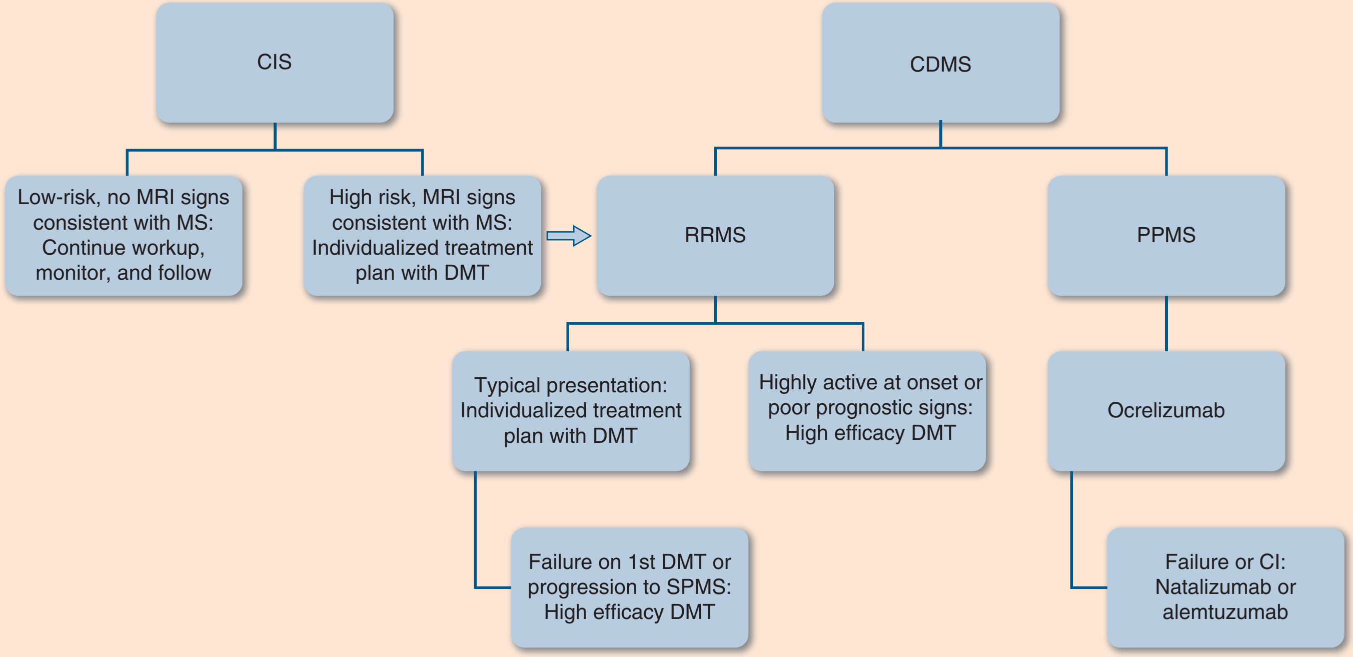
Table 31–1

Disease-Modifying Therapies (*Continued*)

Drug	Indications	Dose	Route	Frequency	Selected Adverse Effects	Black Box Warnings
Monomethyl fumarate (Bafiertam)	Relapsing forms of MS CIS Active SPMS	Initial 95 mg twice daily for 1 week, then 190 mg twice daily	PO	Twice daily	Flushing 40% Abdominal pain 18% Diarrhea 14% Nausea 12% Infection 60% Rash 8% Erythema 5% AST elevation 4%	None
Sphingosine-1-Phosphate Receptor Modulators						
Fingolimod (Gilenya)	Relapsing forms of MS	0.5 mg	PO	Daily	ALT/GGT/AST elevations 15% Hypertension 8% Lymphopenia 7%	None
Siponimod (Mayzent)	Relapsing forms of MS CIS Active SPMS	Specific titration schedules and maintenance doses are recommended depending on CYP2C9 genotype	PO	Daily	ALT/AST elevation 11% Peripheral edema 8% Nausea 5% Dizziness 7% Diarrhea 6% Bradycardia 6%	None
Ozanimod (Zeposia)	Relapsing forms of MS Active SPMS CIS	Days 1–4: 0.23 mg Days 5–7: 0.46 mg Maintenance: 0.92 mg	PO	Daily	Upper respiratory tract infection 26% ALT/AST elevation 10% Hypertension 4%	None
Anti-CD20 Monoclonal Antibodies						
Ocrelizumab[a] (Ocrevus)	Relapsing forms of MS PPMS	Course 1: 300 mg Other courses: 600 mg	IV	Course 1: once, then once 2 weeks later Other courses: every 6 months	Infection 58%–70% Infusion reactions 34%–40%	None
Ofatumumab (Kesimpta)	Relapsing forms of MS	20 mg	SQ	Initial once weekly for 3 doses (weeks 0, 1, and 2) Maintenance once monthly starting at week 4	Infections 52% Systemic injection reaction 21% Local injection reaction 11% Headache 13% Urinary tract infection 10% Upper respiratory tract infection 39%	Hepatitis B reactivation Progressive multifocal leukoencephalopathy Immunoglobulin reduction
Other Agents						
Alemtuzumab[a] (Lemtrada)	RRMS	Course 1: 12 mg/day Course 2: 12 mg/day	IV	Course 1: Daily for 5 days Course 2: Daily for 3 days, 12 months after course 1	Infusion reaction 92% Infections 71% Thyroid disorders 34% Diarrhea 12% Blood in urine 8% Dyspnea 8%	Autoimmunity Infusion reactions Malignancies
Mitoxantrone (Novantrone)	SPMS PRMS RRMS	12 mg/m^2 up to 140 mg/m^2 (maximum lifetime dose)	IV	Infuse over 30 minutes every 3 months	Nausea 76% Arrhythmia 3%–18% Cardiotoxicity 2.7% Alopecia 61% Menstrual disorders 61% Urinary tract infection 32% Leukopenia 19% GGT elevation 15%	Bone marrow suppression Cardiotoxicity Secondary acute myelogenous leukemia
Natalizumab[a] (Tysabri)	Relapsing forms of MS	300 mg	IV	Every 4 weeks	Headache 38% Fatigue 27% Arthralgia 19% Urinary tract infection 20%	Progressive multifocal leukoencephalopathy

[a] Considered highly efficacious agents.

Data from References [18,19,26,27,30,33,37,49].


CIS
CDMS
Low-risk, no MRI signs consistent with MS: Continue workup, monitor, and follow
High risk, MRI signs consistent with MS: Individualized treatment plan with DMT
RRMS
PPMS
Typical presentation: Individualized treatment plan with DMT
Highly active at onset or poor prognostic signs: High efficacy DMT
Ocrelizumab
Failure on 1st DMT or progression to SPMS: High efficacy DMT
Failure or CI: Natalizumab or alemtuzumab

Abbreviations: CIS=clinically isolated syndrome; CDMS=clinically definite multiple sclerosis; MRI=magnetic resonance imaging; MS=multiple sclerosis; DMT=disease modifying therapy; RRMS=relapsing-remitting multiple sclerosis; SPMS=secondary progressive multiple sclerosis; PPMS=primary progressive multiple sclerosis; CI=contraindication

Definitions:

- Individualized treatment plan with DMT=patient factors such as age, gender, comorbidities, lifestyle, activity level of disease, preference on administration method, safety parameters, presence of JC virus antibody and insurance coverage should all be taken into consideration to determine the best therapeutic option for each individual patient when starting DMT therapy.
- Highly active disease=onset with significant disabling symptoms, poor recovery from relapses, recurrent or breakthrough disease over short period of time, significant MRI findings, or rapid progression to disability.
- High efficacy DMTs=monoclonal antibodies (natalizumab, ocrelizumab, alemtuzumab), fingolimod and cladribine.
- Poor prognostic signs=age above 40 years, male gender, African American, motor/sphincter/brainstem/cerebellar symptoms, MRI lesions on brainstem or spinal cord, 2 or more relapses in the first 2 years of onset with significant disability sustained following relapses.

FIGURE 31–5. Treatment algorithm for CIS and MS.[38] A definition of highly active MS has been proposed as follows: two or more relapses in the preceding year and two or more gadolinium-enhancing lesions on brain MRI scans or a significant T2 lesion burden.[39] There can also be poor recovery between relapses, rapid progression to disability, certain patient characteristics (age≥ 40, male gender, African American, lesions on brain stem and spinal cord), significant recurrent or breakthrough disease in a short-time period, and onset of disease accompanied with disability.[9]

Efficacy Dimethyl fumarate reduced relapses approximately 50% compared to placebo. It slowed RRMS progression in some studies.[25] Data from pharmacokinetic studies comparing dimethyl fumarate and diroximel fumarate were used to confirm the similar efficacy of both drugs.[26] The efficacy of monomethyl fumarate was based on bioavailability studies in healthy patients, which compared dimethyl fumarate to monomethyl fumarate.[27]

Adverse Effects Dimethyl fumarate causes a transient, dose-dependent flushing sometimes with itching that is likely due to histamine release. The incidence of this reaction decreases after the first month and may be improved by slower dose titration, administration with food, and/or H2-blocking antihistamines.[25] Gastrointestinal adverse effects may be lessened with a slow dose increase and administration with food but is the main reason for discontinuation in patients taking dimethyl fumarate.[25] Diroximel fumarate and monomethyl fumarate had lower incidences of gastrointestinal adverse effects compared to dimethyl fumarate.[27,28]

▶ *Sphingosine 1-Phosphate Receptor Modulators*

Pharmacology and Mechanism of Action Fingolimod, siponimod, and ozanimod are sphingosine 1-phosphate (S1P) receptor modulators. They retain T cells in lymphoid tissues, deplete peripheral blood and CNS lymphocytes, and reduce inflammatory cytokines.[24] The specific receptor subtypes affected by each agent differentiates their adverse effect profiles. Fingolimod modulates S1P1, S1P3, S1P4, and S1P5 and siponimod and ozanimod offer more selectivity by modulating S1P1 and S1P5.[29–31]

Pharmacokinetics Fingolimod has a half-life of 8 to 9 days (steady-state concentrations achieved in 1–2 months).[29] Siponimod's shorter half-life of 30 hours results in steady-state concentrations within 6 to 7 days.[32] Ozanimod has an active metabolite that extends its half-life to approximately 11 days.[24]

Efficacy Treatment with fingolimod reduced the ARR to 0.18 compared with 0.40 for placebo. It also slowed RRMS progression.[29] Siponimod reduced the number of active lesions on MRI scans and reduced the ARR compared to placebo at 24 months, with maximal improvement in outcomes occurring in patients receiving higher doses.[32] In phase 3 clinical trials, ozanimod reduced ARR and number of active lesions when compared with interferon β.[31]

Adverse Effects S1P receptor modulators target circulating lymphocytes, leading to an increased risk of infections and

Table 31–2

β-Interferon Adverse Effects Prevention or Treatment Strategies

Flu-Like Symptoms	Injection Site Reaction
Inject dose in the evening	Bring medication to room temperature
Begin at 1/4 dose for 2 weeks of treatment, then increase by 25% every 2 weeks to full dose	Ice injection site before and after injection
	Rotate injection sites
Use ibuprofen 200 mg or acetaminophen 325–650 mg before and between 6 and 12 hours after injection	Inject in buttocks or abdomen
	Use an autoinjection device
	If severe, use hydrocortisone 1% cream
	If necrotic, temporarily discontinue; consult dermatologist; do not use topical corticosteroids

Table 31–3

Monitoring Disease-Modifying Therapies

Therapy	Tests	Frequency
All therapies	EDSS, MSFC, neurologic examination	Baseline, every 3 months for 2 years; then every 6 months
β-Interferons	CBC with differential, bilirubin, electrolytes, AST, ALT, GGT, alkaline phosphatase, depression/suicidal ideation	Baseline, 1, 3, and 6 months; then every 3 months
	Thyroid function tests	Baseline and every 6 months in patients with a history of thyroid dysfunction
Cladribine	Hepatitis B and C screening, tuberculosis screening, pregnancy testing, AST, ALT, alkaline phosphatase, and total bilirubin	Baseline
	CBC	Baseline and prior to each infusion; at 2 and 6 months after start of treatment course; then as needed
Teriflunomide	CBC, screen for tuberculosis, pregnancy testing	Baseline
	ALT, AST, bilirubin	Baseline and monthly for first 6 months
	Blood pressure	Baseline; then periodically
Fumaric Acid Derivatives	CBC, ALT, AST, alkaline phosphatase, bilirubin, CYP2C9 genotype (siponimod), first-dose observation	Baseline and every 6 months
S1P Receptor Modulators	Varicella zoster immunity evaluation and/or vaccination and FEV_1, pregnancy test	Baseline
	CBC, ALT, AST, bilirubin	Baseline and every 6 months
	Pulse and blood pressure	Baseline; observe in clinical area for 6 hours after initial dose with hourly monitoring
	Ophthalmology evaluation	Baseline; 3–4 months; then as needed
	Dermatologic evaluation	Baseline; then as needed
	Electrocardiogram	Baseline and 6 hours after initial dose
Natalizumab	HIV, CBC, AST, ALT, MRI	Baseline; repeat MRI at 6 months; then yearly
	MRI, CSF JC virus	Periodically and at the onset of new neurologic symptoms
	Anti-JC virus antibody index	Baseline and every 6 months
Ocrelizumab	Hepatitis B screening	Baseline
	Infection assessment	Prior to every infusion
Ofatumumab	Hepatitis B screening, CBC, serum creatinine, serum immunoglobulins, MRI, signs/symptoms of PML	Baseline and every 6 months or as clinically necessary
Alemtuzumab	Thyroid function	Baseline, every 3 months until 48 months after last infusion
	CBC with differential, serum creatinine, urinalysis with cell counts	Baseline, monthly until 48 months after last infusion
	Varicella zoster immunity evaluation and/or vaccination, tuberculosis screening, hepatitis B and C screening	Baseline
	Vital signs	Baseline, during, and 2 hours after infusion
	Skin examination	Baseline and yearly
Mitoxantrone	CBC, bilirubin, AST, ALT, alkaline phosphatase, pregnancy test	Before each infusion
	Echocardiogram/MUGA scan	Baseline; prior to each infusion, and yearly after stopping mitoxantrone

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; FEV_1, forced expiratory volume in 1 second; GGT, gamma-glutamyl transferase; HIV, human immunodeficiency virus; JC, John Cunningham; MRI, magnetic resonance imaging scan; MSFC, Multiple Sclerosis Functional Composite; MUGA, multiple-gated acquisition scan; S1P, sphingosine 1-phosphate.

Data from References [16,18,20,21,22,25,26,27,29,30,31,33,35,43].

malignancies.[24] Modulation of S1P receptors can cause first-dose bradycardia, although the risk is lower with siponimod and ozanimod because this effect is related to S1P3 and S1P4 receptors located on cardiac tissue. Other adverse effects associated with these drugs include macular edema, hypertension, and reduced forced vital capacity.[29] Use of S1P receptor modulators is contraindicated in patients with myocardial infarctions, unstable angina, stroke, transient ischemic attacks, or some types of congestive heart failure within the last 6 months or in patients with many types of atrioventricular block, prolonged QT interval, or who are taking class Ia or III antiarrhythmic medicines.[29] Siponimod is also contraindicated in patients with a CYP2C9*3/*3 genotype.[30,32] Ozanimod should not be used in individuals with severe sleep apnea or those taking monoamine oxidase inhibitors.[31] Baseline and first-dose monitoring is required (see Table 31–3); monitoring must be repeated if therapy is interrupted.[29] All of these agents require a medication guide when dispensed due to the risk of infection and bradycardia.

▶ *Cladribine*

Pharmacology and Mechanism of Action Cladribine is a deoxyadenosine analog. It reduces circulating lymphocytes by inhibiting DNA synthesis and promoting cell death.[33,34] Maximal lymphocyte reduction occurs approximately 2 to 3 months after each treatment cycle and is dose-dependent.[34]

Efficacy Two courses of oral cladribine lowered the ARR by 58% and prolonged the time to first relapse compared to placebo.[34] Maximum lifetime cumulative dosing is 3.5 mg/kg divided into two treatment courses (1.75 mg/kg per treatment course).

Adverse Effects Due to its safety profile, cladribine requires a medication guide and is recommended as a second-line treatment option and is not recommended for treatment of patients with CIS. Cladribine can increase the risk of malignancy and upper respiratory tract infections, and frequent complete blood count (CBC) monitoring is recommended before, during, and after treatment.[33,34] The most common adverse reactions include lymphopenia, leukopenia, alopecia, and viral upper respiratory tract infection.[34] Prophylaxis for herpes infection should be initiated in patients with lymphocyte counts less than 200 cells/microliter (0.2×10^9/L).[34] Cladribine is contraindicated in pregnant, breastfeeding, and immunosuppressed patients.

▶ *Natalizumab*

Pharmacology and Mechanism of Action Natalizumab is a α_4-integrin antagonist. It binds to $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins, preventing lymphocyte migration into the CNS and inflammation, and inhibits binding of α_4-positive leukocytes to fibronectin and osteopontin, decreasing the activation of leukocytes within the CNS.[35]

Efficacy Treatment with natalizumab reduced relapses in RRMS by 68% at 1 year and disability by 42% at 2 years versus placebo.[35] Natalizumab is considered to be a highly efficacious DMT compared to previously discussed DMTs.

Adverse Effects Hypersensitivity reactions (itching, dizziness, fever, rash, hypotension, dyspnea, chest pain, and anaphylaxis) may occur within 2 hours of administration and requires treatment discontinuation. A separate infusion reaction (headache, dizziness, fatigue, nausea, sweats, and rigors) may occur within 2 hours of dosing.[18] Histamine 1 and 2 receptor blockers prevent these symptoms, and discontinuation is not required. A serious, but rare, adverse effect is progressive multifocal leukoencephalopathy (PML). PML, caused by the John Cunningham (JC) polyomavirus virus, is rapidly progressive and often results in death or permanent disability. Though most associated with natalizumab, PML has been reported in patients treated with dimethyl fumarate, fingolimod, and alemtuzumab.[18] If a clinician decides to treat with any of these agents that carry a risk of PML, there are a few specific recommendations regarding monitoring parameters. Testing for JC virus before initiating therapy to determine serostatus and ongoing monitoring for seroconversion is recommended since JC virus–positive patients have a higher risk of developing PML than JC virus–negative patients. Carefully assess for immune compromise in patients previously treated with immunosuppression, radiation therapy, or chemotherapy as this also increases the risk of developing PML. Other recommendations include using these DMTs as monotherapy (never in combination) and carefully monitor patients for any signs or symptoms of the development of PML and JC virus antibodies.[18,35] Vigilance is paramount because PML can mimic MS symptoms.[35] **KEY CONCEPT** These concerns lead to the recommendation that natalizumab be reserved for patients with a highly active disease course who have failed other therapies and has an accompanying Risk Evaluation and Mitigation Strategy (REMS) known as the TOUCH program. Antinatalizumab antibodies develop in 9% to 12% of patients. If patients have antibodies 6 months after the start of therapy, relapse rates, disability, and hypersensitivity reaction risk increase.[35]

▶ *Alemtuzumab*

Pharmacology and Mechanism of Action Alemtuzumab is a monoclonal antibody that eliminates circulating B and T cells. Repopulation of these cells takes 8 to 35 months.[36]

Efficacy Treatment reduced relapse rates compared to interferon β with 77% of patients relapse free for 2 years.[36] Similar to natalizumab, alemtuzumab is also considered a DMT with higher efficacy.

Adverse Effects Infusion-associated reactions (headache, rash, pyrexia, nausea, itching, and fatigue) occur in more than 90% of patients, requiring pretreatment with methylprednisolone and often antihistamines and antipyretics.[37] Acyclovir cotreatment is required due to the risk of herpesvirus infections. Secondary autoimmune diseases can also develop as well as thyroid disorders.[36] Because of these safety concerns, alemtuzumab has a REMS program and is generally reserved for patients who have failed two therapies. Neutralizing antibodies are present in up to 94% of patients but do not seem to decrease efficacy.

▶ *Anti-CD20 Monoclonal Antibodies*

Pharmacology and Mechanism of Action Ocrelizumab, rituximab, and ofatumumab are monoclonal antibodies that specifically target and deplete B cells.[38] Ocrelizumab is the only drug that is FDA-approved for the treatment of relapsing or primary-progressive MS (PPMS); rituximab is commonly used off-label for MS and ofatumumab is approved for relapsing forms of MS.

Efficacy in Patients with RRMS Rituximab, ocrelizumab, and ofatumumab demonstrated significantly reduced ARR and disease progression in patients compared to placebo.[39–42]

Efficacy in Patients with PPMS Fewer patients had confirmed disability progression when treated with ocrelizumab compared to placebo.[39] Ocrelizumab is the only drug that is FDA-approved for the treatment of PPMS.[39–41] Studies evaluating rituximab did not show clinical benefit in patients with PPMS.

Adverse Effects Infusion reactions (pruritus, rash, erythema, bronchospasm, dyspnea, flushing, hypotension, pyrexia, headache, nausea, and tachycardia) can occur after administration of these medications.[40,41] Premedication with corticosteroids and antihistamines is required, and antipyretics considered before each infusion. Ocrelizumab and ofatumumab are contraindicated in patients with active hepatitis B infections.[41,42] Ocrelizumab has had few cases of PML associated with use but attributed to prior DMT use with higher risk, such as natalizumab.

▸ *Mitoxantrone*

Pharmacology and Mechanism of Action Mitoxantrone is an anthracenedione antineoplastic. It causes apoptosis in T cells and APCs, preventing initial T-cell activation; inhibits DNA and RNA synthesis, decreasing proliferation of T cells, B cells, and macrophages; decreases cytokine release, preventing inflammation; and inhibits macrophages, preventing myelin degradation.[43]

Efficacy Mitoxantrone reduces the relapse rate and attack-related MRI outcome measures and MS progression.[43] **KEY CONCEPT** Because of its potential for significant toxicities, mitoxantrone is reserved for patients with a highly active disease course who have failed in most other therapies.

Adverse Effects Bluish discoloration of the sclera and urine lasts 24 hours or more postinfusion.[18] Amenorrhea may be permanent and lead to infertility.[43] Cardiotoxicity is a serious adverse effect. Mitoxantrone is contraindicated in patients with cardiomyopathy, even if asymptomatic. Cyclooxygenase-2 inhibitors potentially worsen cardiac toxicity and should be avoided.[43] Maximum lifetime dose of mitoxantrone is 140 mg/m^2.

▸ *Issues with Self-Injected Disease-Modifying Therapies*

Adherence **KEY CONCEPT** Adherence to injectable medications is a significant problem, with 22% to 59% discontinuation. Providing realistic therapy expectations, higher educational levels and better patient injection techniques improve adherence. However, depression and cognitive problems lower adherence of β-interferon DMTs and may warrant a switch to another DMT.[46]

Patient Education Refer to Table 31–4 for patient self-injection education.

Table 31–4

Self-Injection Patient Education

Keep supplies together and out of reach of children/pets
Allow medication to warm to room temperature
Wash hands
Choose injection site, rotating among sites
Ice area (≤ 15 minutes) prior to injection, if desired
Clean site with alcohol or soap/water
Administer injection
Ice site (≤ 15 minutes) after injection, if desired

▸ *Other Therapy Considerations*

Pregnancy Because MS affects women of childbearing age, the teratogenicity potential of many DMTs can be concerning for patients and healthcare practitioners alike. Although none of the DMTs are specifically recommended for use during pregnancy, pregnancy registry analysis demonstrates minimal adverse outcomes with interferon β, glatiramer acetate, and natalizumab (first two trimesters only).[47] S1P receptors are important in fetal formation; thus, these medications should be discontinued for at least 2 months before conception. Mitoxantrone, cladribine, and teriflunomide are teratogenic and therefore contraindicated during pregnancy. Teriflunomide is contraindicated for men who have sexual intercourse with women who may become pregnant.[47] Because of the long half-life of teriflunomide, the accelerated elimination process is recommended for women who wish to become pregnant.[47] The risks and benefits of continuing a DMT throughout pregnancy should be weighed carefully. Pregnancy is considered to have a protective effect for the mother and may lower the risk of relapses during this time. If a patient is still at high risk of relapsing, one of the DMTs discussed above may be considered to continue throughout pregnancy. During the postnatal stage, the risk will return for mother, and the DMT should be reinitiated.

Vaccinations In general, patients taking DMT should avoid receiving live or live-attenuated virus vaccines.[48] Vaccines may be

Patient Encounter, Part 2

PMH: She has had periodic changes in her visual acuity that resolve spontaneously over weeks and previously experienced an acute episode of decreased sensation and tingling in both of her hands requiring corticosteroids. She also reports recently quitting her part-time job as a dog walker due to frequent loss of balance leading to multiple falls.

FH: Mother with trigeminal neuralgia; father alive and well

SH: Elementary school teacher. Married and actively trying to have children. She smokes one pack/day. She does not drink alcohol or use illicit drugs.

Allergies: Shellfish

Meds: None

ROS: (–) HA, SOB, chest pain, cough

PE:

VS: 122/76, P 76, RR 20, T 36°C (96.8°F)

Skin: Warm, dry

HEENT: Right pupillary response to light is sluggish, decreased visual acuity right eye

CV: RRR, normal S1 and S2, no m/r/g

Chest: CTA

Abd: Soft, NT/ND

Neuro: A & O × 3; CN II-XII intact

Motor: Paresthesia to touch and decreased pin sensation in bilateral upper extremities. Tandem gait mildly unstable

Labs: WNL

Imaging: T2-weighted MRI shows two enhancing T2-weighted lesions in left cortex and a nonenhancing T2-weighted lesion on the right optic nerve

Given this additional information, what is your assessment of this patient's condition?

Identify your treatment goals for this patient.

What pharmacologic alternatives are available for this patient?

Table 31–5

Pharmacologic and Nonpharmacologic Fatigue Treatments

Nonpharmacologic	Pharmacologic	Renal Dosing
Appropriate rest-to-activity ratio Use assistive devices to conserve energy Environmental modifications to make activities efficient	*First-line therapy:* Amantadine 100 mg orally every morning and early afternoon	CrCl 30–50 mL/min (0.50–0.83 mL/s): 100 mg/day CrCl 15–29 mL/min (0.25–0.49 mL/s): 100 mg every other day CrCl < 15 mL/min (0.25 mL/s): 200 mg every 7 days
Cooling strategies to avoid fatigue caused by elevations in core body temperature Regular aerobic exercise	*Second-line therapy:* Methylphenidate 10–20 mg every morning and noon	No renal dose adjustment required
Lower extremity muscle resistance training Stress management	*Other options:* Modafinil 100–400 mg every morning	No renal dose adjustment required
	Fluoxetine 10–40 mg every morning	No renal dose adjustment required

CrCl, creatinine clearance.

Data from Reference [52].

less effective while on several disease-modifying therapies so they should be given 6 weeks before therapy starts. Vaccines should be held for 4 to 6 weeks after DMT dose.[48] See Table 31–3 for specific viral monitoring parameters and potential vaccines required prior to initiation with certain DMTs.

▶ *Outcome Evaluation*

- Assess symptom changes periodically (every 3–12 months).
- In β-interferon-treated patients with frequent relapses, test for neutralizing antibodies and consider switching therapy.[49]
- Monitor medication-specific adverse effects (see Tables 31–1 and 31–3).
- Assess adherence and provide continual patient education as needed.
- Assess disability with the Expanded Disability Status Scale[50] or the Multiple Sclerosis Functional Composite Score.[51]

▶ *Symptomatic Therapies*

Symptoms most unique to MS are fatigue, spasticity, impaired ambulation, and pseudobulbar affect. Treatment of other symptoms such as urinary incontinence, pain, depression, cognitive impairment, and sexual dysfunction is addressed elsewhere in this text and does not differ in MS.

Fatigue There are nonpharmacologic and pharmacologic strategies for coping with fatigue (Table 31–5).[50]

Spasticity Spasticity treatment goals are patient specific, and optimizing treatment may require multimodal therapy. For ambulatory patients, reducing spasticity may improve mobility and decrease pain. For bedbound patients, treating spasticity may relieve pain and facilitate care. Physical therapy is a nonpharmacologic treatment for spasticity.[53] **KEY CONCEPT** MS patients must be treated with agents specific for upper motor neuron spasticity (Table 31–6).[53] MS spasticity is classified as focal (one muscle group) or generalized. Botulinum toxin may benefit

Table 31–6

Antispasticity Agents

Place in Therapy	Medication	Mechanism of Action	Dose
First-line	Baclofen	Presynaptic and postsynaptic γ-aminobutyric acid type B receptor agonist	5 mg orally three times daily; increase by 5 mg/dose every 3 days; maximum 80 mg/day *Renal dysfunction:* Dose reduction
	Tizanidine	Centrally acting α_2-receptor agonist	2 mg orally three times daily; increase gradually by 2 mg at each dose every 1–4 days; maximum 36 mg/day *Hepatic and renal dysfunction:* Dose reduction
Second-line	Dantrolene	Direct inhibitor of muscle contraction by decreasing the release of calcium from skeletal muscle sarcoplasmic reticulum	25 mg orally daily; increase to 25 mg three to four times daily after 7 days; then increase by 25 mg every 4–7 days; maximum 400 mg/day
	Diazepam	γ-aminobutyric acid agonist	2–10 mg orally three to four times daily *Cirrhosis:* Reduce dose by 50%
	Nabiximols	CB_1 and CB_2 receptor agonist	Up to 12 sprays (2.7 mg delta-9-tetrahydrocannabinol and 2.5 mg cannabidiol) onto oromucosal surface in 24-hour period
Third-line	Intrathecal baclofen	Presynaptic and postsynaptic γ-aminobutyric acid type B receptor agonist	Titrated individually; usual range: 62–749 mcg/day
Focal spasticity	Botulinum toxin	Prevents release of acetylcholine in the neuromuscular junction	Individualized

Data from References [53,54].

Patient Encounter, Part 3

Based on the information available, create a care plan for this patient's MS. The plan should include (a) a statement of the drug-related needs and/or problems, (b) a patient-specific detailed therapeutic plan, and (c) monitoring parameters to assess efficacy and safety.

focal spasticity.[53] Systemic medications are used for generalized spasticity. No conclusion can be reached regarding efficacy superiority of one agent.[53]

Impaired Ambulation Nonpharmacological treatment includes assistive devices, physical therapy, and/or exercise. Extended-release dalfampridine is indicated for improvement in walking speed in patients with MS. This potassium channel blocker prolongs action potentials, improving conduction in demyelinated neurons.[55] Not all patients respond to this agent so response can be assessed at 2 months and discontinued if not showing benefit.[55] Urinary tract infections, insomnia, dizziness, headache, nausea, asthenia, back pain, and balance disorder all occur frequently with dalfampridine.[55] Seizures are an uncommon adverse effect; therefore, patients with seizure disorders should not receive dalfampridine.[55]

Pseudobulbar Affect Ten percent of patients with MS develop pseudobulbar affect, which is characterized by inappropriate laughing or crying and can lead to social isolation.[56] A combination of dextromethorphan and quinidine is a treatment option for pseudobulbar affect. Dextromethorphan prevents the release of excitatory neurotransmitters. Low-dose quinidine blocks first-pass metabolism of dextromethorphan and increases serum concentrations. Episodes decrease 49% with this treatment.[56]

▶ *Outcome Evaluation*

- Assess symptom improvement/recurrence.
- Assess quality of life.
- Monitor adverse effects.
- Monitor adherence.

Patient Care Process

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary vitamins or supplements. Identify allergies to medications and other substances.
- Review the medical history and physical assessment findings.
- Speak with the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and care.

Assess the Information:

- Based on physical examination and review of systems, determine whether patient is experiencing an MS exacerbation currently. Determine the presence of other symptoms such as urinary incontinence.
- Based on the medical history and MRI findings, determine the following. Does the patient meet the 2017 McDonald Criteria for CDMS? How many relapses has the patient experienced? How active is the patient's MS disease course (Figure 31–5)? Is patient currently pregnant or wants to become pregnant in the near future?
- Review available laboratory tests.
- Based on the medication history, has patient been treated with any DMT or immunosuppressants previously? Is patient experiencing adverse effects from current therapy?
- If patient is receiving DMT or symptomatic pharmacotherapy, assess efficacy, safety, and patient adherence. Are there any significant drug interactions?

Develop a Care Plan:

- If patient is having relapses, select corticosteroids.
- Select DMT (Table 31–1, Figure 31–5), considering:
- Route and frequency of administration
- Type of MS (RRMS, SPMS, PPMS) or CIS
- Pregnancy (if female)
- Adverse effect profile
- Cost, including insurance preauthorization needs

Implement the Care Plan:

- Obtain baseline laboratory testing (Table 31–2) and appropriate vaccine screenings.
- Educate patient regarding self-injection, if necessary (see Table 31–4), and adherence.
- Initiate needed symptomatic treatments.
- Address any concerns about MS and management.
- Refer patient to the National MS Society for information, newsletters, and local support groups (www.nationalmssociety.org).
- Instruct patient to contact clinician for any sudden symptom changes indicating relapse or adverse effects.

Follow-up: Monitor and Evaluate:

- Monitor patient for efficacy and adverse effects of DMT and symptomatic therapies (Table 31–2).
- Obtain MRI annually or more frequently as dictated by symptoms and selected therapy.
- Assess adherence to medications.
- Monitor quality of life, disability, and further symptom development.

Abbreviations Introduced in This Chapter

ALT	Alanine aminotransferase
APC	Antigen-presenting cell
ARR	Annualized relapse rate
AST	Aspartate aminotransferase
CBC	Complete blood count
CDMS	Clinically definite multiple sclerosis
CIS	Clinically isolated syndrome
CNS	Central nervous system
CrCl	Creatinine clearance
CSF	Cerebrospinal fluid
DC	Dendrite cell
DMT	Disease-modifying therapy
EDSS	Expanded Disability Status Scale
FEV_1	Forced expiratory volume in 1 second
HIV	Human immunodeficiency virus
IgG	Immunoglobulin G
IL	Interleukin
INF	Interferon
MHC	Major histocompatibility complex
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MUGA	Multiple-gated acquisition
OPC	Oligodendrocyte precursor cell
PML	Progressive multifocal leukoencephalopathy
PPMS	Primary progressive multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
S1P	Sphingosine 1-phosphate
TGF	Transforming growth factor
Th1	T-helper-1 cells
Th2	T-helper-2 cells
TNF	Tumor necrosis factor
VCAM	Vascular cell adhesion molecule
VLA	Very late antigen

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Epilepsy

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the epidemiology and social impact of epilepsy.
2. Define terminology related to epilepsy, including seizure, convulsion, and epilepsy.
3. Describe the basic pathophysiology of seizures and epilepsy.
4. Differentiate and classify seizure types given a description of the clinical presentation of the seizure and electroencephalogram.
5. Identify key therapeutic decision points and therapeutic goals in the treatment of epilepsy.
6. Discuss nonpharmacologic treatments for epilepsy.
7. Recommend an appropriate pharmacotherapeutic regimen with monitoring parameters for the treatment of epilepsy.
8. Devise a plan for switching a patient from one antiepileptic regimen to a different regimen.
9. Manage potential drug interactions with antiseizure medications (ASMs).
10. Determine when and how to discontinue ASM therapy.
11. Educate a patient or caregiver on epilepsy and pharmacotherapy for this disorder.

EPIDEMIOLOGY

Epilepsy is a disorder that afflicts approximately 2 million individuals in the United States, with an age-adjusted prevalence of approximately 4 to 7 cases per 1000 persons.[1] The incidence of epilepsy in the United States is estimated at 35 to 75 cases per 100,000 persons per year.[2,3] About 8% of the US population will experience a **seizure** during their lifetime. New-onset seizures occur most frequently in infants younger than 1 year and in adults after age 55.[2] Worldwide, there are 50 million people with epilepsy and 5 million new cases are diagnosed every year.[4] Nearly 80% of people with epilepsy live in low-income countries.

SOCIAL IMPACT

Epilepsy has a profound impact on a patient's life. Due to restrictions on driving, individuals who have recently had a seizure face major impediments to engage in simple activities.[5] Precisely 50% of patients with epilepsy report cognitive and learning difficulties.[6,7] Underemployment and unemployment are major concerns for individuals with epilepsy, due to limited transportation options, cognitive and learning difficulties, and seizures, resulting in problems paying for health care. Additionally, the social stigma of embarrassment or injury due to seizures in public results in isolation of the patient.[8]

Patients with epilepsy often depend on caregivers to assist with medications, transportation, and ensuring the patient's safety, so they should be informed about treatments and managing seizures.

ETIOLOGY

In approximately 80% of patients with epilepsy, the underlying etiology is unknown.[9] The most common causes of epilepsy are head trauma and stroke. Developmental and identifiable genetic defects cause about 5% of cases. Genetic causes are presumed in up to 25% of patients but are often unproven. Brain tumors, central nervous system (CNS) infections, and neurodegenerative diseases are other common causes. Human immunodeficiency virus infection and neurocysticercosis infection are also important causes.

Isolated seizures can be caused by stroke, CNS trauma, CNS infections, metabolic disturbances (eg, hyponatremia, hypoglycemia), and hypoxia. Failure to correct these causes may lead to the development of epilepsy. Drugs commonly associated with causing seizures are tramadol, bupropion, theophylline, select antidepressants and antipsychotics, amphetamines, cocaine, carbapenems, lithium, excessive doses of penicillins or cephalosporins, some antineoplastic agents, and sympathomimetics or stimulants. Alcohol intoxication and withdrawal can also cause seizures. Likewise, abrupt withdrawal of ASMs and benzodiazepines can precipitate seizures.

PATHOPHYSIOLOGY

Seizures

Regardless of the underlying etiology, all seizures involve a sudden electrical disturbance of the cerebral cortex. A population of neurons fires rapidly and repetitively for seconds to minutes. Cortical electrical discharges become excessively rapid, rhythmic, and synchronous. This phenomenon is presumably related to an excess of excitatory neurotransmitter action, a failure of inhibitory neurotransmitter action, or a combination of the two. In individual patients, it is usually impossible to identify which neurochemical factors are responsible.

Neurotransmitters

The primary excitatory neurotransmitter is glutamate.[10] When glutamate is released from a presynaptic neuron, it attaches to postsynaptic receptors. The result is the opening of membrane channels allowing sodium or calcium to flow into the neuron, depolarizing it, and transmitting an excitatory signal.[11] Many ASMs (eg, phenytoin, carbamazepine, and lamotrigine) work by blocking the release of glutamate or blocking sodium or calcium channels.[12] At usual doses, these drugs only halt the excessive rapid neuronal firing characteristic of seizures and do not affect normal brain function.

The primary inhibitory neurotransmitter is ***γ-aminobutyric acid*** (GABA). It attaches to neuronal membranes and opens chloride channels. Chloride flow into the neuron causes hyperpolarization and less excitability. This mechanism is probably critical for suppressing seizure activity. Barbiturates and benzodiazepines primarily enhance the action of GABA.

Cortical function is modulated by many other neurotransmitters, but their role in epilepsy is poorly understood.

Neuronal Mechanisms

Seizures originate in a group of neurons with abnormal electrical behavior, presumably due to an imbalance of neurotransmitter function.[12] In individual neurons, firing is excessively prolonged and repetitive. Instead of firing a single action potential, these neurons stay depolarized too long, firing many action potentials. This long, abnormal depolarization is called a paroxysmal depolarizing shift (PDS).

Excessive electrical discharges can spread to adjacent neurons or distant ones connected by fiber tracts.[13] The seizure spreads to other areas by recruiting neurons into uncontrolled firing patterns. Recruited neurons may be normal but are diverted from their normal functioning to participate in the excessive discharges, forming abnormal neuronal networks. The area of spread determines the clinical manifestations of the seizure.

Nearly all seizures stop spontaneously, because inhibitory mechanisms overcome abnormal excitation.

Epilepsy

Epilepsy is a disease where individuals have at least two unprovoked seizures more than 24 hours apart, one unprovoked seizure with at least a 60% probability of another seizure in the next 10 years, or diagnosis of an epilepsy syndrome.[14] Practically, this implies a permanent change in cortical function, rendering neurons more likely to participate in a seizure discharge, epileptogenesis.

Epilepsy may develop days, months, or years after a brain insult. A small group of abnormal neurons causes adjacent or connected normal neurons to gradually become abnormal. When a network of abnormal neurons becomes sufficiently large, it causes an excessive firing pattern for at least several seconds: a seizure.

If the change in cortical electrical characteristics is permanent, why do seizures not occur all the time? The occurrence of an individual seizure depends on an interplay of environmental and internal brain factors that intermittently results in loss of the normal mechanisms that control abnormal neuronal firing. It is impossible to determine what triggers a specific seizure.

Epilepsy may remain stable, decrease in severity, or worsen over time. Repeated seizures may cause further damage to the cortex and loss of neurons. Reorganization of connections between groups of neurons may strengthen excitatory connections and weaken inhibitory connections.

Epilepsy is associated with an increased mortality rate, from injuries with seizures or sudden death.[15] Early control of epileptic seizures may reduce permanent changes in brain function, although this hypothesis is unproven.

Genetic Factors

Patients with seizures may be concerned that their children or other family members will inherit epilepsy. Patients with acquired causes of seizures, such as head trauma or stroke, will not transmit epilepsy. Most patients with inherited epilepsy have generalized-onset epilepsy and develop seizures during childhood.[16,17] Complex inheritance patterns are usually seen, indicating the likely involvement of several abnormal genes or other factors for seizures to occur in offspring. Most patients can be reassured that their children and siblings are unlikely to develop epilepsy.

SEIZURE CLASSIFICATION AND PRESENTATION

General Principles

Careful diagnosis and identification of seizure types is essential to proper treatment of epilepsy. The International League Against Epilepsy (ILAE) established the classification of seizures (Table 32–1) that integrates the concept of onset of seizures with their clinical presentation.[18] Classification of epileptic seizures emphasizes electroencephalographic (EEG) findings combined with the clinical symptoms of the seizure events. Clinical presentation of seizures varies widely depending on the region and the amount of brain involved in the seizure.

Generalized Seizures

If the entire cerebral cortex is involved in the seizure from the onset, the seizure is classified as a **generalized seizure**. There are multiple types of generalized seizures. Two major categories of generalized seizures are motor, seizures that involve involuntary muscle activity, and nonmotor, seizures without involuntary muscle activity. In these seizures, the EEG demonstrates involvement of the entire brain from the onset of the seizure.

Focal Seizures

When the seizure begins in a localized area of the brain, it is defined as a **focal seizure**. There are two main types of focal seizures, with or without loss of consciousness. Focal seizures can be further categorized as motor and nonmotor. The EEG demonstrates that the seizure begins in a small region of the brain. Focal seizures can spread to involve the entire brain.

Unknown-Onset Seizures

Unknown-onset seizures are where the distinction between generalized and focal cannot be made. In these seizures, the EEG is unclear as to the start of the seizure.

Epilepsy Syndromes

Currently, there are no officially recognized epilepsy syndromes. Epilepsy syndromes that are often described in publications

Table 32–1

ILAE 2017 Classification of Seizure Types[17]

Focal Onset[a,b]			
Aware[c] or Impaired Awareness[d]	Generalized Onset[a,f]	Unknown Onset	Unclassified
Motor	**Motor**	**Motor**	
Automatisms	Tonic-clonic	Tonic-clonic	
Atonic	Clonic	Epileptic spasms	
Clonic	Tonic	**Nonmotor**	
Epileptic spasms	Myoclonic	Behavior arrest	
Hyperkinetic	Myoclonic-tonic-clonic		
Myoclonic	Myoclonic-atonic		
Tonic	Atonic		
Nonmotor	Epileptic spasms		
Autonomic	**Nonmotor (absence)[g]**		
Behavior arrest	Typical		
Cognitive	Atypical		
Emotional	Myoclonic		
Sensory	Eyelid myoclonia		
Focal to bilateral tonic-clonic[e]			

[a] The word "onset" is assumed when the seizure type begins with focal, generalized, or absence.

[b] Formerly partial seizures.

[c] Formerly simple partial seizures.

[d] Formerly complex partial seizures.

[e] Do not have a level of awareness specified.

[f] Formerly secondary generalized seizures.

[g] Formerly primary generalized seizures.

[h] Formerly absence seizures.

include Dravet syndrome, juvenile myoclonic epilepsy (JME), Lennox–Gastaut syndrome (LGS), mesial temporal lobe epilepsy (MTLE), severe myoclonic epilepsy of infancy (SMEI), and infantile spasms (West syndrome).

Sudden Unexpected Death in Epilepsy Patients

Sudden unexpected death in epilepsy patients (SUDEP) is a catastrophic event that results in the death of a patient. The precise causes of SUDEP are poorly understood. Abrupt discontinuation of ASMs may result in serious seizures associated with SUDEP. Patients should be told about SUDEP and strongly encouraged to be strictly adherent to their ASM therapy.

DIAGNOSIS

A correct and accurate diagnosis is essential prior to starting pharmacotherapy. KEY CONCEPT A distinction between a single seizure and epilepsy must be made, and other seizure-like disorders (eg, syncope, psychogenic, anxiety attacks, cardiac arrhythmias, hypoglycemia, transient ischemic attacks, tics, and complicated migraine headaches) should be ruled out. Seizures are typically brief spells, lasting less than 5 minutes. However, prolonged seizures lasting greater than or equal to 5 minutes or occurring one after another without recovery in between are status epilepticus, which requires immediate medical attention (Chapter 33).

A proper diagnostic workup of a patient presenting with seizures includes the following elements:

- Complete neurologic examination
- EEG
- Laboratory tests (complete blood count [CBC], complete serum chemistry, which includes liver function tests [LFTs], toxicology screening)
- Neuroimaging (preferably magnetic resonance imaging [MRI])

Many of the tests are done to rule out other causes of seizures (eg, infection, electrolyte imbalance, and overdose), and in most patients will be normal. Often the EEG appears normal between seizures. Sleep deprivation, photic stimulation, prolonged (> 20 minutes) EEG recording, and 24-hour EEG monitoring with video correlation can be done to capture seizure or seizure-like activity on the EEG.

TREATMENT

Desired Outcomes

The goal for any patient with epilepsy is elimination of all seizures without adverse effects from treatment. An effective treatment plan allows the patient to live a normal lifestyle with complete control of seizures. The treatment should enable the patient to drive, perform well in school, hold a reasonable job, and function effectively in the family and community. However, 30% to 50% of patients are not able to fully achieve these outcomes. In these cases, the goal of therapy is to provide a tolerable balance between reduced seizure frequency and/or severity and medication adverse effects, enabling the individual to live a lifestyle as nearly normal as possible.

General Approach to Treatment

Once it is concluded that the patient has epilepsy, the type of seizure must be determined.

Clinical Presentation and Diagnosis of Epilepsy

General

Typically, health care providers are not able to observe a patient's seizures, and for most types of seizures, the patient has no memory of the event. It is important to obtain a careful history from the patient and any individuals who witness the seizures.

Common Descriptions of Seizures

The clinical presentation of seizures varies from patient to patient depending on the portion of brain involved in the seizure. Events tend to be stereotypical for an individual patient.

Patients who experience seizures may complain of paroxysmal spells of:

- Lapses in memory, periods of altered consciousness
- Warnings or auras consisting of various sensations or automatic, uncontrolled movements
- Daydreaming
- Jerks, shoulder shrugs, sudden chills of spine
- Falling out

Associated Symptoms

- Incontinence, usually of urine
- Tongue or cheek biting
- Traumatic injuries, usually associated with falling during a seizure

Diagnosis

Description of events: The patient and any witnesses to the seizures should be carefully interviewed to obtain a full and complete description of typical seizures from start to end, and any behaviors after the seizure has stopped.

Neurologic examination: Usually, the neurologic physical examination is completely normal. Any neurologic deficits identified should be fully investigated, because seizures do not usually cause permanent, detectable neurologic deficits.

Electroencephalogram (EEG): A routine EEG can be helpful if epileptiform discharges are seen. However, the EEG may be normal between seizures, and most routine EEGs are not performed during a seizure. Maneuvers such as sleep deprivation, photic stimulation, hyperventilation, or prolonged monitoring can help expose EEG changes consistent with epilepsy.

Neuroimaging (preferably an MRI of the brain): Imaging of the brain is important to rule out obvious causes of seizures such as stroke or tumors. An MRI scan is also helpful in detecting hippocampal changes associated with focal seizures.

Video EEG monitoring: A procedure consisting of continuous video monitoring of the patient with a simultaneous EEG. Usually a patient is monitored in the hospital for 3 to 5 days. This procedure is used to determine if the patient is truly having seizures, to determine the specific type of seizures the patient is having, and to localize the area of the brain that is the origin of the seizures.

KEY CONCEPT Selection of appropriate pharmacotherapy depends on distinguishing, identifying, and understanding different seizure types. Without an accurate classification of the seizure type, it is possible to select a medication that is ineffective or even harmful to the patient.

KEY CONCEPT Prior to starting pharmacologic therapy, it is essential to determine the risk of having a subsequent seizure. If there is an underlying treatable etiology, such as hyponatremia or a CNS infection, the risks of another seizure and the development of epilepsy are very small. In these cases, the only necessary pharmacotherapy is to correct the underlying problem and possibly use an ASM short term. Risk factors for repeated seizures in patients without an underlying disorder include[19]

- Structural CNS lesion
- Abnormal EEG
- Focal seizure type
- Positive family history
- Postictal motor paralysis

If no risk factors are present, the risk of another seizure is 10% to 15%. However, if two or more risk factors are present, the risk of another seizure is 100%. If the estimated risk is over 60%, the patient has epilepsy by definition. When a patient is diagnosed with epilepsy, pharmacotherapy is usually started (Table 32–2). There are some ASM that are only used in very specific types of epilepsy (Table 32–3). The patient or caregiver should agree with the plan, be willing to take the medication, and be able to monitor seizure frequency and adverse drug effects. **KEY CONCEPT** Mechanisms of action, effectiveness for specific seizure types, common

Table 32–2

Evidence-Based Selection of Antiepileptic Drugs for Initial Monotherapy Treatment of Epilepsy[24–27]

Seizure Type	Drugs
Generalized onset: Motor	Carbamazepine (except myoclonic) Lamotrigine Levetiracetam Oxcarbazepine (except myoclonic) Perampanel Phenobarbital Phenytoin Topiramate Valproate
Generalized onset: Nonmotor (Absence)	Clobazam Clonazepam Ethosuximide (preferred) Lamotrigine Topiramate Valproate Zonisamide
Focal onset: Motor and nonmotor	Carbamazepine Cenobamate Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Phenobarbital Phenytoin Topiramate Valproate

Table 32–3

Specialized Seizure Medications

Indication	Medication
Dravet Syndrome	Cannabidiol Fenfluramine Stiripentol
Tuberous Sclerosis	Cannabidiol Everolimus

adverse effects, and potential drug interactions are key elements in selecting a medication. Other patient factors such as gender, concomitant drugs, age, economic factors, and lifestyle also need to be considered.

Nonpharmacologic Therapy

Nonpharmacologic treatments for epilepsy include surgery, vagal nerve stimulation, deep brain stimulation, and dietary modifications. For some patients, surgery has the greatest probability of eliminating seizures. The most common surgery for epilepsy is temporal lobectomy. When the seizure focus can be localized and it is in a region of the brain that is not too close to critical areas, such as those responsible for speech or muscle control, surgical removal of the focus can result in 80% to 90% of patients becoming seizure free.[20] Other surgical procedures that are less likely to make a patient seizure free include corpus callosotomy and extratemporal lesion removal.

Vagal nerve stimulation is another nonpharmacologic approach to treating all types of seizures.[21] The unit that generates an intermittent electrical current is placed under the skin in the chest. A wire is tunneled under the skin to the left vagus nerve in the neck and delivers a small electrical stimulus to the vagus nerve. This efficacy of this treatment is essentially equivalent to starting a new medication, with fewer than 10% of refractory patients becoming seizure free. Vagal nerve stimulation is usually reserved for patients who do not respond to several drugs and are not surgical candidates. Deep brain stimulation devices are approved for individuals with seizures refractory to other treatments. Some ASM therapy is usually continued in patients with these devices.

Another nonpharmacologic treatment is the ketogenic diet.[22] This diet produces a keto-acidotic state through the elimination of nearly all carbohydrates. The diet consists of high dietary fats (eg, butter, heavy cream, and fatty meats) and low protein with no added sugar. Daily urinalysis for ketones is performed to ensure the patient remains in ketosis. Any inadvertent consumption of sugar results in the diet needing to be reinitiated. Clinicians must be vigilant in maintaining the diet, by determining the sugar or carbohydrate content of medications the patient is taking. This diet is typically used only in children with difficult-to-control seizures. In certain patients, the diet can be extremely effective, resulting in complete seizure control and reduction of ASMs. However, it is difficult to maintain, and palatability of the diet, growth retardation, and hypercholesterolemia are concerns. Less stringent diets, such as a modified Atkins diet, may produce seizure control similar to a rigorous ketogenic diet.

Pharmacologic Therapy

▶ *Special Considerations*

The use of ASMs presents some unique challenges due to their pharmacokinetic and pharmacodynamic properties.

Zero-order Pharmacokinetics Phenytoin metabolism is capacity limited. Small changes in doses result in large changes in serum concentrations. Individual differences in metabolism result in differing relationships between dose and serum concentrations. For routine clinical practice, dosage adjustments for adults with normal protein binding of phenytoin and a steady-state serum concentration can be made using the following plan:

- For serum concentrations less than 7 mcg/mL (mg/L; 28 μmol/L), the total daily dose is increased by 100 mg.
- For serum concentrations of 7 to 12 mcg/mL (mg/L; 28–48 μmol/L), the total daily dose is increased by 50 mg.
- For serum concentrations more than 12 mcg/mL (mg/L; 48 μmol/L), the total daily dose is increased by no more than 30 mg.[23]

Protein Binding Some ASMs, especially phenytoin and valproate, are highly bound to plasma proteins. When interpreting a reported concentration for these drugs, it is important to remember the value represents the total (ie, bound and unbound) concentration in the blood. Because of differences in the metabolism of these drugs, the clinical effects of altered protein binding are different.

For phenytoin and valproate, certain patient groups have decreased protein binding, resulting in an increased unbound percentage of drug. The clinical impact of protein binding changes with valproate is less than with phenytoin. These patient groups include:

- Those with kidney failure
- Those with hypoalbuminemia
- Neonates
- Pregnant women
- Those taking multiple highly protein-bound drugs
- Patients in critical care settings

In patients with suspected changes in protein binding, it is useful to measure unbound phenytoin concentrations.

When valproate protein binding is altered, the risk for severe dose-related adverse effects is less compared with phenytoin. Hepatic enzymes are able to efficiently metabolize the additional unbound portion.

Autoinduction Carbamazepine is a potent inducer of hepatic microsomal enzymes. It increases the rate of metabolism for many other drugs and the rate of its own metabolism. Hepatic enzymes become maximally induced over several weeks, necessitating a small initial dose of carbamazepine that is increased over time to compensate for the enzyme induction (Table 32–4). Most dosage regimens for carbamazepine use a starting dose that is 25% to 30% of the typical maintenance dose of 15 mg/kg/day. The dosage is increased weekly until the target maintenance dose is achieved within 3 to 4 weeks. Titration of the carbamazepine dose reduces the risk for severe dose-related adverse effects.

▶ *Drug Selection and Seizure Type*

The key to selecting effective pharmacotherapy is to base the decision on the seizure type. Several consensus treatment guidelines from the Scottish Intercollegiate Guidelines Network (SIGN), the National Institute for Clinical Excellence (NICE) in the United Kingdom, the American Academy of Neurology (AAN), and ILAE all link seizure type to the selection of pharmacotherapy (Table 32–2).[24-27] Table 32–2 summarizes recommendations from

Patient Encounter 1: New-Onset Seizures

BD is a 21-year-old woman who is brought to the ED following a seizure. Her friends describe the seizure as her falling and shaking all over. By the time emergency medical care arrived, she was groggy but no longer in a seizure.

Her physical examination is completely normal, and no focal neurologic deficits were observed. An MRI was ordered and reported as normal. An EEG shows occasional generalized 3- to 4-Hertz spike-wave activity consistent with generalized seizures.

What additional information is needed to decide about pharmacotherapy?

How should this information be used to make choices concerning ASM therapy?

She remembers several weeks ago that when she woke up in the morning, her muscles ached all over and there was some blood in her mouth and on her pillow.

Is pharmacotherapy indicated?

If it is indicated, what drug should be used and how should it be started?

What adverse effects are important to monitor?

Six months later, she still is having 1 to 2 episodes a month of single-body jerks, but no larger seizures.

What adjustments in pharmacotherapy should be made at this point?

Is it possible for her to discontinue ASM therapy at some time in the future?

these treatment guidelines and US Food and Drug Administration (FDA)-approved indications.

For initial treatment of generalized nonmotor seizures (absence), ethosuximide is preferred but valproate is an alternative. In generalized nonmotor (absence) and generalized motor (myoclonic) seizures, carbamazepine, oxcarbazepine, gabapentin, tiagabine, and pregabalin should be avoided due to association with worsening of these seizure types.

KEY CONCEPT ASM therapy should usually be initiated carefully using a titration schedule to minimize adverse events. Moderate target doses are chosen until the patient's response can be further evaluated in the clinic. If seizures continue, the dose is increased gradually until the patient becomes seizure free or adverse effects appear. For some drugs like lamotrigine, specific titration guidelines are established by the manufacturer.

Treatment of refractory seizures (ie, unresponsive to at least two first-line ASMs) is somewhat different. Combinations of drugs may be useful in patients with difficult-to-control seizures. All ASMs, except ethosuximide, are effective in combination therapy for focal seizures.

▸ Complications of Pharmacotherapy

Adverse effects of ASMs are frequently dose limiting or cause a drug to be discontinued. Two types of adverse effects occur with ASMs: serum concentration-related and idiosyncratic (Table 32–3). Concentration-related adverse effects occur with increasing frequency and severity as the dose or serum concentration of a drug is increased. Common concentration-related adverse effects include sedation, ataxia, and diplopia. Adverse effects should be considered in the selection of ASM. For example, if a patient has a job that requires mental alertness, it is best to choose an ASM that is less likely to cause sedation (eg, lamotrigine, levetiracetam).

Idiosyncratic adverse effects are not dose or concentration related and almost always result in the ASM being discontinued. Typically, these types of reactions occur during the first 6 to 12 months of taking the ASM. Rash is the most common of these. Prior to initiating carbamazepine and oxcarbazepine, genetic testing for human leukocyte antigen (HLA) HLA-B∗1502 and HLA-A∗3101 should be done for at-risk patients. Polymorphisms of these HLA genes are associated with increased risk of severe skin reactions. Likewise, with phenytoin, genetic polymorphisms of HLA-B∗1502 and the CYP 2C9∗3 have been associated with increased risk of severe skin reactions. Severe skin, hepatic, or hematological reactions occur rarely but are potentially life-threatening. The ASM should be discontinued immediately when these reactions occur. Carbamazepine, phenytoin, phenobarbital, valproate, lamotrigine, oxcarbazepine, and felbamate are most likely to cause reactions. There is a possibility of cross-reactivity for these adverse effects, especially for carbamazepine, phenytoin, phenobarbital, and oxcarbazepine.

▸ Chronic Adverse Effects

Because ASMs are administered for long periods of time, adverse effects due to prolonged drug exposure are of concern. Some chronic adverse effects associated with ASMs include peripheral neuropathy, cerebellar atrophy, and weight gain.

Osteoporosis is a major chronic adverse effect of several drugs.[28,29] Carbamazepine, phenytoin, phenobarbital, oxcarbazepine, and valproate decrease bone mineral density after 6 months of treatment. The risk of osteoporosis due to chronic ASM use is comparable to the risk with chronic use of corticosteroids. Patients taking carbamazepine, oxcarbazepine, phenytoin, phenobarbital, or valproate for more than 6 months should take supplemental calcium and vitamin D. Routine monitoring for osteoporosis should be performed every 2 years, and patients should be instructed on ways to protect themselves from fractures.

Psychiatric adverse effects may occur with ASM. All ASM have a warning for suicidality. There does seem to be some differences between seizure medications related to causing depression. Levetiracetam is associated with a greater risk of depression and agitation. Perampanel has a warning for suicidality and homicidality.

Patient Encounter 2: Managing Chronic Adverse Reactions

PL is a 45-year-old man with a long history of seizures. He has taken carbamazepine for 20 years with good control of his seizures. Other than some occasional dizziness, he reports no adverse effects from the carbamazepine.

What chronic adverse effects are important to monitor in this patient?

How should monitoring for these adverse effects be done?

What measures can be taken to prevent these adverse effects?

Table 32–4

Characteristics of Common ASMs

Drug	Mechanism of Action	Dose	Pharmacokinetic Parameters	Usual Serum Concentration Range	Dose-Related Adverse Effects	Idiosyncratic Adverse Effects
Brivaracetam (Briviact)	Modulate synaptic vesicle protein 2A	*Maintenance Dose*: 50–100 mg twice daily	*Half-life*: 9 hours *Apparent Vd*: 0.5 L/kg *Protein binding*: 17.5% *Primary elimination route*: Hepatic	Not established	Ataxia, dizziness, fatigue, somnolence	Angioedema, bronchospasm, suicidal behavior and ideation
Cannabidiol (Epidiolex)	Unknown mechanism, does not work through cannabinoid receptors	*Maintenance Dose:* 10–20 mg/kg/day in two divided doses. Titrate by starting at 5 mg/kg/day in two divided doses and increase to target maintenance dose.	*Half-life:* 56–61 hours *Apparent Vd:* 300–600 L/kg *Protein Binding: > 94%* *Primary elimination route:* hepatic	Not established	Somnolence, fatigue, malaise	Hepatotoxicity, anorexia, pyrexia, vomiting, diarrhea
Carbamazepine (Tegretol and generic, Tegretol XR, generic), Carbatrol, Epitol, Equetro	Fast sodium channel inactivation	*Maintenance dose*: Titrate dosage to target over 3–4 weeks Adults: 800–1200 mg/day in divided doses Children: 20–30 mg/kg/day as a divided dose Intravenous: Indicated for oral replacement therapy at 70% of the total oral maintenance dose divided into four equal doses given every 6 hours	*Half-life*: 10–25 hours with chronic dosing *Apparent Vd*: 0.8–1.9 L/kg *Protein binding*: 67%–81% *Primary elimination route*: Hepatic	4–12 mcg/mL (mg/L; 17–51 µmol/L)	Diplopia, drowsiness, nausea, sedation	Aplastic anemia, hyponatremia, leukopenia, osteoporosis, rash
Cenobamate (Xcopri)	Modulate voltage-gated sodium channels, modulate $GABA_A$ ion channel	*Maintenance dose:* Target dose 200 mg/day; 12.5 mg/day for 2 weeks, 25 mg/day for 2 weeks, 50 mg/day for 2 weeks, 100 mg for 2 weeks, 150 mg for 2 weeks, then 200 mg/day. Titration schedule should not be exceeded	*Half-life:* 50–60 hours *Apparent Vd:* 0.6–0.7 L/kg *Protein binding: 60%* *Primary elimination route:* Hepatic	Not established	Somnolence, fatigue, diplopia	Drug reaction with eosinophilia and systemic symptoms, QT interval shortening
Clobazam (Onfi)	Enhance GABA activity	Weight< 30 kg, start 5 mg/day, titrate to 20 mg/day in divided doses Weight> 30 kg start 10 mg/day in divided doses, titrate to 40 mg/day in divided doses CYP 2C19 poor metabolizers: start 5 mg/day, titrate to 10–20 mg/day, maximum dose 40 mg/day	*Half-life*: 10–50 hours *Apparent Vd*: ~0.9 L/kg *Protein binding*: ~90% *Primary elimination route*: Hepatic; metabolized to active metabolite that is further metabolized by CYP 2C19	Not established	Sedation, somnolence, lethargy, pyrexia, irritability, drooling, aggression	
Clonazepam (Klonopin, generic)	Enhance GABA activity	*Maintenance dose*: Initiate at 0.5 mg one to three times daily, titrate dose to effectiveness, usually 3–5 mg daily in two or three divided doses Pediatric dosing in children < 10 years or < 30 kg: Initiate at 0.01–0.03 mg/kg/day in two to three divided doses, titrate dose to effectiveness	*Half-life*: 30–40 hours *Apparent Vd*:3.2 L/kg *Protein binding*: 47%–80% *Primary elimination route*: Hepatic	Not established	Ataxia, memory impairment, sedation, slowed thinking	

(Continued)

Table 32–4

Characteristics of Common ASMs (*Continued*)

Drug	Mechanism of Action	Dose	Pharmacokinetic Parameters	Usual Serum Concentration Range	Dose-Related Adverse Effects	Idiosyncratic Adverse Effects
Eslicarbazepine (Aptiom)	Fast sodium channel inactivation	*Maintenance dose*: Adults: Initiate at 400 mg daily and titrate in increments of 400–600 mg daily to a maintenance dose of 800–1600 mg daily Pediatrics: Initial, incremental increases, and maintenance dose based on body weight	*Half-life*: 13–20 hours in adults *Apparent Vd*: 0.85–0.9 L/kg *Protein binding*: < 40% *Primary route of elimination*: Renal	Not established	Ataxia, dizziness, diplopia, drowsiness, sedation, nausea, vomiting, hyponatremia	
Ethosuximide (Zarontin, generic)	Modulate calcium channels	*Maintenance dose*: Initiate at 250 mg twice daily and titrate to 500–1000 mg twice daily	*Half-life*: 60 hours *Apparent Vd*: 0.6–0.7 L/kg *Protein binding*: None *Primary elimination route*: Hepatic	40–100 mcg/mL (mg/L; 283–708 µmol/L)	Ataxia, sedation, GI upset	Hepatotoxicity, neutropenia, rash
Everolimus (Afinitor)	Inhibits mammalian target of rapamycin (mTOR) downstream of the PI3K/AKT pathway.	*Maintenance dose: 5 mg/m^2 adjusted to maintain concentrations in target range*	*Half-life: 30 hours* *Apparent Vd: highly variable depending on age* *Protein binding: 74%* *Primary elimination route: Hepatic*	5–15 mg/mL (mcg/L; 5.2-15.7 nmol/L)		Stomatitis, noninfectious pneumonitis, angioedema, myelosuppression, increase infections
Felbamate (Felbatol)	Inhibit glutamate activity	*Maintenance dose*: 1200–3600 mg/day in three or four divided doses	*Half-life*: Monotherapy: 20 hours Concurrent enzyme inducers: 11–16 hours *Apparent Vd*: 0.7–0.8 L/kg *Protein binding*: 25%–35% *Primary elimination route*: Hepatic	Not established	Anxiety, insomnia, nausea	Anorexia, aplastic anemia, headache, hepatotoxicity, weight loss
Fenfluramine (Fintepla)	Mechanism unknown	*Maintenance dose: 0.1 mg/kg twice daily with maximum daily dose of 26 mg without stiripentol; 0.1 mg/kg twice daily with maximum daily dose of 17 mg with stiripentol*	*Half-life:* 20 hours *Apparent Vd:* 11.9 L/kg *Protein Binding:* 50% *Primary elimination route:* Hepatic	Not established	Somnolence, fatigue, lethargy, ataxia, gait disturbance	Pulmonary arterial hypertension, valvular heart disease
Gabapentin (Neurontin, generic)	Modulate calcium channels and enhance GABA activity	*Maintenance dose*: Adults: 900–3600 mg/day in three or four divided doses Pediatrics: Age 3–4 Initial dose 10–15 mg/kg/day, titrate to a maximum of 50 mg/kg/day divided in divided three doses; age 5–11 initial dose 10–15 mg/kg/day, titrate to maximum of 50 mg/kg/day in three divided doses; age > 12 Initial dose 300 mg thrice daily, titrate to a maximum of 360 mg/day divided in three doses Renal dosing: CrCl 30–50 mL/min (0.50–0.84 mL/s) decrease by 25% and give twice daily; CrCl 10–29 mL/min (0.17–0.49 mL/s) decrease dose by 25% and give once daily; CrCl < 10 mL/min (0.17 mL/s) decrease dose 25% and give every other day	*Half-life*: 5–7 hours (proportional to creatinine clearance) *Apparent Vd*: 0.6–0.8 L/kg *Protein binding*: < 10% *Primary elimination route*: Renal	Not established	Drowsiness, sedation	Peripheral edema, weight gain

Lacosamide (Vimpat)	Slow sodium channel inactivation; modulate collapsin response; mediator protein-2	*Maintenance dose*: 200–400 mg/day; start at 100 mg/day in two divided doses and titrate upward according to response	*Half-life*: Approximately 13 hours *Volume of distribution*: 0.6 L/kg *Protein binding*: < 15% *Primary elimination route*: 40% renal 60% hepatic	Not established	Ataxia, dizziness, diplopia, headache, nausea, vomiting	PR interval prolongation. first-degree AV block
Lamotrigine (Lamictal, Lamictal XR, generic)	Fast sodium channel inactivation	*Initial dose*: With valproate 25 mg every other day for 2 weeks, then 25 mg daily for 2 weeks, then 25 mg twice daily for a week, increase by 25 mg/day every week until maintenance dose of 150 mg/day is achieved; without enzyme inhibitor or inducer 25 mg daily for 2 weeks, then 25 mg twice daily for 2 weeks, then increase by 25 mg daily every week maintenance dose of at least 200 mg/day is achieved; with enzyme inducer 25 mg twice daily for 2 weeks, then 50 mg twice daily for 2 weeks, then increase by 100 mg/day every week until maintenance dose of 300–500 mg/day is achieved *Maintenance dose*: 150–800 mg/day in two or three divided doses Pediatric: age 2–12 with valproate 0.15 mg/kg/day for 2 weeks, then 0.3 mg/kg/day for 2 weeks, then increase by 0.3 mg/kg/day every week until maintenance dose of 1–5 mg/kg/day achieved; without inhibitor or inducer 0.3 mg/kg/day for 2 weeks, then 0.6 mg/kg/day for 2 weeks, then increase by 0.6 mg/kg/day weekly until maintenance dose of 4.5–7.5 mg/kg/day achieved; with inducer 0.6 mg/kg/day in two divided doses for 2 weeks, then 1.2 mg/kg/day in two divided doses for 2 weeks, then increase by 1.2 mg/kg/day weekly until maintenance dose of 5–15 mg/kg/day is achieved	*Half-life*: Monotherapy: 24 hours Concurrent enzyme inducers: 12–15 hours Concurrent enzyme inhibitors: 55–60 hours *Apparent Vd*: 1.1 L/kg *Protein binding*: 55% *Primary elimination route*: Hepatic	Not established	Ataxia, drowsiness, headache, insomnia, sedation	Rash, cardiac arrhythmia

(*Continued*)

Table 32–4

Characteristics of Common ASMs (*Continued*)

Drug	Mechanism of Action	Dose	Pharmacokinetic Parameters	Usual Serum Concentration Range	Dose-Related Adverse Effects	Idiosyncratic Adverse Effects
Levetiracetam (Keppra, Keppra XR, generic)	Modulate synaptic vesicle protein 2A	*Adult Maintenance dose*: 1000–3000 mg/day. Start at 1000 mg/day and titrated upward as indicated by response *Pediatric*: 1–6 months 7 mg/kg twice daily titrate by 7 mg/kg twice daily every 2 weeks to maintenance dose of 21 mg/kg twice daily; 6 months to 4 years 10 mg/kg twice daily then increase by 10 mg/kg twice daily every 2 weeks to maintenance dose of 25 mg/kg twice daily; 4–16 years 10 mg/kg twice daily then increase by 30 mg/kg twice daily Renal failure: CrCl 50–80 mL/min (0.84–1.33 mL/s) 500–1000 mg twice daily, CrCl 30–50 mL/min (0.50–0.84 mL/s) 250–750 mg twice daily, CrCl < 30 mL/min (0.50 mL/s) 250–500 mg twice daily, end stage on dialysis 500–1000 mg daily	*Half-life*: 6–8 hours *Apparent Vd*: 0.5–0.7 L/kg *Protein binding*: < 10% *Primary elimination route*: 70% renal 30% hepatic	Not established	Somnolence, dizziness	Depression, agitation, aggressive behavior
Perampanel (Fycompa)	Antagonist of glutamate receptors on postsynaptic neurons	*Maintenance dose*: without CYP3A4 inducers 8–12 mg once daily. Start at 2 mg once daily, increase by 2 mg/day increments to desired response With CYP3A4 inducers Start at 4 mg once daily, increase by 2 mg/day increments to desire response with maximum dose of 12 mg daily	*Half-life*: 105 hours *Apparent Vd*: 0.7–1.5 L/kg *Protein binding*: 95%–96% *Primary elimination route*: Hepatic	Not established	Ataxia, dizziness, drowsiness, somnolence	Suicidal behavior and ideation, agitation, hostility, aggression, hypersensitivity reactions
Oxcarbazepine (Trileptal, generic)	Fast sodium channel inactivation	*Maintenance dose*: 600–1200 mg/day. Start at 300 mg twice daily and titrated upward as indicated by response Pediatric dosing *Maintenance dose*: 20 kg 300–450 mg twice daily; 25–30 kg 450–600 mg twice daily; 35–40 kg 450–750 mg twice daily; 40–50 kg 600–750 mg twice daily; 50–55 kg 600–900 mg twice daily; 60–65 kg 600–1050 mg twice daily Renal failure dosing CrCl < 30 mL/min (0.50 mL/s) starting dose of 150 mg twice daily and titrate at a slower rate to desired effect	*Half-life*: *Parent drug*: Approximately 2 hours *10-monohydroxy metabolite*: Approximately 9 hours *Apparent Vd*: 0.5–0.7 L/kg *Protein binding*: 40% *Primary elimination route*: Hepatic	Not established	Diplopia, dizziness, somnolence	Hyponatremia, 25%–30% cross-sensitivity in patients with hypersensitivity to carbamazepine

Phenobarbital (Luminal, generic) Primidone (Mysoline, generic) gets metabolized to phenobarbital	Fast sodium channel inactivation	*Loading dose*: 10–20 mg/kg as single or divided IV infusion or orally in divided doses over 24–48 hours *Maintenance dose*: Adults: 1–4 mg/kg/day as a single or divided dose Children: 3–6 mg/kg/day as divided dose Neonates: 1–3 mg/kg/day as divided dose	*Half-life*: Adults: 49–120 hours Children: 37–73 hours Neonates: approximately 115 hours *Volume of distribution*: 0.7–1 L/kg *Protein binding*: Approximately 50% *Primary elimination route*: Hepatic	15–40 mcg/mL (mg/L; 65–172 μmol/L)	Ataxia, drowsiness, sedation	Attention deficit, cognitive impairment, hyperactivity, osteoporosis, passive–aggressive behavior
Phenytoin (Dilantin, Phenytek, generic)	Fast sodium channel inactivation	*Loading dose*: Adults: 15–20 mg/kg single IV dose or divided oral dose Infants younger than 3 months: 10–15 mg/kg single IV dose Neonates: 15–20 mg/kg single IV dose *Maintenance dose*: Adults: 5–7 mg/kg/day, as single or divided dose Children: 6–15 mg/kg/day, as divided dose Neonates: 3–8 mg/kg/day, as divided dose	*Half-life*: Follows capacity-limited or Michaelis–Menten pharmacokinetics. Half-life increases as the dose and serum concentration increases. *Volume of distribution*: Adults: 0.7 L/kg Children: 0.8 L/kg Neonates: 1.2 L/kg *Protein binding*: Adults, children: 88%–92% Neonates: 65% *Primary elimination route*: Hepatic	10–20 mcg/mL (mg/L; 40–79 μmol/L) total concentration 1–2 mcg/mL (mg/L; 4–8 μmol/L) unbound concentration	Ataxia, diplopia, drowsiness, sedation, nystagmus	Anemia, gingival hyperplasia, hirsutism, lymphadenopathy, osteoporosis, rash IV ADE: phlebitis, hypotension
Rufinamide (Banzel)	Unknown, may enhance inactivation of sodium channels	*Maintenance dose*: Adults: 3200 mg/day; start at 400–800 mg/day in two divided doses and titrate upward according to response Children: 45 mg/kg/day or 3200 mg/day; start at 10 mg/kg/day in two divided doses and titrate upward according to response	*Half-life*: 6–10 hours *Apparent Vd*: Approximately 0.7 L/kg, varies with dose *Protein binding*: 34% (27% to albumin) *Primary elimination route*: Hepatic	Not established	Dizziness, fatigue, headache, nausea, somnolence, vomiting	
Stiripentol (Diacomit)	Mechanism unknown	*Maintenance dose: 50 mg/kg/day in two to three divided doses*	*Half-life: 4.5–13 hours* *Apparent Vd: 1 L/kg* *Protein binding: 99%* *Primary elimination route: hepatic*	Not established	Somnolence, anorexia, agitation, ataxia, nausea tremor, dysarthria	
Tiagabine (Gabitril, generic)	Enhance GABA activity	*Maintenance dose*: With concomitant hepatic enzyme inducers Initiate with 4 mg/day for 1 week, increase weekly by 4–8 mg/day in two to three divided doses with maximum dose of 56 mg/day Without concomitant hepatic enzyme inducers Initiate with 2–4 mg/day for 1 week, increase weekly by 2–4 mg/day to maintenance dose of 12–22 mg/day in two to three divided doses Pediatric dosing Age > 12 Initiate with 4 mg/day for 1 week, then 4 mg twice daily for 1 week, then titrate by 4–8 mg/day in two to four divided doses with maximum dose of 32 mg/day	*Half-life*: Monotherapy: 7–9 hours Concurrent enzyme inducers: 2.5–4.5 hours *Apparent Vd*: 0.6–0.8 L/kg *Protein binding*: 96% *Primary elimination route*: Hepatic	Not established	Dizziness, somnolence, irritability, slowed thinking	Suicidal ideation

(*Continued*)

Table 32–4

Characteristics of Common ASMs (*Continued*)

Drug	Mechanism of Action	Dose	Pharmacokinetic Parameters	Usual Serum Concentration Range	Dose-Related Adverse Effects	Idiosyncratic Adverse Effects
Topiramate (Topamax, generic) Qudexy, Trokendi XR, Topiragen	Fast sodium channel inactivation, inhibit glutamate activity, enhance GABA activity	*Maintenance dose*: 100–400 mg/day in two or three divided doses. Doses should be started at 25–50 mg/day and gradually titrated upward over 3–6 weeks to avoid excessive adverse effects Pediatric dosing Ages 2–16 Initiate at 5–9 mg/kg/day in two divided doses for 1 week, then titrate by 1–3 mg/kg/day every 1–2 weeks to desired response maximum dose of 400 mg/day	*Half-life*: Monotherapy: 21 hours Concurrent enzyme inducers: 11–16 hours *Apparent Vd*: 0.55–0.8 L/kg *Protein binding*: 13%–17% *Primary elimination route*: 60% renal 40% hepatic	Not established	Ataxia, dizziness, drowsiness, slowed thinking	Acute glaucoma, metabolic acidosis, oligohidrosis, paresthesia, renal calculi, weight loss
Valproic acid/ divalproex sodium (Depakene, Depakote, Depakote ER, Depacon, generic), Stavzor	Fast sodium channel inactivation	*Loading dose*: 20–40 mg/kg *Maintenance dose*: Adults: 15–45 mg/kg/day in two to four divided doses Pediatric dosing: 5–60 mg/kg/day in two to four divided doses Do not administer to children < 2 years of age Doses of extended release products should be 8%–20% higher than immediate release products	*Half-life*: Adults: 8–15 hours Children: 4–15 hours Infants younger than 2 months: 65 hours *Volume of distribution*: 0.1–0.5 L/kg *Protein binding*: 90% (decreases with increasing serum concentrations) *Primary elimination route*: Hepatic	50–100 mcg/mL (mg/L; 346–693 μmol/L) Children may require concentrations up to 150 mcg/mL (mg/L; 1040 μmol/L)	Drowsiness, nausea, sedation, tremor	Hepatotoxicity, osteoporosis, pancreatitis, weight gain, thrombocytopenia, alopecia
Vigabatrin (Sabril)	Inhibits GABA transaminase	*Adults*: Initiate at 1000 mg/day in two divided doses, titrate up to 3000 mg/day *Children*: 1 month–2 years: 50 mg/kg/day in two divided doses *Renal failure*: CrCl 50–80 mL/min (0.84–1.33 mL/s), decrease dose by 25%; CrCl 30–50 mL/min (0.50–0.84 mL/s), decrease dose by 50%; CrCl 10–30 mL/min (0.17–0.50 mL/s), decrease dose by 75%	*Half-life*: 7.5 hours, proportional to creatinine clearance *Volume of distribution*: 1.1 L/kg *Protein binding*: negligible *Primary route of elimination*: Renal	Not established	Convulsion, dizziness, headache, nasopharyngitis, somnolence, weight gain	Vision loss and blindness, suicidality
Zonisamide (Zonegran, generic)	Modulate sodium and calcium channels	*Maintenance dose*: 100–600 mg/day; start at 100 mg/day and titrated upward as indicated by response	*Half-life*: Approximately 63 hours *Apparent Vd*: 1.45 L/kg *Protein binding*: 40% *Primary elimination route*: Hepatic	Not established	Dizziness, somnolence	Metabolic acidosis, oligohidrosis, paresthesia, renal calculi

GABA, γ-aminobutyric acid.

Tiagabine and vigabatrin also seem to have higher rates of depression. Patients may not recognize these effects, but family members and other close friends often comment about these adverse effects. Patients should be regularly monitored for depression and agitation, and medication may need to be changed due to psychiatric adverse effects.

▶ *Practical Issues*

Comorbid Disease States Patients with epilepsy often have comorbid disease states. Care must be taken when treating comorbid conditions, as numerous drugs can interact with ASM. These interactions necessitate close monitoring for changes in efficacy or increased toxicity, and dosage changes of other drugs may be necessary when an ASM is added or removed. Patients with headaches need special attention in the selection of an ASM. Agents known to prevent headache (eg, valproate and topiramate) may be preferred.

Depression is common in patients with epilepsy. Approximately 30% of patients have symptoms of major depression at some point.[30] Routine assessment for depression should be done using a validated screening tool, and treatment initiated if necessary. Some ASMs (eg, levetiracetam) can exacerbate depression, and patients should be warned to watch for mood changes. Other ASMs (eg, lamotrigine, carbamazepine, and oxcarbazepine) may have a role in treating mood disorders. If treatment for depression is necessary, an agent that is unlikely to increase seizures and does not interact with ASMs should be chosen. However, treatment with an appropriate antidepressant should not be withheld because of a small risk of increasing seizure frequency.

Switching Drugs Changing from one ASM to another can be a complex process. If the first drug is stopped too abruptly, breakthrough seizures may occur. KEY CONCEPT Changes in ASM regimens should be done in a stepwise fashion, keeping in mind drug interactions that may be present and may necessitate dosage changes in concomitant drugs. Typically, the new drug is started at a low initial dose and gradually increased over several weeks. Once the new drug is at a minimally effective dose, the drug to be discontinued is gradually tapered while the dose of the new drug continues to be increased to the target dose. During a transition between drugs, patients should be cautioned about the possibility of increased seizures or adverse reactions.

Stopping Therapy Epilepsy is generally considered to be a lifelong disorder requiring ongoing treatment. However, some patients who are seizure free may desire to discontinue their medications.[31,32] Patients who become seizure free following surgery for epilepsy may have medications slowly tapered starting 1 to 2 years after surgery. Many patients will choose to stay on at least one medication, following successful surgery, to ensure they remain seizure free. Epilepsy is considered to be cured if a patient remains seizure free for 10 years and has been not taken an ASM for at least 5 years. KEY CONCEPT Discontinuation of ASMs should be done gradually, only after the patient has been seizure free for 2 to 5 years and with careful consideration of the following factors predictive of seizure recurrence:

- No seizures for 2 to 5 years
- Normal neurologic examination
- Normal intelligence quotient
- Single type of focal or generalized seizure
- Normal EEG with treatment

Individuals who fulfill all of these criteria have a 60% chance of remaining seizure free after ASMs are discontinued. Additionally, there is a direct relationship between the duration of seizure freedom with medications and the chance of remaining seizure free after medications are withdrawn. Withdrawal of ASMs is done slowly, usually with a tapering dose over at least 1 to 3 months.

▶ *Dosing*

Dosing of ASMs is determined by dosing guidelines and response of the patient. Serum concentrations may be helpful in benchmarking a specific response. Therapeutic ranges are broad guidelines for dosing but should never replace careful evaluation of the patient's response. It is usually best to obtain ASM concentrations immediately before a dose, preferably the first morning dose. Sufficient time should have elapsed for the ASM to be at steady state when a concentration is measured. In acute care, concentrations may be measured more frequently to ensure proper dosing and check for alterations in ASM pharmacokinetics (eg, altered protein binding, poor oral absorption, and increased metabolism). There is no standard initial dose of ASMs for all patients. Doses are established by balancing seizure control with adverse effects. Some patients may require doses higher than the usual recommended range, and some can be seizure free on unusually low doses. It is best to target initial doses in the middle of the usual therapeutic range and then adjusted according to patient response.

▶ *Drug Interactions*

ASMs are associated with many different drug interactions.[33-36] Most interactions occur due to alterations in absorption, metabolism, and protein binding. Tube feedings and antacids are known to reduce the absorption of phenytoin and carbamazepine. Phenytoin, carbamazepine, and phenobarbital are potent inducers of various CYP450 isoenzymes, increasing the clearance of other drugs metabolized through these pathways (Table 32–5). In contrast, valproate is a CYP450 and UDP-glucuronosyltransferase (UGT) isoenzyme inhibitor and reduces the clearance of some drugs. Phenytoin and valproate are highly protein bound and can be displaced when taken together or with other highly protein-bound drugs. Whenever a change in a medication regimen occurs, drug interactions should be considered and appropriate adjustments in the dose of ASMs made.

▶ *Special Populations*

KEY CONCEPT Children and women with epilepsy have unique problems related to the use of ASMs. In children, developmental changes occur rapidly, and metabolic rates are greater than those seen in adults. When treating a child, it is imperative to control seizures as quickly as possible to avoid interference with development of the brain and cognition. ASM doses are increased rapidly, and frequent changes in the regimen are made to maximize seizure control. Due to rapid metabolic rates seen in children, doses of ASMs are typically higher on a milligram-per-kilogram basis compared with adults, and serum concentrations are used more extensively to help ensure an adequate trial of a drug has been given.

For women, the treatment of epilepsy poses challenges, including teratogenicity, breastfeeding, interactions between ASMs and hormonal contraceptives, and reduced fertility.[37-39] Recommendations are developed for managing women of childbearing potential and who are pregnant (Table 32–6). Several ASMs are implicated in causing birth defects.[40] Neural tube defects (eg, spina bifida, microcephaly, and anencephaly) are associated most commonly with valproate and possibly carbamazepine. Additionally, valproate is associated with impaired cognitive development and increased risk of autism in children born to women taking valproate during pregnancy. The use of valproate should be avoided, if possible, in women of childbearing potential. All

Table 32–5

Cytochrome P450 and ASM Interactions

Enzyme	Substrate	Common Inducers	Common Inhibitors
CYP 1A2	Carbamazepine Fenfluramine Perampanel Stiripentol	Carbamazepine Phenytoin Phenobarbital Rifampin	Cimetidine Ciprofloxacin Erythromycin Fluvoxamine Clarithromycin
CYP 2C9	Brivaracetam Phenobarbital[a] Phenytoin[a] Carbamazepine Valproate	Carbamazepine Phenytoin Phenobarbital Rifampin	Amiodarone Cimetidine Fluconazole Valproate
CYP 2C19	Brivaracetam[a] Cannabidiol Phenobarbital Phenytoin Stiripentol Valproate Lacosamide		Felbamate Omeprazole Oxcarbazepine Ticlopidine Topiramate
CYP 2D6	Fenfluramine Zonisamide	Carbamazepine	
CYP 3A4	Cannabidiol Carbamazepine[a] Clobazam Clonazepam Ethosuximide Everolimus Lacosamide Perampanel[a] Stiripentol Tiagabine[a] Zonisamide[a]	Carbamazepine Oxcarbazepine Phenytoin Phenobarbital Topiramate (> 200 mg/day) Rifampin	Amiodarone Erythromycin Ketoconazole
Uridine diphosphate glucuronyl-transferase	Lamotrigine[a] Cannabidiol Carbamazepine Eslicarbazepine Valproate	Lamotrigine Phenobarbital Phenytoin Hormonal contraceptives	Valproate

[a] Primary route of metabolism.

women of childbearing potential who take ASMs should take 1 to 4 mg daily of supplemental folic acid to reduce the risk of birth defects. Many ASMs are excreted in breast milk. However, infants were exposed to higher concentrations of ASM in utero, so it is

Table 32–6

Management of ASMs During Pregnancy[40]

Give supplemental folic acid 1–4 mg daily to all women of childbearing potential
Use monotherapy whenever possible
Use lowest doses that control seizures
Continue pharmacotherapy that best controls seizures prior to pregnancy
Monitor ASM serum concentrations at start of pregnancy and monthly thereafter
Adjust ASM doses to maintain baseline serum concentrations
Administer supplemental vitamin K during eighth month of pregnancy to women receiving enzyme-inducing ASMs
Monitor postpartum ASM serum concentrations to guide adjustments of drug doses
Avoid valproate, if possible

Patient Encounter 3: Pregnancy

AM is a 28-year-old woman who is newly diagnosed with epilepsy. Her medications consist of lamotrigine and nonprescription antihistamines. She states that she and her husband want to start a family and she is concerned about her medications. She continues to titrate her lamotrigine upward in accordance with the recommended schedule. The seizures have decreased in frequency, but she is not at her target lamotrigine dose.

What advice should be given regarding birth control?

What is the risk of birth defects if she gets pregnant while taking ASMs?

What can be done to limit the risk of birth defects?

What ASMs should generally be avoided in women of childbearing potential?

How should lamotrigine be managed when she becomes pregnant and after delivery?

unclear if drugs in breast milk are harmful to the child. Decisions about breastfeeding are made on an individual basis.

Some ASMs induce hepatic microsomal enzyme systems and reduce the effectiveness of hormonal contraceptives. Women taking ASMs that may reduce the effectiveness of hormonal contraceptives should also use other forms of birth control. In contrast to these interactions, oral hormonal contraceptives induce glucuronidation of lamotrigine and valproate and cause reductions in serum concentrations of these drugs during days of the cycle when hormones are taken; serum concentrations increase during days when hormones are not taken. Serum concentrations of many ASMs drop during pregnancy and dose increases based on frequent serum concentration monitoring is necessary. Following delivery of the baby, serum concentration monitoring is helpful in guiding reduction of doses to the prepregnancy baseline. Due to induction or inhibition of sex hormone metabolism and changes in binding of hormones to sex hormone-binding globulin, some ASMs reduce fertility. Valproate has been associated with a drug-induced polycystic ovarian syndrome. Women who experience difficulties with fertility should seek the advice of health care professionals with expertise in fertility.

KEY CONCEPT Outside of infants, adults older than 55 years have the highest incidence of newly diagnosed epilepsy and face unique challenges in treatment. Cerebrovascular disease, tumors, trauma, and neurodegenerative diseases are the primary causes of epilepsy in this age-group. Diagnosis of epilepsy in older adults is difficult. This is due to the subtle symptoms of seizures, often compromised memory in the elderly, and the fact that many older adults live alone. Carbamazepine, lamotrigine, levetiracetam, topiramate, and gabapentin are effective in controlling seizures in older adults. Elderly patients are more sensitive to adverse events, so smaller doses tend to be used in this age-group. Patients in this age-group are at a greater risk for drug interactions due to age-related changes in drug clearance and the likelihood they are taking concomitant medications for other disease states.

Patient Encounter 4: Seizures in Older Adults

A 72-year-old woman reports new episodes of loss of time for a few seconds that occur several times a day. A friend has seen her have a few of these spells and notes some movement of her right hand and arm. An EEG shows possible epileptiform activity in the left temporal lobe.

Should pharmacotherapy be started in this patient?

If medication is started, which ASM should be started?

How should the efficacy and toxicity be monitored in this patient?

OUTCOME EVALUATION

KEY CONCEPT Patients receiving ASMs for seizures should be instructed on and have regular monitoring for seizure frequency, seizure patterns, acute adverse effects, chronic adverse effects, comorbid conditions, and possible drug interactions.

Patient Care Process

Collect Information:

- Description of seizure events
- EEG report
- Neuroimaging report
- Laboratory results (eg, serum chemistry, complete blood count, renal function, hepatic function, toxicology screen, ASM serum concentrations)
- History of prematurity or difficult delivery at birth, febrile seizures, head injury, infections of the central nervous system
- Family history of seizures or other neurological disorders
- Medication history
- Adherence to medications
- Allergies
- Social history (eg, employment, driving, living situation, recreational activities)

Assess the Information:

- Type of seizure
- Risk of a recurrent seizure
- Impact of potential pharmacotherapy on lifestyle
- Ability to adhere to medication regimen
- Need for modifying lifestyle (eg, ability to drive, modifications at work, avoidance of recreational activities that could result in harm with a seizure)

Develop a Care Plan:

- Determine optimal goals of pharmacotherapy.
- Select medication that is effective for the seizure type and minimizes the risk of adverse effects that negatively impact the patient's lifestyle; evaluate the risk of important drug interactions.
- Design a dosing schedule to optimize adherence.
- Identify important patient education points (eg, driving, safety, pregnancy, birth control, adherence).
- Determine when emergency medical services should be accessed.
- Select a seizure rescue medication, if indicated.

Implement the Care Plan:

- Select and initiate the best medication for the patient at an appropriate starting dose.
- Provide a medication titration schedule, if needed.
- Assist patient to determine the best ways to monitor efficacy (eg, seizure frequency and severity) and adverse events.
- Instruct patient on important patient education points (eg, driving, safety, pregnancy, birth control, adherence).

Follow-up: Monitor and Evaluate:

- Seizure frequency and severity
- Adverse events (eg dose-related, idiosyncratic, chronic)
- Serum concentrations, when appropriate
- Possible drug interactions
- Adherence

Efficacy

- Seizure counts are the standard way to evaluate the efficacy of treatment.
- Encourage patients to keep a seizure calendar that notes the time and day a seizure occurs and the type of seizure. Compare seizure counts on a monthly basis to determine the level of seizure control.

Toxicity

- Monitor acute toxicity of ASMs at every clinic visit.
- Question patients about common adverse effects of the ASMs they are receiving. Weigh the impact of acute adverse effects against the extent of seizure control. If it is determined that the adverse effects negatively impact the patient more than the extent of seizure control benefits the patient, adjust the therapeutic regimen. Continuously monitor chronic adverse effects of ASMs.

Comorbid Conditions

Routinely evaluate patients for signs and symptoms of depression.

Abbreviations Introduced in This Chapter

AAN	American Academy of Neurology
ASM	Antiseizure Medication
CBC	Complete blood count
CNS	Central Nervous System
CYP	Cytochrome P450
EEG	Electroencephalograph
GABA	γ-aminobutyric acid
HLA	Human leukocyte antigen
ILAE	International League Against Epilepsy
JME	Juvenile myoclonic epilepsy
LFT	Liver function tests
LGS	Lennox–Gastaut syndrome
MRI	Magnetic resonance imaging
MTLE	Mesial temporal lobe epilepsy
NICE	National Institute for Clinical Excellence in the United Kingdom
PDS	Paroxysmal depolarizing shift
SIGN	Scottish Intercollegiate Guidelines Network
SMEI	Severe myoclonic epilepsy in infancy
SUDEP	Sudden Unexpected Death in Epilepsy Patients
UGT	Uridine 5’-diphospho-glucuronosyltransferase

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33

Status Epilepticus

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the pathophysiology of status epilepticus.
2. Explain the urgency in diagnosis and treatment of status epilepticus.
3. Recognize the signs and symptoms of status epilepticus.
4. Identify the treatment goals for a patient with status epilepticus.
5. Formulate an initial treatment strategy for a patient in generalized convulsive status epilepticus.
6. Compare the pharmacotherapeutic options for refractory status epilepticus.
7. Describe adverse drug events associated with the pharmacotherapy of status epilepticus.
8. Recommend monitoring parameters for a patient in status epilepticus.

INTRODUCTION

KEY CONCEPT Status epilepticus (SE) is a neurologic emergency that can lead to permanent brain damage or death. **KEY CONCEPT** SE is defined as continuous seizure activity lasting more than 5 minutes or 2 or more seizures without a complete recovery of consciousness.[1] Refractory status epilepticus (RSE) is unresponsive to emergent (first-line) and urgent (second-line) therapy.

SE can present as nonconvulsive status epilepticus (NCSE) or generalized convulsive status epilepticus (GCSE). NCSE is characterized by persistent impaired consciousness without physical convulsions and is diagnosed with electroencephalography (EEG). GCSE is characterized by full-body motor seizures and involves the entire brain.

EPIDEMIOLOGY AND ETIOLOGY

The incidence of SE ranges from 9.9 to 41 per 100,000/year, with a mortality rate of 26%,[2] and an estimated annual direct cost for inpatient admissions of $4 billion.[3] It occurs most frequently in males, African Americans, children, and the elderly.

KEY CONCEPT It is important to evaluate etiologies of SE for timely and optimal seizure control. Causes of SE include metabolic disturbances (e.g., hyponatremia, hypernatremia, hyperkalemia, hypocalcemia, hypomagnesemia, hypoglycemia), central nervous system (CNS) disorders, infections, injuries, hypoxia, and drug toxicity (e.g., theophylline, isoniazid, cyclosporine, cocaine).[4] Chronic causes of SE include preexisting epilepsy, chronic alcoholism (withdrawal seizures), CNS tumors, and strokes.[4] In patients with epilepsy, common causes of SE are anticonvulsant withdrawal or subtherapeutic levels.

PATHOPHYSIOLOGY

Status epilepticus occurs when the brain fails to stop isolated seizures, due to a mismatch of neurotransmitters. Glutamate, the primary excitatory neurotransmitter, stimulates postsynaptic *N*-methyl-D-aspartate (NMDA) receptors, causing neuronal depolarization. Sustained depolarization causes neuronal injury and death.[5] The primary inhibitory neurotransmitter, γ-aminobutyric acid (GABA), opposes excitation by stimulating GABA_A receptors, producing hyperpolarization and inhibition of the postsynaptic cell membrane. GABA-mediated inhibition diminishes with continuous seizure activity, causing a decreased response to GABA-receptor agonists.[6] Seizures lasting more than 30 minutes cause significant injury and neuronal loss because of excessive electrical activity and cerebral metabolic demand. Decreased GABA_A-receptor response and increasing neuronal injury with prolongation of seizure activity necessitate rapid control of SE.

Systemic changes appear in two phases during SE. Phase I occurs during the first 30 minutes, and phase II occurs after 30 to 60 minutes.[7]

Phase I

During phase I, autonomic activity increases, resulting in hypertension, tachycardia, hyperglycemia, hyperthermia, sweating, and salivation. Cerebral blood flow increases to preserve oxygen supply to the brain. Increases in sympathetic and parasympathetic stimulation with muscle hypoxia can cause ventricular arrhythmias, severe acidosis, and rhabdomyolysis, which can lead to hyperkalemia, hypotension, acute kidney injury, and shock.

Phase II

After 30 to 60 minutes of continuous seizure activity, loss of cerebral autoregulation, decreased cerebral blood flow, increased intracranial pressure (ICP), and systemic hypotension occur. Cerebral metabolic demand remains high; however, the body is unable to compensate, resulting in hypoglycemia, hyperthermia, respiratory failure, hypoxia, respiratory and metabolic acidosis, hyperkalemia, hyponatremia, and uremia. Motor activity may not be clinically evident during prolonged seizures, but electrical activity may still exist (i.e., NCSE) requiring prompt recognition and aggressive treatment.

Patient Encounter 1, Part 1

A 46-year-old woman with a history of hypertension, diabetes, hypothyroidism, and COPD was admitted with bilateral traumatic epidural hematomas, skull fractures, and frontal contusions after being involved in a motor vehicle accident. She underwent surgery 2 days ago to treat the hematomas and skull fractures and is currently recovering in the intensive care unit (ICU). She was initiated on fosphenytoin for seizure prophylaxis upon admission along with her home medications. She has only one peripheral intravenous (IV) line and has very poor vascular access. Her nurse reports that she was alert and awake at the start of his shift, but now she is unarousable and is having jerky, convulsive movements on both sides of her body. The intensivist comes and quickly evaluates her when the shaking activity stops but resumes after 5 minutes. She never regained consciousness between these episodes. Her diagnosis is status epilepticus. Ht 165 cm (5′5″), Wt 117 kg (257 lbs).

What initial assessments should be performed?

What are some possible etiologies for her seizure?

What nonpharmacologic interventions are needed at this time?

CLINICAL PRESENTATION AND DIAGNOSIS

History

KEY CONCEPT When a patient presents with seizures, a thorough history is needed to determine the type and duration of previous seizure activity. This will help guide therapy and clarify necessary laboratory and diagnostic tests. Emergent treatment should not be delayed if seizure activity is diagnosed or is suspected based on the patient's family or emergency response personnel.

Physical Examination

Once clinical seizures are halted, a neurologic examination should evaluate the level of consciousness (coma, lethargy, or somnolence), motor function and reflexes (rhythmic contractions, rigidity, spasms, or posturing), and pupillary response. A physical examination can identify secondary injuries.

Clinical Symptoms

Patients with SE usually present with generalized, convulsive, tonic-clonic seizures. They may also be hypertensive, tachycardic, febrile, and diaphoretic, which resolve after seizure termination. A loss of bowel or bladder function, respiratory compromise, and nystagmus may also be observed. When seizure activity exceeds 30 to 60 minutes, muscle contractions may no longer be visible, necessitating an EEG to diagnose SE. Twitching of the face, hands, or feet may be seen in these comatose patients with prolonged seizures.

Laboratory Parameters

It is important to obtain a serum chemistry profile to help identify possible causes of SE, such as hypoglycemia, hyponatremia or hypernatremia, hypomagnesemia, and hypocalcemia; patients with renal and liver failure are at high risk as well.[1] In febrile patients with elevated white blood cell (WBC) counts, active infections should be considered and treated appropriately. Cultures from the blood, cerebrospinal fluid (CSF), respiratory tract, and urine should be collected once seizures are controlled. Blood alcohol level and urine toxicology screen should be ordered to determine if SE is caused by alcohol withdrawal, illicit drug use, or a drug overdose. Serum drug levels should be obtained in an overdose situation to rule out toxicity. **KEY CONCEPT** Knowing the cause of SE will guide initial antiepileptic therapy and increase the probability of seizure termination.

In patients taking anticonvulsants, a baseline serum concentration can help determine if the concentration is below the desired range and whether a loading dose (LD) is needed. Albumin levels

Clinical Presentation of Status Epilepticus

General

- The patient may present with or without clinically noticeable seizures.

Symptoms

- Impaired consciousness, from lethargy to coma
- Disorientation after GCSE cessation
- Pain from associated injuries (e.g., tongue lacerations, dislocated shoulder, head/facial trauma)

Signs

Phase I (≤ 30 minutes of SE):	Phase II (> 30 minutes of SE):
Generalized convulsions	Cardiac failure (arrhythmias, shock)
Hypertension, tachycardia	Hypotension
Fever and sweating	Hyperthermia
Muscle contractions, spasms	Rhabdomyolysis and multiorgan failure
Respiratory compromise	Respiratory failure with pulmonary edema
Incontinence	

Laboratory Tests

- Hyperglycemia (phase I) and hypoglycemia (phase II) can occur.
- Hyponatremia, hypernatremia, hyperkalemia, hypocalcemia, hypomagnesemia, and hypoglycemia can cause SE.
- The white blood cell (WBC) count may slightly increase.
- Abnormal arterial blood gases (ABGs) due to hypoxia and respiratory or metabolic acidosis.
- Elevated serum creatinine will be present in renal failure patients.
- Myoglobinuria can occur in patients with continuous seizures.

Diagnostic Tests

EEG to confirm seizure activity.

Computed tomography (CT) or magnetic resonance imaging (MRI) may reveal mass lesions or hemorrhage.

and renal and liver function tests should also be utilized to assess therapy.

Hypoxia and respiratory or metabolic acidosis are common in patients with SE. Pulse oximetry and arterial blood gas (ABG) measurements are used to assess pulmonary status and determine the need for protection or supplemental oxygen. Metabolic acidosis may resolve without treatment after the termination of clinical seizures.

Diagnostic Tests

EEG is required to identify SE in a comatose patient.[1] Continuous EEG monitoring should be used in patients who remain unconscious after initial antiepileptic treatment, those receiving long-acting paralytic agents, or those requiring prolonged RSE therapy. Treatment should not be delayed while awaiting EEG results. CT and MRI scans are useful to identify traumatic injury, mass lesions, or evidence of infection as the cause of SE.

TREATMENT

Desired Outcomes

KEY CONCEPT The goal of therapy is to terminate physical and electroencephalographic evidence of seizures, prevent recurrence, and minimize adverse drug events. Poor outcomes are associated with prolonged SE and refractory SE.[8] Complications of SE should also be treated.

General Approach

The initial approach to SE involves removing the patient from harmful surroundings and ensuring maintenance of airway, breathing, and circulation. Benzodiazepines are the preferred initial drugs to stop acute seizure activity (emergent therapy), followed by an anticonvulsant (urgent therapy) for suppression of subsequent seizures.[1] Medications are given intravenously for immediate onset of action, but if IV access is not available, select medications may be given rectally, intramuscularly (IM), buccally, or nasally. After seizures stop, clinicians must identify and treat underlying causes of the seizures, such as toxins, hypoglycemia, or brain injury. Patients with known seizure disorders should be evaluated for abrupt cessation of their medications, nonadherence, or drug interactions. Clinical guidelines provide treatment algorithms for SE.[1,9]

Nonpharmacologic Treatment

Oxygen administration or intubation for mechanical ventilation should be performed in cases of hypoxia, and temperature management should be considered for febrile seizures. Specialists in neurology or epileptology should be consulted as appropriate. Admission to an intensive care unit (ICU) allows for aggressive treatment and monitoring.

Pharmacologic Treatment

▶ *Initial Treatment*

Hypoglycemia-induced SE is treated with IV dextrose. Intravenous thiamine is given to patients with alcohol use disorder and acute toxicity prior to administering any dextrose-containing solution to prevent encephalopathy.

▶ *Benzodiazepines*

KEY CONCEPT Initial or emergent drug therapy begins with IV administration of a benzodiazepine. This class of agents is highly effective in terminating seizures.[10,11] Intravenous bolus doses of diazepam, lorazepam, and midazolam have been used in SE because of their rapid effects on GABA receptors. Lorazepam is the preferred agent of most clinicians. When treating patients on chronic benzodiazepine therapy, consider using higher doses to overcome tolerance. Diazepam and lorazepam should be diluted 1:1 with normal saline before parenteral administration via peripheral veins to avoid vascular irritation from the propylene glycol diluent.

Diazepam Being extremely lipophilic, diazepam penetrates the CNS quickly but rapidly redistributes into body fat and muscle.[1] This results in a rapid decline in CNS levels and early recurrence

Patient Encounter 1, Part 2

Physical examination, chart review, and recent laboratory studies reveal the following information:

PE:

VS: BP 188/87 mm Hg, HR 115 beats/min, RR 25 breaths/min, T 39.2°C (102.6°F)

CNS: Unresponsive, unarousable

CV: Sinus tachycardia; normal S1, S2; no murmurs, rubs, gallops

Pulm: Tachypneic; oxygen saturation 84% (0.84) on room air; no rhonchi, wheezes, rales

Abd: Deferred

Exts: Rhythmic tonic-clonic movements of all extremities

GU: Incontinent of urine and stool

HEENT: Persistent upward gaze

Current medications: Fosphenytoin 100 mg phenytoin equivalent (PE) IV every 8 hours; famotidine 20 mg IV every 12 hours; fluticasone furoate 100 mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg inhaler 1 puff daily; levothyroxine 150 mcg PO daily; metoprolol 50 mg orally every 12 hours; Insulin glargine 25 units subcutaneous (SQ) at bedtime; insulin aspart 5 units SQ with meals; acetaminophen/hydrocodone 325 mg/5 mg tablet PO every 4 hours as needed for pain; morphine 2 mg IV push (IVP) every 2 hours as needed for pain

Labs: Sodium 125 mEq/L (mmol/L), potassium 4.5 mEq/L (mmol/L), phenytoin 2.7 mcg/mL (mg/L; 11 μmol/L), albumin 3.1 g/dL (31 g/L), chloride 105 mEq/L (mmol/L), carbon dioxide 12 mEq/L (mmol/L), blood urea nitrogen 12 mg/dL (4.3 mmol/L), serum creatinine 1.2 mg/dL (106 μmol/L), glucose 54 mg/dL (3.0 mmol/L); WBC 14 × $10^3/\text{mm}^3$ (14 × 10^9/L), hemoglobin 9.2 g/dL (92 g/L or 5.71 mmol/L), hematocrit 28% (0.28 volume fraction), platelets 215 × $10^3/\text{mm}^3$ (215 × 10^9/L), prothrombin time 14 seconds; international normalized ratio 1.2, activated partial thromboplastin time 31 seconds.

What is your assessment of the cause of this patient's condition?

What pharmacologic interventions are needed at this time?

Identify goals of therapy for this patient.

What therapies must be instituted next?

of seizures. Doses can be given every 5 minutes until seizure activity stops or toxicities are seen (e.g., respiratory depression).[1] Diazepam can be administered as a rectal gel enabling nonmedical personnel to provide timely therapy at home or in public areas.[12] Intramuscular administration of diazepam is not recommended because of erratic absorption.[13]

Lorazepam Less lipophilic than diazepam, lorazepam has a longer redistribution half-life, resulting in longer duration of action and decreased need for repeated doses.[14] Both lorazepam and diazepam are effective in stopping seizures,[15] but lorazepam is currently preferred due to a longer duration of action. It can be redosed every 5 to 10 minutes (up to a maximum cumulative dose of 8 mg) until seizure activity stops or side effects such as respiratory depression occur. Intramuscular administration is not preferred due to slow and unpredictable absorption.[14]

Midazolam Midazolam is water soluble and can be administered IM,[16] buccally,[17,18] and nasally.[19,20] Compared to diazepam and lorazepam, it has less respiratory and cardiovascular side effects. Its short half-life requires that it be redosed frequently or administered as a continuous IV infusion.[14] Liquid or injectable formulations can be given buccally or intranasally (0.2 mg/kg, maximum of 5 mg per dose in one nostril, may repeat once in other nostril) in pediatric patients. Rapid breathing and increased secretions can interfere with nasal administration. A study in adults and children showed that IM midazolam was as safe and effective as IV lorazepam for prehospital termination of seizures.[21]

▶ *Anticonvulsants*

KEY CONCEPT After administering the first dose of benzodiazepine, an anticonvulsant such as phenytoin, valproate sodium, levetiracetam, or phenobarbital should be started to prevent further seizures (urgent therapy). Anticonvulsants must not be given as first-line therapy since they are infused relatively slowly to avoid adverse effects, delaying their onset of action. If the underlying cause of the seizures has been corrected (e.g., hypoglycemia) and seizure activity has ceased, an anticonvulsant may be unnecessary. This may be reasonable when patients become alert and oriented or if an EEG confirms the absence of seizure activity.

After the LD of the anticonvulsant is administered, maintenance doses should be initiated to ensure that therapeutic levels are sustained. Chronic and idiosyncratic side effects and potential drug interactions should be considered if the patient continues anticonvulsant therapy. Drugs should be adjusted for any hepatic or renal dysfunction. Table 33–1 summarizes the doses used in SE, and Table 33–2 is an example algorithm for the treatment of patients in SE.

Phenytoin The most widely used anticonvulsant for urgent treatment of SE is phenytoin. It is available in its original form or as a prodrug, fosphenytoin, which is the most commonly used dosage form. Phenytoin doses are infused no faster than 50 mg/min due to risks of hypotension or arrhythmias. Continuous monitoring of electrocardiogram (ECG) and blood pressure is recommended. Maintenance doses can be started 12 hours after the LD. Phenytoin should not be infused with other medications to avoid instability (it is soluble in propylene glycol and compatible only in 0.9% sodium chloride solutions). It should not be given IM due to its alkalinity. Extravasation of phenytoin can cause local tissue discoloration, edema, pain, and, sometimes, necrosis (purple glove syndrome). Oral loading is not recommended due to the limitations of single-dose absorption (i.e., doses > 400 mg are not fully absorbed) and delayed peak concentrations when given orally.[22] Phenytoin/fosphenytoin loading doses for obese patients (≥ 30 kg/m^2) can be calculated based on actual body weight: 15mg/kg for obese males and 20 mg/kg for obese females.[23] Another option is to calculate a dosing weight (DW) using total body weight (TBW) and ideal body weight (IBW): DW = IBW + 1.33(TBW – IBW). Volume of distribution (V_d) can be calculated as follows: $V_d = 0.7$ L/kg × DW (in kg). An LD can then be calculated using V_d and a target concentration: LD = $C_{target} \times V_d$.

Patient Encounter 2, Part 1

A 29-year-old man is admitted for an elective cervical discectomy. He has a past medical history of epilepsy for which he takes levetiracetam (he has an allergic rash to phenytoin) and atrial fibrillation for which he is taking apixaban. He tells the nurse he has not taken any of his medications for 2 days because he was told to stop taking them in preparation for surgery. Suddenly, he becomes unresponsive and begins shaking his arms. His diagnosis is status epilepticus after this seizure activity does not stop over the next 5 minutes.

VS: BP 115/75 mm Hg, HR 118 beats/min, RR 25 breaths/min, T 37.0°C (98.6°F), Wt 73 kg (160 lb), Ht 183 cm (6 ft).

What is the most likely cause of this patient's SE?

What are possible treatment options at this time?

How would you optimize his outcome?

Fosphenytoin Fosphenytoin is a water-soluble phosphoester prodrug that is rapidly converted to phenytoin in the body. It is compatible with most IV solutions. It is dosed in phenytoin equivalents (PEs), and it can be infused up to 150 mg PE/min. Although it has fewer cardiovascular side effects than phenytoin, clinicians should continuously monitor blood pressure, ECG, and heart rate. Paresthesias, especially around the lips and groin, are common but typically resolve within a few minutes and should not necessitate stopping the infusion. If a postload serum level is desired, it should be obtained 2 hours after an IV load; if subtherapeutic, an additional LD is indicated.

Valproate Sodium Valproate sodium has been successfully used as an IV in various types of SE, including generalized tonic-clonic, myoclonic, and NCSE.[24] It is particularly useful in patients with cardiorespiratory compromise and/or those allergic to phenytoin and phenobarbital.[25]

Phenobarbital If phenytoin or valproate sodium fails to prevent seizure recurrence, phenobarbital can be considered.[1] However, phenobarbital may not be effective if SE persists despite benzodiazepines and phenytoin. This may be due to progressive resistance of the $GABA_A$ receptor, where barbiturates also act.[26] Adverse reactions of phenobarbital include sedation, hypotension, and respiratory depression; therefore, patients receiving a rapid IV LD of phenobarbital should have hemodynamic monitoring and be mechanically ventilated if at high risk of respiratory compromise. Its long half-life makes it a popular agent for both acute treatment and chronic maintenance therapy or as adjunct therapy to prevent withdrawal seizures when weaning refractory SE patients off pentobarbital infusions.

▶ *Levetiracetam*

Levetiracetam does not have the cardiopulmonary, hepatic, and sedative side effects seen with the other agents, nor does it have significant drug interactions. Both IV and oral formulations

Table 33–1

Medications Used in Adult Status Epilepticus[1]

Drug Name (Brand Name)	Loading Dose and RSE Maintenance Dose (If Applicable)	Administration Rate	Therapeutic Level	Side Effects	Comments
Diazepam (Valium)	0.15 mg/kg (up to 10 mg/dose); may repeat in 5 minutes	5 mg/min (IVP)	N/A	Hypotension, respiratory depression	Rapid redistribution rate; can be given rectally
Lorazepam (Ativan)	0.1 mg/kg (up to 4 mg/dose); repeat in 5–10 minutes	2 mg/min (IVP)	N/A	Hypotension, respiratory depression	May be longer acting than diazepam
Midazolam (Versed)	13-40kg: 5mg IM >40kg: 10mg IM RSE: 0.2 mg/kg (2 mg/min) IV then 0.05–2 mg/kg/hour		N/A	Sedation, respiratory depression	Can also be given buccally, intranasally
Phenytoin (Dilantin)	20 mg/kg	Up to 50 mg/min	Total phenytoin level: 10–20 mcg/mL (mg/L; 40–79 μmol/L) Free phenytoin level: 1–2 mcg/mL (mg/L; 4–8 μmol/L)	Arrhythmias, hypotension	Hypotension, especially in older adults
Fosphenytoin (Cerebyx)	20 mg PE/kg	Up to 150 mg PE/min	Total phenytoin level: 10–20 mcg/mL (mg/L; 40–79 μmol/L) Free phenytoin level: 1–2 mcg/mL (mg/L; 4–8 μmol/L)	Paresthesias, hypotension	Less CV adverse effects than phenytoin
Phenobarbital (Luminal)	20 mg/kg	50–100 mg/min	15–40 mcg/mL (mg/L; 65–172 μmol/L)	Hypotension, sedation, respiratory depression	Long-acting
Valproate sodium (Depacon)	20–40 mg/kg	3–6 mg/kg/min	50–150 mcg/mL (mg/L; 347–1040 μmol/L)		Less CV adverse effects than phenytoin
Levetiracetam (Keppra)	1000–3000 mg IV or 60 mg/kg (max 4500 mg)	2–5 mg/kg/min			Minimal drug interactions
Lacosamide (Vimpat)	200–400 mg IV	Over 15 minutes		PR prolongation, hypotension	
Topiramate (Topamax)	200–400 mg NG/PO every 6 hours		2–20 mcg/mL (mg/L; 6–59 μmol/L)	Metabolic acidosis	
Propofol (Diprivan)	Bolus: 1–2 mg/kg RSE: 30–250 mcg/kg/min	Approximately 40 mg every 10 seconds	N/A (typically titrated to EEG)	Hypotension, respiratory depression, PRIS	Requires mechanical intubation; high lipid load (increased calories)
Pentobarbital (Nembutal)	Bolus: 10–15 mg/kg RSE: 0.5–4 mg/kg/hour	Up to 50 mg/min	10–20 mcg/mL (mg/L; 44–89 μmol/L) (typically titrated to EEG)	Hypotension, respiratory depression, cardiac depression, infection, ileus	Requires mechanical intubation, vasopressors, hemodynamic monitoring
Ketamine (Ketalar)	RSE: 0.5–4.5 mg/kg IV bolus, then infusion up to 5 mg/kg/hour		N/A	Hypertension, arrhythmias	Associated cerebral atrophy

CV, cardiovascular; EEG, electroencephalogram; IM, intramuscular; IV, intravenous; IVP, intravenous push; N/A, not applicable; NG, nasogastric; PE, phenytoin equivalents; PO, by mouth; PR, per rectum; PRIS, propofol-related infusion syndrome; RSE, refractory status epilepticus.

have been used in SE patients with some success, and evidence is emerging for use of IV loading doses (60 mg/kg up to 4500 mg) earlier in SE.[34,35]

Treatment of Refractory Status Epilepticus

KEY CONCEPT Seizure activity unresponsive to emergent and urgent therapy is considered RSE.[27] Refractory SE can occur in up to 30% of patients with SE and has a mortality rate approaching 50%.[28] Patients in RSE are unlikely to regain independent function, even if seizures are controlled. Clinical signs may become subtle and an EEG may be required to detect ongoing seizure activity. **KEY CONCEPT** Even patients in SE without clinical signs of seizing are at risk for brain damage or death.

Optimal therapy for RSE is undetermined.[29] Clinicians must aggressively investigate and treat possible causes, including infection, tumors, drugs or toxins, metabolic disorders, liver failure,

Table 33–2

Algorithm for Treatment of Status Epilepticus

Time (minutes)	Assessment/Monitoring	Treatment
0	Vital signs (HR, RR, BP, T) Assess airway Monitor cardiac function (ECG) Pulse oximeter Check blood glucose Check laboratory tests: complete blood count, serum chemistries, liver function tests, arterial blood gas, blood cultures, serum anticonvulsant levels, urine drug/alcohol screen	Stabilize airway (intubate if necessary) Administer oxygen Secure IV access and start fluids Give IV thiamine (100 mg), then IV dextrose (50 mL of 50% solution) if hypoglycemic
0–10	Vital signs Physical examination Patient history, including medications (prescription, OTC, and herbals)	Lorazepam 0.1 mg/kg (maximum 4 mg) IVP at 2 mg/min (may repeat in 5–10 minutes to maximum of 8 mg if no response) If no IV access, can give diazepam 10 mg PR (may repeat in 10 minutes if no response); midazolam 10mg IM if > 40kg (may repeat in 10 minutes if no response) Anticonvulsant may not be necessary if underlying cause is corrected and seizures have ceased
10–20	Vital signs Review laboratory results and correct any underlying abnormality CT scan (if seizures controlled)	Phenytoin 15–20 mg/kg IV at a maximum rate of 50 mg/min (or fosphenytoin 15–20 mg PE/kg IV at a maximum rate of 150 mg PE/min) In patients allergic to phenytoin, give valproate sodium 20 mg/kg IV at a maximum rate of 6 mg/kg/min Treat for possible infection
20–30	Vital signs Consult neurologist/epileptologist Consider admission to ICU Consider EEG	If seizures continue, additional phenytoin bolus 5–10 mg/kg (or fosphenytoin 5–10 mg PE/kg) **OR** start phenobarbital at 20 mg/kg IV at a maximum rate of 100 mg/min **OR** start valproate sodium 20 mg/kg IV at a maximum rate of 6 mg/kg/min in patients who are not intubated
> 30–60 *refractory status epilepticus*	Vital signs Transfer to ICU Obtain EEG Consider MRI when controlled	Midazolam 0.2 mg/kg IV bolus followed by 0.05–2 mg/kg/hour CI **OR** propofol 1 mg/kg bolus followed by 30–250 mcg/kg/min CI **OR** pentobarbital 10–15 mg/kg bolus over 1–2 hours followed by 0.5–4 mg/kg/hour Consider intubation and/or vasopressor support if needed Optimize anticonvulsant levels: repeat boluses of phenobarbital 10 mg/kg **OR** valproate sodium 20 mg/kg at 6 mg/kg/min max
> 24 hours *super refractory status epilepticus*	Vital signs Continuous EEG	Optimize anticonvulsant therapy Consider ketamine infusion, immunomodulation (e.g., steroids, IV immunoglobulin), inhaled anesthetics, ketogenic diet

BP, blood pressure; CI, continuous infusion; CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalograph; HR, heart rate; ICU, intensive care unit; IM, intramuscular; IV, intravenous; IVP, intravenous push; MRI, magnetic resonance imaging; OTC, over the counter; PE, phenytoin equivalents; PR, per rectum; RR, respiratory rate; T, temperature.

or fever. In general, patients with RSE are managed in an ICU with hemodynamic and respiratory support and frequent monitoring. Continuous EEG monitoring is essential and should not be delayed. Any anticonvulsant initiated before the treatment for RSE should be continued, and their serum levels optimized to prevent breakthrough or withdrawal seizures. KEY CONCEPT Treatment of RSE consists of intensive monitoring, supportive care, and a continuous intravenous infusion of midazolam, propofol, or pentobarbital to suppress clinical and EEG evidence of seizures (Tables 33–1 and 33–2).[30] These agents are typically titrated to achieve burst suppression on the EEG, although this practice lacks strong evidence.[1] Patients should be intubated and mechanically ventilated before initiating treatment for RSE. Seizure control per EEG should be maintained for 24 to 48 hours before considering the tapering therapy.[1] Consultation with neurologists or epileptologists is highly recommended.

▶ *Midazolam*

Midazolam infusions must be adjusted, especially in patients with renal impairment, as the active metabolite can accumulate.[31] Breakthrough seizures are common with midazolam infusions and usually respond to boluses and a 20% increase in infusion rate. Despite this, tachyphylaxis can occur, and patients should be switched to another agent if seizures continue.[14]

Patien Encounter 2, Part 2

Over the next hour, he is treated with your recommendations for emergent and urgent treatment of SE as above. His jerky movements have stopped, but he remains comatose.

VS: BP 95/62 mm Hg, HR 120 beats/min, RR 14 breaths/min, T 37.1°C (98.8°F)

A continuous EEG is started and reveals the patient *remains* in SE.

What is your assessment of the patient's current condition?

What do you recommend for further nonpharmacologic and pharmacologic therapy?

How would you optimize his outcomes?

▶ *Propofol*

LDs of the anesthetic propofol can be given every 3 to 5 minutes until clinical response, after which an infusion can be initiated. Propofol causes hypotension, especially with LDs; therefore, some clinicians avoid LDs and quickly titrate with a continuous infusion. Long-term, high-dose (> 80 mcg/kg/min) propofol infusions are associated with rhabdomyolysis, acidosis, and cardiac arrhythmias (propofol-related infusion syndrome), especially in children.[32] Propofol has a very short serum half-life and should be tapered off slowly to avoid withdrawal seizures. Propofol infusions are a source of calories (1 kcal/mL [4.2 kJ/mL]), so nutritional support must be adjusted accordingly.

▶ *Pentobarbital*

Barbiturate infusions are reported to be highly effective in treating RSE[33] and decreasing elevated ICP, but they cause significant hypotension, myocardial and respiratory depression, ileus, and infections. Therefore, patients require mechanical ventilation and invasive hemodynamic monitoring. Patients often require IV vasopressor therapy and total parenteral nutrition.

A meta-analysis reported a lower incidence of treatment failure with pentobarbital (3%) compared to midazolam (21%) or propofol (20%), although the risk of hypotension requiring vasopressor therapy was higher with pentobarbital.[33] This relative efficacy for pentobarbital must be considered together with its complications when determining which agent to use. Patients who fail midazolam and/or propofol should be switched to pentobarbital.

▶ *Other Agents*

Ketamine,[36] topiramate, and inhaled anesthetics have also been used for RSE. Ketamine is an NMDA-receptor antagonist that has been given orally and intravenously for pediatric RSE.[37] Topiramate is an oral anticonvulsant with multiple mechanisms of action in RSE. The oral dose in adults ranges from 300 to 1600 mg/day.[38] Children have also been administered topiramate at a starting dose of 2 to 3 mg/kg/day and titrated to a maintenance dose of 5 to 6 mg/kg/day.[18] Topiramate can induce metabolic acidosis, requiring careful monitoring. The inhaled anesthetics, desflurane, and isoflurane[39] require special equipment for administration in an ICU. Lacosamide, an enhancer of slow inhibition of sodium channels, has limited drug interactions.[40] It has been used orally[41] and intravenously[42] in the setting of refractory partial SE and NCSE.[43]

Special Populations

Certain patients require special considerations due to their altered metabolism, unique volume of distribution, or increased risk for side effects.[44] Although many of these patients are excluded from clinical trials in SE, the standard algorithm for SE still applies in terms of immediate care, assessment, and drugs (see Table 33–2).

▶ *Pediatrics*

The treatment approach for SE in children is similar to that in adults with a few exceptions (see Table 33–3). The doses are also weight-based but are typically higher than those used in adults due to increased hepatic clearance. Timely IV access in children may be difficult, so alternate routes of administration have been used, including intranasal, buccal, rectal, and IM. Early administration of benzodiazepines and reduced time to hospital admission are important in decreasing prolonged seizures.[45]

▶ *Geriatrics*

Older adults are often vulnerable because of multiple disease states and polypharmacy. Seizures in older adults often arise from metabolic disorders, drug interactions, or incorrect dosing of medications in patients with impaired renal and hepatic function and decreased protein binding.[46] Clinicians treating older adult patients with SE should investigate drug- and disease state–induced causes, since treating these etiologies alone may terminate seizures. Acute treatment with benzodiazepines and anticonvulsants is no different in older adults, but they may experience more profound sedative and cardiorespiratory side effects.[46] Phenytoin/fosphenytoin LDs should be carefully calculated in older adults

Table 33–3

Medications Used in Pediatric Status Epilepticus[9]

Drug	Dose	Comments
Diazepam (Valium injection, Diastat rectal gel)	IV: 0.2–0.3 mg/kg over 2–5 minutes	Maximum dose in children < 5 years: 5 mg Maximum dose in children > 5 years: 15 mg
	PR: 2–5 years: 0.5 mg/kg 6–11 years: 0.3 mg/kg > 12 years: 0.2 mg/kg	A second rectal dose can be given 4–12 hours after the first dose if necessary
Lorazepam (Ativan)	0.05–0.1 mg/kg IV over 2–4 minutes	May redose twice in 10–15 minutes if necessary
Midazolam (Versed)	IM dose: 0.2mg/kg (maximum 10mg) RSE dose: 0.2 mg/kg IV bolus followed by 0.05–0.6 mg/kg/hour continuous infusion	Bolus dose may also be given intranasally, buccally, or intramuscularly
Phenytoin (Dilantin)	15–20 mg/kg IV at 1–3 mg/kg/min *max*	
Fosphenytoin (Cerebyx)	15–20 mg PE/kg IV at 3 mg PE/kg/min *max*	
Phenobarbital (Luminal)	15–20 mg/kg IV at 100 mg/min *max*	
Levetiracetam (Keppra)	20–60 mg/kg IV at 2 mg/kg/min	Few drug interactions
Valproate sodium (Depacon)	15–20 mg/kg IV at 1.5–3 mg/kg/min	May have fewer cardiovascular side effects than other agents
Propofol (Diprivan)		Not recommended due to adverse events (e.g., propofol-related infusion syndrome)
Pentobarbital (Nembutal)	10–15 mg/kg IV over 1–2 hours followed by continuous infusion at 1 mg/kg/hour	Titrated to EEG

EEG, electroencephalograph; IV, intravenous; PE phenytoin equivalent; PR, per rectum.

Patient Care Process

Collect Information:

- Review time of onset of seizure activity and past medical/surgical history.
- Obtain vital signs and relevant laboratory testing.
- Perform a medication history of prescription and nonprescription medications and identify medication allergies.
- Obtain patient's weight.

Assess the Information:

- Determine airway patency, breathing status, and circulatory status.
- Determine precipitating factors or etiology of SE.
- Identify drug interactions.
- Assess efficacy of and adherence to anticonvulsants if appropriate.
- Review laboratory results for electrolyte and glucose abnormalities and anticonvulsant serum levels.

Develop a Care Plan:

- Correct reversible causes of SE.
- Select initial benzodiazepine agent, route, and dose appropriate for patient.
- Select initial anticonvulsant for patient based on IV access and vital signs.
- If patient is taking anticonvulsants that can be monitored, evaluate for subtherapeutic serum levels and calculate appropriate LDs.

Implement the Care Plan:

- Administer therapeutic doses within the appropriate time frame (see Tables 33–1 and 33–2). Provide maintenance dosing of anticonvulsants when indicated.
- Identify potential drug interactions and adjust therapy as needed.
- Obtain expertise of a neurologist or epileptologist when appropriate.

Follow-up: Monitor and Evaluate:

- Determine if physical seizures have stopped and the patient regains consciousness. If not, consider continuous EEG monitoring for at least 24 to 48 hours to identify possible nonconvulsive SE.
- Obtain trough serum anticonvulsant levels at steady state, or sooner if seizures continue. Adjust anticonvulsants based on levels, maximizing seizure control and minimizing adverse effects.

whose weights may be overestimated, and who may not tolerate high doses. They should also be infused more slowly to minimize hypotension and arrhythmias. Phenobarbital may cause respiratory depression earlier in older adults, especially after benzodiazepines. Clinicians should consider using smaller doses and evaluate for renal and hepatic insufficiency if repeated doses are to be given.

▶ *Pregnancy*

The main concern in the treatment of pregnant women in SE is the safety of the fetus which is at risk of hypoxia during periods of prolonged seizures. Although many drugs used in SE are teratogenic, clinicians should still use them acutely to stop seizures but consider alternative agents with lower risks, such as lamotrigine, for maintenance therapy.[47] The volume of distribution and clearance of many drugs are increased during pregnancy and must be considered when calculating doses.[48]

OUTCOME EVALUATION

Start pharmacologic treatment as soon as possible.

- First-line (emergent) treatment for SE should halt seizure activity within minutes of administration.
- In patients who are unarousable following treatment, confirm termination of seizures with an EEG.
- Perform a physical examination and evaluate laboratory results to help determine if the cause or complications of seizure activity are being appropriately treated.
- Once seizure activity has ceased and the patient has stabilized, review the patient's therapeutic regimen.
- Evaluate and monitor serum trough concentrations of anticonvulsants with defined target ranges to determine patient-specific therapeutic goals.
- In patients with RSE on multiple continuous infusion agents, slowly decrease the dose of one drug at a time while continuing to evaluate the patient for seizure activity.
- Continue to monitor anticonvulsant serum trough concentrations approximately every 3 to 5 days until the anticonvulsants have reached steady-state concentrations.
- Monitor for signs of drug toxicity and seizures until drug concentrations have stabilized.
- Closely evaluate medication profiles, and change drugs or doses to minimize any drug interaction, if possible.

Abbreviations Introduced in This Chapter

ABG	Arterial blood gas
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
ECG	Electrocardiogram
EEG	Electroencephalography
GABA	γ-Aminobutyric acid
GCSE	Generalized convulsive status epilepticus
ICP	Intracranial pressure
ICU	Intensive care unit
IM	Intramuscular
IV	Intravenous
LD	Loading dose
MRI	Magnetic resonance imaging
NCSE	Nonconvulsive status epilepticus
NMDA	*N*-methyl-D-aspartate
PE	Phenytoin equivalent
RSE	Refractory status epilepticus
SE	Status epilepticus
WBC	White blood cell

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34

Parkinson Disease

Thomas R. Smith

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the pathophysiology of Parkinson disease (PD) related to neurotransmitter involvement and targets for drug therapy.
2. Recognize the cardinal motor symptoms of PD and determine a patient's clinical status and disease progression based on clinical signs, symptoms, and assessment tools.
3. When initiating therapy for PD, recommend appropriate drug therapy and construct patient-specific treatment goals.
4. Recognize and recommend appropriate treatment for nonmotor symptoms.
5. Formulate a plan to minimize patient off time and maximize on time including timing, dosage, and frequency of medications as well as the use of adjunctive medications.
6. Recognize and treat motor complications in PD.
7. Construct appropriate patient counseling regarding medications and lifestyle modifications for PD.
8. Develop a monitoring plan to assess effectiveness and adverse effects of treatment.

INTRODUCTION

KEY CONCEPT Parkinson disease (PD) is a slow, progressive neurodegenerative disease of the extrapyramidal motor system. Dopamine neurons in the **substantia nigra** are primarily affected, and degeneration of these neurons causes a disruption in smooth motor control. Cardinal features of PD include tremor at rest, rigidity, **akinesia**/bradykinesia, and postural instability; however, nonmotor symptoms are also common and may present earlier than these motor symptoms. There is no cure, and treatment aims at controlling symptoms and maintaining quality of life (QOL) or functioning.[1-3]

EPIDEMIOLOGY AND ETIOLOGY

PD is the second most common neurodegenerative illness occurring in 1% to 2% of people older than 60 years.[2] While it is typically diagnosed in older patients, juvenile onset is possible but rare, and an early onset before age 50 can also occur. Genetics play a role in this disorder with about 10% to 15% of patients having an affected relative.[2,4]

The etiology of neuron degeneration in PD remains unknown, but aging is a primary risk factor.[4] Pigmented cells in the substantia nigra that make and store dopamine are lost.[3] Neurons have lost about 30% to 70% of their activity in the striatum at the onset of PD.[2] Cortical **Lewy bodies** along with Lewy neurites in the central nervous system (CNS) and the gastrointestinal (GI) system may explain some of the nonmotor symptoms (e.g., psychiatric, autonomic) of PD.[1,5]

The cause of cell death and PD symptoms is likely multifactorial, with both endogenous and exogenous factors such as genetic susceptibility and environmental toxin exposure (eg, pesticides and solvents).[6] Numerous genetic mutations are linked to PD, and particular mutations may predict early versus late onset of the disease, possibly explaining why the presentation and course of illness varies substantially. Genome-wide association studies have linked at least 26 single-nucleotide polymorphisms (SNPs) to PD.[6] In contrast, protective factors have also been documented and include a history of smoking and coffee consumption.[6]

PATHOPHYSIOLOGY

The extrapyramidal motor system controls muscle movement through pathways that connect the cerebral cortex, **basal ganglia**, thalamus, cerebellum, reticular formation, and spinal neurons. The substantia nigra, where dopamine neurons in PD are lost, sends nerve fibers to the corpus striatum. The corpus striatum is composed of the caudate nucleus and the lentiform nuclei that consist of the pallidum (globus pallidus) and putamen (**Figure 34–1**).[7] As dopamine neurons die, dopamine-relayed messages cannot communicate to other motor centers of the brain, and patients develop motor symptoms. Lewy bodies, inclusions of proteins (primarily alpha-synuclein) which accumulate in neurons, contribute to cell death and may start in the peripheral autonomic nervous system and then spread.[8] A variety of other neurotransmitters active in the basal ganglia lose concentration as well. These deficits possibly explain specific nonmotor symptoms seen in PD; losses of dopamine and norepinephrine in the limbic system correlates with depression and anxiety, while losses of acetylcholine and serotonin in the limbic system are associated with cognitive impairment.[8,9]

Theorized to begin in the autonomic system, olfactory system, or vagus nerve in the lower brainstem, the disease may then spread to the upper brainstem and cerebral hemisphere affecting dopamine pathways later.[9] This would explain why it is typical for patients to recall nonmotor symptom onset prior to manifestation

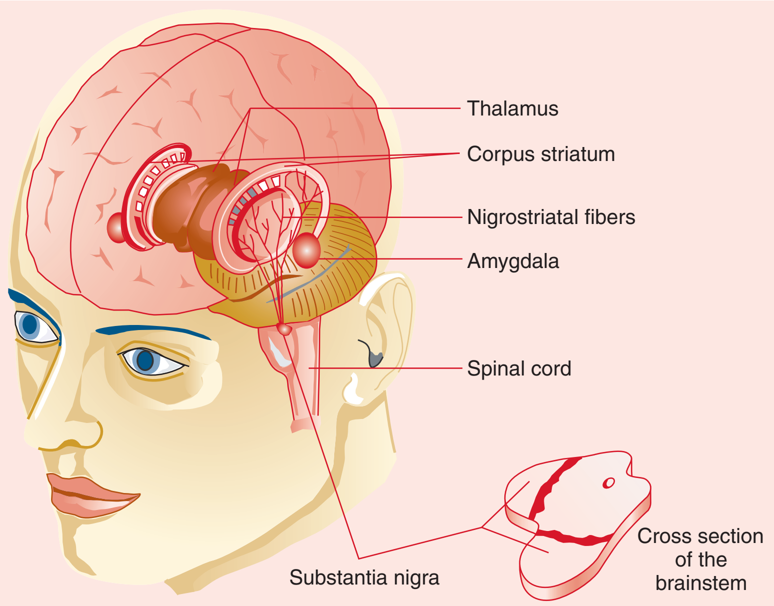

FIGURE 34–1. Anatomy of the extrapyramidal system. The extrapyramidal motor system controls muscle movement through a system of pathways and nerve tracts that connect the cerebral cortex, basal ganglia, thalamus, cerebellum, reticular formation, and spinal neurons. Patients with PD have a loss of dopamine neurons in the substantia nigra in the brainstem that leads to depletion of dopamine in the corpus striatum. The corpus striatum is made up of the caudate nucleus and the lentiform nuclei that are made up of the putamen and the globus pallidus.

of classic motor symptoms and diagnosis. It is essential to rule out drug-induced pseudoparkinsonism due to dopamine antagonists such as antipsychotics, metoclopramide, and antiemetics (prochlorperazine) before diagnosis. Removing the offending agent generally resolves symptoms.[7,9]

Clinical Presentation of PD

Motor Symptoms (TRAP)

T = Tremor at rest ("pill rolling")

R = Rigidity (stiffness and cogwheel rigidity)

A = Akinesia or bradykinesia

P = Postural instability and gait abnormalities

Nonmotor Symptoms (SOAP)

S = Sleep disturbances (insomnia, REM sleep behavioral disorder RLS)

O = Other miscellaneous symptoms (nausea, fatigue, speech, pain, **dysesthesias**, vision problems, seborrhea)

A = Autonomic symptoms (drooling, constipation, sexual dysfunction, urinary problems, sweating, orthostatic hypotension, dysphagia)

P = Psychological symptoms (anxiety, psychosis, cognitive impairment, depression)

Response Fluctuations (MAD)

M = Motor fluctuations (delayed on, wearing off, random off, freezing)

A = Akathisia

D = Dyskinesias (eg, chorea, dystonia, diphasic dyskinesia)

CLINICAL PRESENTATION AND DIAGNOSIS

The diagnosis of PD is based substantially on signs and symptoms rather than diagnostic tests or imaging; however, this can be difficult as other illnesses have characteristics similar to PD and patients' presentations vary initially and progression is patient-specific.[2] DaTscan, a radiopharmaceutical contrast agent, may help differentiate PD from other disorders such as essential

Patient Encounter Part 1: Initial Visit—Medical History

A 66-year-old woman presents to the movement disorder clinic for assessment after a diagnosis of suspected PD 6 months prior by her PCP. Her complaints initially included "stiff muscles, trouble with balance, and a tremor that is bothersome." She was started on rasagiline 1 mg by mouth daily; however, she does not believe this to be very effective. She works as an adjunct professor at a community college and is having problems delivering her lectures (walking, balance, and her voice is softer), working on her computer, and grading papers (her handwriting has changed and the tremor is bothersome). She complains of some dizziness upon standing. Her affect is flat and she can be difficult to hear at times during the interview.

What questions should be asked to determine if a correct diagnosis was made?

What assessments should be completed at this time?

Identify this patient's motor and nonmotor symptoms of PD and assess her functioning.

Assess the choice of her initial drug therapy and make recommendations for optimizing her plan.

tremor but not from similar Parkinson-plus syndromes.[4] Therefore, a thorough patient history and detailed description of symptoms are essential.

Motor Symptoms

KEY CONCEPT As the pathophysiology of PD affects the extrapyramidal motor system, classic motor symptoms of tremor, rigidity, akinesia/bradykinesia, and postural/gait instability (TRAP) develop. Diagnostic criteria developed by the International Parkinson and Movement Disorder Society (MDS) focus on identifying parkinsonism (bradykinesia with rigidity or resting tremor) with supporting signs and symptoms and ruling out "red flags" that are present that would indicate another illness.[2,10] The onset of PD is gradual, and movement impairment may initially go unnoticed. Tremor occurs during rest and disappears with purposeful movement. Hand tremor may mimic a patient rolling a pill between his or her fingers. Rigidity manifests as stiffness with uniform muscle resistance on examination. Examiners may notice cogwheel rigidity on extension or flexion of extremities and feel rhythmical jerking as if hitting a series of teeth on the rim of a wheel. Bradykinesia presents as hesitancy in movement initiation, slowness in movement, or rapid fatiguing. Decreased automatic activity (eg, eye blinking, **hypomimia**, minimal arm swing while walking) is common. Rigidity and bradykinesia may make handwriting difficult as **micrographia** is common. Loss of reflexes to maintain balance as well as stooped posture causes postural instability and unsteadiness. This, combined with gait abnormalities such as slow shuffling, leg dragging, **festination**, or **freezing**, increases the risk of falls.[2,10-15]

Nonmotor Symptoms

Nonmotor symptoms in PD may precede the onset of motor symptoms by many years and result from PD itself or medications. Sleep disturbances, autonomic impairment, psychological disturbances, and sensory disturbances (**anosmia**) are common.[2,12,15,16]

Speech problems manifest as **hypophonia**, slurring, monotone speech, rapid speech, or stammering. When ocular muscles are impaired, difficulty reading, double vision, decreased blinking, and burning or itchy eyes are possible.[2,12,15,17]

Autonomic nervous system disruption may produce orthostatic hypotension as well as GI, urinary, sexual, and dermatologic symptoms. Orthostatic hypotension may cause dizziness, lightheadedness, fainting, or falls. Constipation is very common and **dysphagia** may lead to weight loss, **sialorrhea**, and aspiration.[15,16,17] Genitourinary symptoms include incontinence, urgency, and frequency causing nocturia. Sexual dysfunction includes reduced libido or the inability to achieve orgasm and erectile or ejaculatory dysfunction. Dermatologic symptoms include sweating and intolerance to temperature changes.[12,15,16]

Psychological symptoms of psychosis, dementia, impaired cognitive function, depression, and anxiety may result from PD, during symptom exacerbation, or from medications. Psychosis occurs in nearly 60% of PD patients.[18] Depression is common, but decreased facial expression and bradykinesia may give a false appearance of depression; thus, proper assessment of mood is necessary. Anxiety may be present and can correlate with motor fluctuations.[15,16]

Sleep disorders may be due to PD itself or medication adverse effects. Excessive daytime sleepiness, insomnia, and abnormal sleep events, such as rapid eye movement sleep behavior disorder (REM SBD), may occur.[12,15,16,19]

Motor Complications

Motor complications appear with either disease progression or as a complication of treatment, particularly with levodopa. Motor complications include **delayed peak response (delayed on)**, early and unpredictable wearing off, freezing, and **dyskinesias**—namely, **chorea** and **dystonia**.[3] Risk factors for developing motor complications include younger age at diagnosis, high dosage of levodopa, and longer duration and severity of disease.[3] Wearing off occurs when the therapeutic window of levodopa—the minimum effective concentration required to control PD symptoms (on without dyskinesia) through the maximum concentration before experiencing side effects from excessive levodopa (on with dyskinesia)—narrows over time.[3] Although the plasma half-life of levodopa is 1.5 to 2 hours, the therapeutic effect in early PD lasts about 5 hours, and the patient experiences no dyskinesias. This is due to supplemental dopamine production in the CNS. As PD progresses, this endogenous supply is lost, the therapeutic window narrows, and each dose of levodopa acts less functionally, with the effect decreasing to only 2 to 3 hours.[9,20] Additionally, dyskinesias manifest during the on state, particularly as the dosage of levodopa is increased.[21]

KEY CONCEPT The Unified Parkinson Disease Rating Scale (MDS UPDRS) describes total symptom burden, tracks disease progression, and assesses treatment efficacy. This clinician and patient-rated scale has four parts, which allow for evaluation of nonmotor symptoms, activities of daily living (ADL), motor symptoms, and complications of therapy. Each symptom is given a numerical score from 0 to 4 (none to severe) to describe severity.[22] The scale is used in both the research and clinical setting and available in multiple languages. Higher scores indicate more severe illness, and similarly, change in score over time will indicate a worsening of illness or improvement of symptoms.

TREATMENT

Desired Outcomes

KEY CONCEPT The goals of treatment include: (a) maintaining patient independence, ADL, and QOL, (b) minimizing motor complications, and (c) limiting medication-related adverse effects.

General Approach to Treatment

KEY CONCEPT Treatment of PD is categorized into three types: (a) lifestyle changes, nutrition, and exercise; (b) pharmacologic intervention; and (c) surgical or other advanced treatments after pharmacologic interventions fail.

Generally, nonpharmacologic approaches such as nutritional adjustments and implementation of an exercise regimen are utilized early and throughout therapy; pharmacologic treatment depends on the patient's age, risk of adverse effects, degree of physical impairment, and readiness to initiate therapy (**Figure 34–2**).[1,23,24]

While older guidance and experts recommended delaying pharmacologic treatment to achieve long-term success, the 2017 guidelines by the National Institute for Health and Care Excellence (NICE) recommend dopamine agonists, levodopa, or monoamine oxidase B (MAO-B) inhibitors be offered to patients even before QOL is affected.[24,25] Ideally, a drug could be utilized early to attain a disease-modifying effect and delay progression of the illness, but no agent has conclusively demonstrated this effect.[15] One must decide when it is best to initiate pharmacotherapy for each individual patient.[5,25-28] Surgical approaches are withheld until after pharmacologic therapies fail or are problematic for most patients.

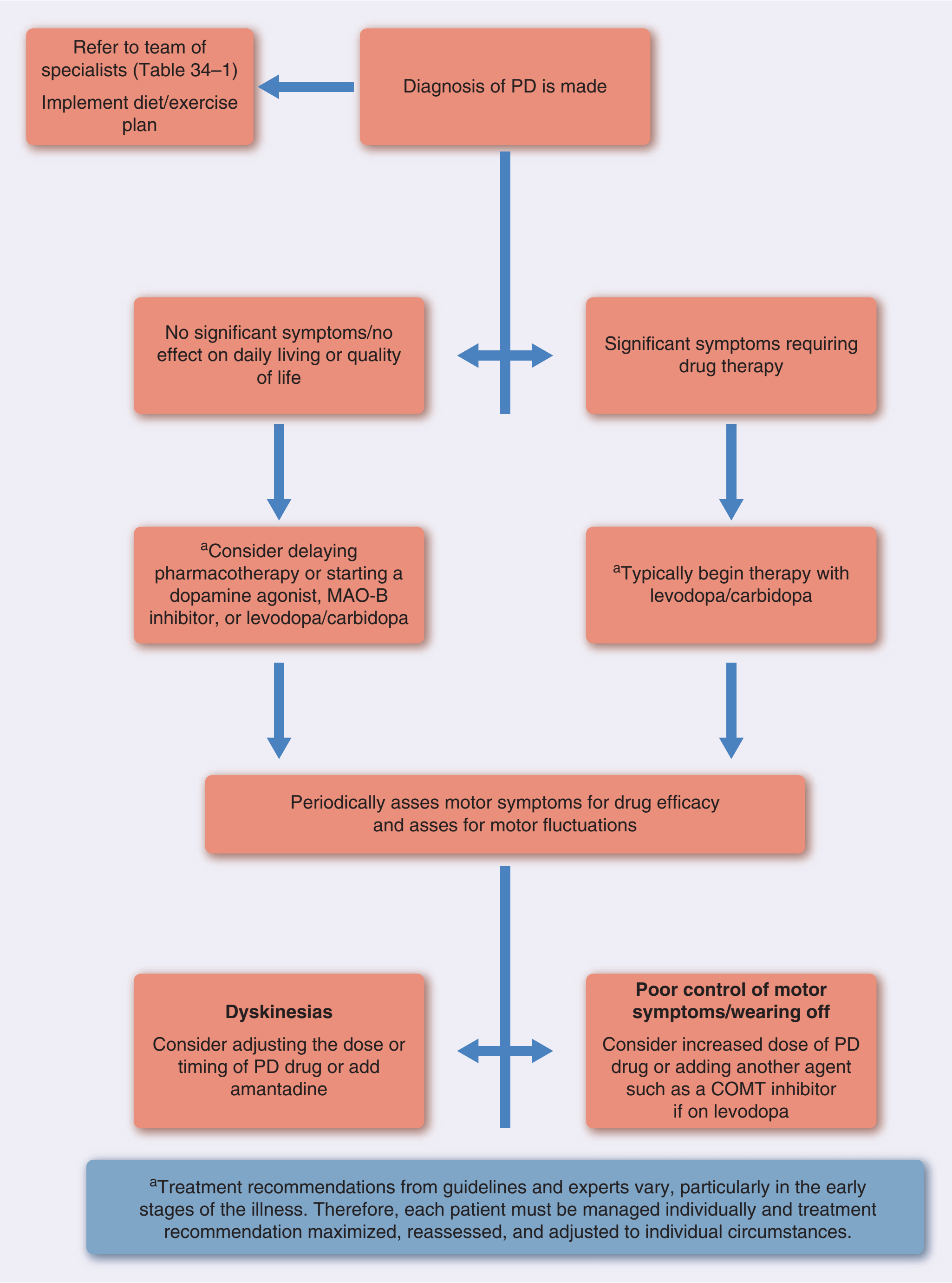
Refer to team of specialists (Table 34–1)
Implement diet/exercise plan
Diagnosis of PD is made
No significant symptoms/no effect on daily living or quality of life
Significant symptoms requiring drug therapy
aConsider delaying pharmacotherapy or starting a dopamine agonist, MAO-B inhibitor, or levodopa/carbidopa
aTypically begin therapy with levodopa/carbidopa
Periodically asses motor symptoms for drug efficacy and asses for motor fluctuations
Dyskinesias
Consider adjusting the dose or timing of PD drug or add amantadine
Poor control of motor symptoms/wearing off
Consider increased dose of PD drug or adding another agent such as a COMT inhibitor if on levodopa
aTreatment recommendations from guidelines and experts vary, particularly in the early stages of the illness. Therefore, each patient must be managed individually and treatment recommendation maximized, reassessed, and adjusted to individual circumstances.

FIGURE 34–2. Algorithm for diagnosis and management of Parkinson disease. Data from Rizek P, Kumar N, Jog MS. An update on the diagnosis and treatment of Parkinson disease. CMAJ. 2016;188(16):1157–1165; Parkinson's Disease in Adults. NICE guideline [NG71]. National Institute for Health and Care Excellence. Available from: https://www.nice.org.uk/guidance/ng71. Accessed July 17, 2021; Nutt JG, Wooten GF. Diagnosis and initial management of Parkinson's disease. N Engl J Med. 2005;353:1021–1027.

Nonpharmacologic Therapy

▶ *Lifestyle Modifications*

Nonpharmacologic therapy and patient education is ideally implemented early and continued throughout treatment. Interventions include maintaining good nutrition, physical condition, and social interactions.[10,29] These treatments may improve ADLs, gait, balance, and mental health. Coordinated care with multiple health care professionals maximizes patient outcomes as each specialist plays a necessary role in the treatment team (Table 34–1).

Surgery

Consider surgery with deep brain stimulation (DBS) when inadequate control of motor symptoms develops despite pharmacotherapy. This procedure electrically stimulates the subthalamic nucleus (STN) or globus pallidus interna. DBS may significantly reduce motor symptoms and complications and improve QOL compared to medication management. Targeting various parts of the brain may decrease the need for escalating drug exposure and better control motor symptoms or decrease the burden of

Patient Encounter Part 2: Initial Visit—Physical Examination and Diagnostic Tests

Chief Complaint: New-onset unilateral tremor and upper body muscle stiffness; decreased sleep quality, depression, problems functioning at work

PMH: Major depressive disorder for 10 years, insomnia for 5 years, hypertension for 3 years

SH: Works part-time as an adjunct professor. Denies alcohol, drug, or tobacco use.

Meds: Rasagiline 1 mg orally once daily, fluoxetine 40 mg orally once daily, metoprolol ER 100 mg orally once daily, doxylamine 50 mg orally at bedtime as needed for insomnia

ROS: (–) Psychosis; reports depression; denies nausea, vomiting, diarrhea, headache, dizziness, or pain

PE:

Gen: Flat affect, looks older than stated age, speaks softly and often difficult to hear, handwriting when completing the intake forms is difficult to read

VS: BP: sitting 135/85, P 60 beats/min, RR 18/min, Wt 47 kg (104 lb), Ht 165 cm (65 in.)

HEENT: Decreased eye blinking and facial expression, CN II-XII intact, PERRLA, TMs intact

CV: RRR, normal S1, S2; no murmurs, rubs, gallop

Abd: Soft, nontender, nondistended; (+) bowel sounds, no hepatosplenomegaly

Exts: Mild-to-moderate tremor in her left arm most noticeable at rest. Mild cogwheel rigidity bilateral elbows

Neuro: Slow, sensory function intact, normal muscle strength, normal reflexes, alert, mental status examination normal

Rating Scales: Patient Health Questionnaire (PHQ-9) = 16; Mini Mental State Examination (MMSE) = 29/30; UPDRS = 65 at current visit; no prior history to compare to

Labs: Normal metabolic profile and CBC

The patient has read about new medications for PD that have been introduced. She would like information on these medications and how to prevent worsening of her symptoms. Plan:

- Discontinue rasagiline
- Initiate pramipexole XR 0.375 mg PO daily

Identify treatment goals for the patient.

Describe nonpharmacologic treatments that should be started for the patient.

Assess the treatment plan and counsel the patient on risks and benefits.

Educate the patient on recently approved drug therapies and on disease modification.

dyskinesias. These surgeries carry risks and are utilized after suboptimal response to drug therapy.[24]

Pharmacologic Therapy of Motor Symptoms

KEY CONCEPT Drug therapy aims to enhance dopaminergic activity in the substantia nigra; they minimize motor symptoms and improve QOL but are not curative (Table 34–2).[7] Even with pharmacotherapy, Patients with PD have greater mortality and morbidity than the general population.[15] **KEY CONCEPT** Choice of pharmacologic agent should be individualized based on patient-specific parameters, and dose regimens based on individual response to maximize on time and minimize off time.

Table 34–1

Specialist Care for Patients with PD[10,34]

Provider	Reason for Referral
Dentist	PD medications may decrease saliva flow and increase the risk of dental caries
Dietician	Recommend appropriate caloric intake, meal selection, and protein consumption which may: • Improve constipation and nausea • Decrease weight loss and aspiration • Minimize erratic drug absorption
Speech therapist	Improved swallowing, articulation, and force of speech
Physical therapy	Improve strength, activity, sleep quality, and reduce fall risk
Occupational therapist	Educate on adaptive environment of home, specialized clothing, and personal training to maximize: • Independence • Safety • ADLs • Driving ability
Social worker	Arrange for community assistance programs and family counseling

Pharmacologic options for motor symptoms in PD include anticholinergics (Ach), amantadine, MAO-B inhibitors, dopamine agonists, levodopa/carbidopa, catechol-*O*-methyltransferase (COMT) inhibitors, and istradefylline. Most experts recommend initial treatment with either levodopa/carbidopa, a monoamine oxidase inhibitor (MAOI) or a dopamine agonist.[14,16,29,30]

Choice between drugs varies based on patient status and preference. Starting with a dopamine agonist may delay the onset of dyskinesias and response fluctuations seen with long-term levodopa use; however, less motor benefit and greater risk of hallucinations or somnolence may occur.[4] Levodopa causes the greatest motor improvement and should be used as initial therapy in the elderly but may increase the risk of motor fluctuations over time.[27] Data are insufficient to recommend initiating treatment with combined drug classes. Initiating treatment with anticholinergic medication or amantadine is recommended only for patients who have mild symptoms because their efficacy is questionable.[16,28-30]

Regardless of the drug initially chosen, the initial dose is low and increased gradually based on symptoms (see Table 34–2). Dose timing and frequency is then adjusted based on the patient's report of on-time duration and wearing off symptoms.[31] Dyskinesias may develop with the use of

Table 34–2

Dosing of Medications Used to Treat PD[35]

Generic Name (Trade Name)	Initial Dose	Titration and Maintenance Dose	Available Formulations	Hepatic or Renal Adjustments
Levodopa Formulations				
Levodopa with carbidopa (Sinemet)	Half tablet (100-mg LD, 25-mg CD) twice daily for 1 week, then half tablet three times daily	Increase by half tablet daily every week; usual MD is 300–2000 mg daily; because the duration of LD is 2–3 hours, patients may require doses every 2 hours	Stalevo—CD/LD/Entacapone tablet	
Sinemet CR	One tablet (100-mg LD, 25-mg CD) two to three times daily	Increase to 200-mg LD tablet two to four times daily; usual MD is 200–2200 mg daily	Sustained-release tablet	
Rytary (extended-release levodopa with carbidopa)	In levodopa-naïve patients: 23.75 mg/95 mg taken orally three times a day for the first 3 days	On the fourth day of treatment, the dosage may be increased to 36.25 mg/145 mg taken three times a day. Individual doses may be increased and doses may be given up to five times a day based on individual response; patients previously on immediate-release levodopa should follow recommended conversions.	Extended-release capsule	
Duodopa (intestinal infusion of LD/CD)	Convert patients to Sinemet and calculate a total daily dose	Dose consists of a morning dose, a continuous infusion, and additional doses. One extra dose per 2 hours is the maximum. Maximum dose is 2000 mg of LD over 16 hours	Intestinal suspension	
Inbrija (inhaled levodopa)	84 mg inhaled up to five times daily as needed	Use as needed for off episodes	Capsule for inhalation	
Dopamine Agonists				
Apomorphine (Apokyn)	Start trimethobenzamide 300 mg for 3 days; then give apomorphine 2 mg SC injection (1 mg if outpatient) while monitoring blood pressure	Continue trimethobenzamide as necessary (generally no longer than 2 months). Increase apomorphine by 1–2 mg every ≥ 2 hours; usual MD is 2–6 mg three to five times daily for off periods	Subcutaneous solution	Reduce initial dose to 1 mg in mild-to-moderate renal failure
Bromocriptine (Parlodel)	1.25 mg twice daily	Increase by 2.5 mg daily every 14–28 days	Capsule, tablet	Dosing adjustments may be necessary with hepatic impairment
Pramipexole (Mirapex)	0.125 mg three times daily	Increase about weekly by 0.375–0.75 mg/day to a MD of 0.5–1.5 mg three times daily	Tablet	Dosage reduction needed in CrCl < 50 mL/min (0.83 mL/s)
Mirapex ER	0.375 mg once daily	Increase up to 0.75 mg/day after a minimum of 5 days. Dose may then be increased in increments of 0.75 mg/day no more frequently than every 5–7 days	Extended-release tablet	
Ropinirole (Requip)	0.25 mg three times daily	Increase about weekly by 0.75–1.5 mg daily to a MD dose of 3–9 mg three times daily Then may increase by 3 mg/day on a weekly basis to a maximum of 24 mg/day	Tablet	
Requip XL	2 mg once daily for 1–2 weeks	Increase by 2 mg/day in 1-week intervals; maximum dose is 24 mg/day	Extended-release tablet	
Rotigotine (Neupro)	2-mg patch once daily for early-stage PD; 4-mg patch for advanced-stage PD	Increase by 2 mg/24 hours on a weekly basis	Patch	

(Continued)

Table 34–2

Dosing of Medications Used to Treat PD[35] (*Continued*)

Generic Name (Trade Name)	Initial Dose	Titration and Maintenance Dose	Available Formulations	Hepatic or Renal Adjustments
MAOIs				
Selegiline (Eldepryl)	5 mg in the morning	If symptoms continue, add 5 mg at noon; 5 mg daily may be as clinically effective as 10 mg daily with fewer side effects	Tablet, capsule	Use is not recommended for CrCl < 30 mL/min (0.5 mL/s) or severe hepatic impairment
Selegiline ODT (Zelapar)	1.25 mg once daily	If symptoms continue after 6 weeks, increase dose to 2.5 mg every morning. Avoid food or liquid for 5 minutes before or after the dose	Dispersible tablet	
Rasagiline (Azilect)	If used with levodopa, 0.5 mg daily	If symptoms continue, increase to 1 mg daily	Tablet	Use 0.5 mg/day in mild hepatic impairment. Do not use in moderate-to-severe impairment
Safinamide (Xadago)	50 mg once daily	May increase after 2 weeks to 100 mg once daily	Tablet	Maximum dose is 50 mg once daily in moderate hepatic impairment and use is contraindicated in severe impairment
COMT Inhibitors				
Tolcapone (Tasmar)	100 mg with first Sinemet dose once daily	If symptoms continue, increase to two and then three times daily, then to 200 mg each dose; usual MD is 100–200 mg three times daily	Tablet	Do not use in patients with active liver disease or SGPT/ALT or SGOT/AST > the upper limit of normal
Entacapone (Comtan)	200-mg tab with each Sinemet dose	Usual MD is 200 mg three to four times daily (up to eight tablets per day)	Tablet	Decrease dose by 50% with hepatic impairment
Opicapone (Ongentys)	50 mg at bedtime	None	Capsule	25 mg in moderate hepatic impairment; avoid in severe impairment
Others				
Amantadine (Symmetrel)	100 mg daily at breakfast	After 1 week, add 100 mg daily; usual MD is 200–300 mg daily with last dose in afternoons	Capsule, tablet, oral syrup	Decrease dose for CrCl < 80 mL/min (1.33 mL/s)
Amantadine XR (Gocovri)	137 mg once daily at bedtime	After 1 week, increase to 274 mg once daily	Extended-release capsule	Start with 68.5 mg once daily in moderate renal impairment and use a maximum dose of 137 mg. In severe renal impairment, use 68.5 mg once daily. Do not use in end-stage renal disease
Amantadine ER (Osmolex ER)	129 mg daily	May increase in weekly intervals to a maximum of 322 mg daily	Extended-release tablet	Start with 129 mg every other day for CrCl 30–59 mL/min (0.5–0.99 mL/s); 129 mg every 96 hours for CrCl 15–29 mL/min (0.25–0.49 mL/s); contraindicated in CrCl < 15 mL/min (0.25 mL/s)
Benztropine (Cogentin)	0.5–1 mg at bedtime	Assess if dose is adequate and titrate by 0.5 mg increments at 5- to 6-day intervals to a maximum of 6 mg if necessary	Tablet, solution for injection	
Istradefylline (Nourianz)	20 mg daily	May increase to 40 mg once daily	Tablet	20 mg daily in moderate hepatic impairment; avoid in severe impairment

Ach, acetylcholine; ALT, alanine transaminase; AST, aspartate aminotransferase; CD, carbidopa; COMT, catechol-*O*-methyltransferase; CR, controlled-release; CrCl, creatinine clearance DA, dopamine; ER, extended-release; LD, levodopa; MAO, monoamine oxidase; MAOI, monoamine oxidase inhibitor; MD, maintenance dose; NMDA, *N*-methyl-D-aspartate; ODT, orally disintegrating tablet; PD, Parkinson disease; SC, subcutaneous; XL, extended release; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; XR, extended-release.

PD drugs and generally relate to dopamine concentrations. Decreasing the dose, frequency, or number of dopaminergic medications may be beneficial. If a PD medication is discontinued, gradual withdrawal is recommended with monitoring of worsening motor symptoms.[30]

▸ *Levodopa/Carbidopa*

Levodopa, a dopamine precursor, remains the most effective agent for PD. Patients experience a 40% to 50% improvement in motor function with levodopa versus 30% with dopamine agonists.[28] However, after 10 years of therapy, close to 90% of patients experience motor complications.[21] Despite this, levodopa is recommended as initial drug therapy and most patients with PD will eventually be treated with it.[15,25,31,32]

Levodopa usually peaks in the plasma in 30 to 120 minutes but the concentration is sensitive to GI variables. Excess stomach acid, food, or medications with anticholinergic properties delay gastric emptying and decrease the amount of levodopa absorbed. Levodopa absorption requires active transport by a large neutral amino acid transporter protein (Figure 34–3). Amino acids in food compete for this transport mechanism. Thus, in advanced disease, avoidance of protein-rich meals in relationship to levodopa doses may be helpful.[3,9]

Controlled-release (CR) formulations act longer than immediate-release tablets but may have erratic absorption. CR preparations are not directly interchangeable with immediate-release but can be added to immediate-release to extend the duration of action. An extended-release (ER) formulation of levodopa (Rytary) is also approved and may provide a more sustained release of levodopa compared to the older CR formulations.[3]

Converting patients from oral formulations to enteral or duodenal levodopa administration improves motor fluctuations and UPDRS scores. The levodopa/carbidopa combination can be administered directly to the duodenum via a small tube. This formulation (Duodopa) is reserved for advanced PD with severe motor fluctuations.[31] Another novel formulation of levodopa includes a dry power inhaler (Inbrija) that can be used for treating off episodes in PD. This is typically reserved for when motor complications develop with standard oral levodopa therapy and as an adjunctive treatment rather than initial monotherapy.[33]

Levodopa is usually administered as a combination product with carbidopa, a dopa-decarboxylase inhibitor, which decreases the peripheral conversion of levodopa to dopamine. This allows for lower levodopa doses and minimizes levodopa peripheral side effects (nausea, vomiting, anorexia, and hypotension). Carbidopa does not cross the blood–brain barrier and does not interfere with

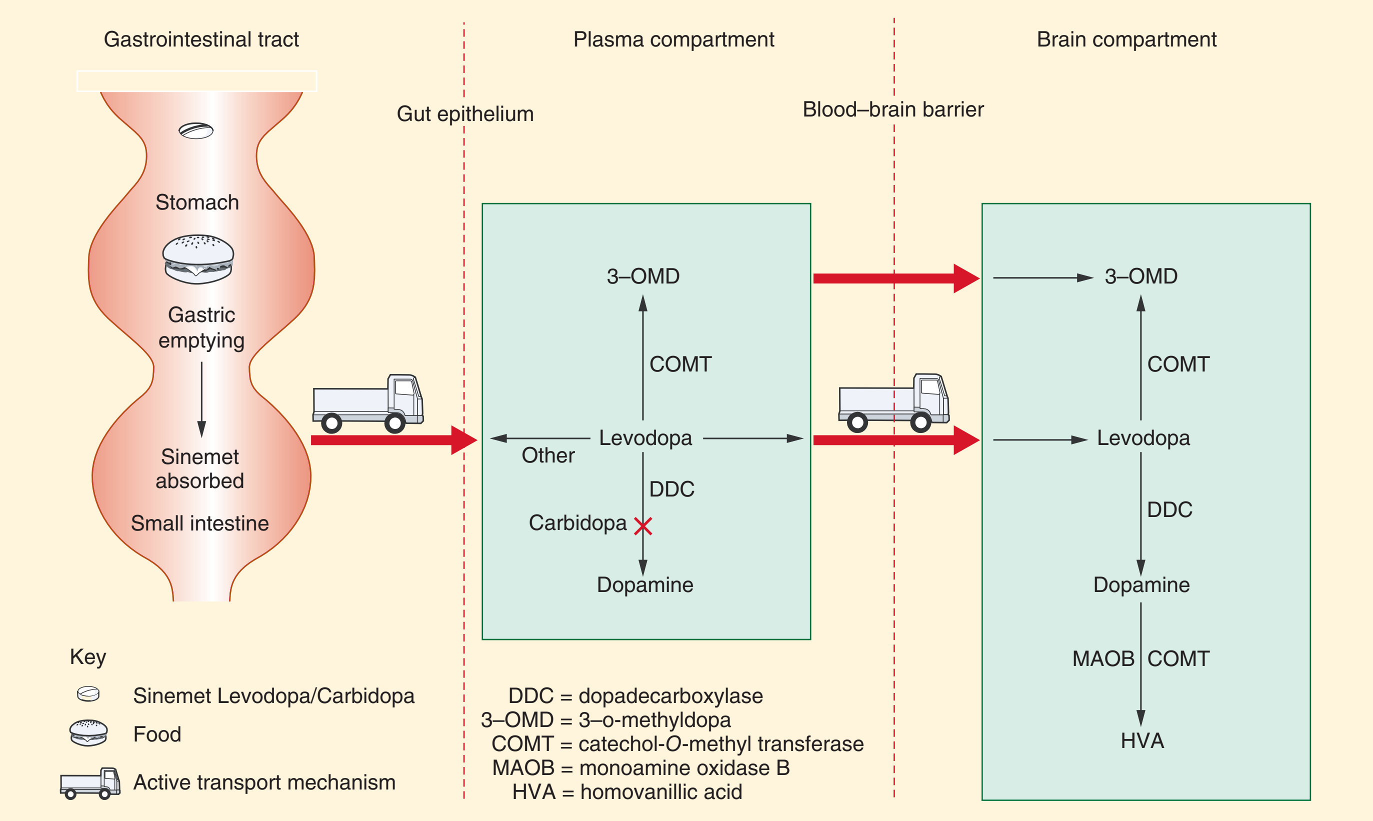
Gastrointestinal tract
Plasma compartment
Brain compartment
Gut epithelium
Blood–brain barrier
Stomach
Gastric emptying
Sinemet absorbed
Small intestine
3–OMD
COMT
Levodopa
Other
DDC
Carbidopa
Dopamine
3–OMD
COMT
Levodopa
DDC
Dopamine
MAOB
COMT
HVA
Key
Sinemet Levodopa/Carbidopa
Food
Active transport mechanism
DDC = dopadecarboxylase
3–OMD = 3–o-methyldopa
COMT = catechol-O-methyl transferase
MAOB = monoamine oxidase B
HVA = homovanillic acid

FIGURE 34–3. Levodopa absorption and metabolism. Levodopa is absorbed in the small intestine and distributed into the plasma and brain compartments by an active transport mechanism. Levodopa is metabolized by dopa-decarboxylase, monoamine oxidase, and catechol-*O*-methyltransferase. Carbidopa does not cross the blood–brain barrier. Large neutral amino acids in food compete with levodopa for intestinal absorption (transport across gut endothelium to plasma). They also compete for transport into the brain (plasma compartment to brain compartment). Food and anticholinergics delay gastric emptying resulting in levodopa degradation in the stomach and a decreased amount of levodopa absorbed. If the interaction becomes a problem, administer levodopa 30 minutes before or 60 minutes after meals.

levodopa conversion in the brain. Generally, 75 to 100 mg daily of carbidopa is required to adequately block peripheral dopa-decarboxylase. Higher doses of carbidopa may reduce nausea when initiating levodopa.[9,34]

Initial levodopa side effects include orthostatic hypotension, dizziness, anorexia, nausea, vomiting, and discoloration of urine/sweat. Most of these effects can be minimized by taking levodopa with nonprotein food and by slowly titrating the dose. Side effects that develop later in therapy include dyskinesias, sleep attacks, **impulse control disorders** (ICDs), and psychiatric effects (confusion, hallucinations, nightmares, and altered behavior). Dyskinesias caused by adding other PD drugs to levodopa may be improved by decreasing the levodopa dose.[9,27,34]

▶ *Catechol-O-Methyltransferase (COMT) Inhibitors*

Inhibitors of COMT, an enzyme that catalyzes levodopa to 3-*O*-methyldopa, are added to levodopa/carbidopa to increase levodopa concentrations, extend its half-life, and decrease wearing off time. Using the COMT inhibitors, entacapone, tolcapone, or opicapone, may allow for a decrease in daily levodopa dose while increasing on time by 1 to 2 hours. Side effects include diarrhea, nausea, vomiting, anorexia, dyskinesias, urine discoloration, daytime sleepiness, sleep attacks, orthostatic hypotension, and hallucinations.[9,27]

Tolcapone should be used only in patients who do not tolerate or respond to others in the class due to its hepatic safety profile. Serum liver function tests should be monitored at baseline and throughout therapy.[35,36]

▶ *MAO-B Inhibitors*

Safinamide, selegiline, and rasagiline work through a selective blockade of dopamine metabolism through MAO-B. These provide a mild symptomatic benefit for patients who choose to delay dopaminergic medications and use MAO-B inhibitors as initial therapy. For patients with motor fluctuations, they reduce off time when added to levodopa therapy.[3,12,28]

Selegiline is generally well tolerated. Adverse effects include nausea, confusion, hallucinations, jitteriness, insomnia, and orthostatic hypotension. Selegiline is available as an orally disintegrating tablet (ODT) designed to avoid first-pass metabolism. This improves bioavailability and decreases serum concentrations of its amphetamine-like metabolite that may cause insomnia.[3,15] Daily doses are limited to 10 mg because MAO-B selectivity may be lost at higher doses, increasing the risk of drug and food interactions. Doses for the ODT are lower because this selectivity may be lost at smaller doses with this formulation.[35]

Rasagiline has a similar, generally well-tolerated adverse effect profile but is less likely to cause insomnia compared to selegiline as it lacks the amphetamine-like metabolite. In contrast to nonselective MAOIs, restriction of tyramine-containing foods is not required at recommended dosages, but high tyramine-containing food or exceeding recommend dosing of rasagiline may increase the risk of hypertensive crisis.[35,37]

Safinamide is a newer MAO-B approved for PD. It is indicated specifically in conjunction with levodopa/carbidopa after patients begin to experience off episodes; however, it will likely be used in similar situations as the other MAO-B antagonists.[37,38]

Risk of dyskinesias is minimized by decreasing the levodopa dose when adding any of these agents. Serotonin syndrome and hypertensive crisis may occur in patients using these medications with opioid analgesics, antidepressants and other serotonergic agents, or sympathomimetic amines (cold and weight loss products) (see Chapter 38).[9,15]

▶ *Dopamine Agonists*

Dopamine agonists bind to postsynaptic dopamine receptors and are reasonable as initial therapy. Their advantages include delay of levodopa therapy and smaller risk of developing motor fluctuations during the first 3 to 5 years of treatment. Eventually, they inadequately control the patient's symptoms, and levodopa is necessary. In advanced disease, they can be added to levodopa to minimize response fluctuations, decrease off time, improve wearing off symptoms, and allow a reduction in levodopa dose.[1,15,29,38]

Dopamine agonists include the ergot derivatives (bromocriptine) and the nonergot derivatives (rotigotine, pramipexole, ropinirole, and apomorphine). Generally, the nonergot agents are preferred due to a more favorable adverse-effect profile. Rotigotine is available as a once-daily skin patch and has demonstrated to improve sleep and control of symptoms in the early morning.[1,25] Apomorphine is subcutaneously injected for acute off episodes in advanced PD when rapid rescue therapy is needed. It requires premedication with an antiemetic due to nausea and vomiting.[1,9]

Common side effects with all dopamine agonists include nausea, sedation, pedal edema, orthostatic hypotension, and psychiatric effects that are greater than with levodopa (nightmares, confusion, and hallucinations). Rare, but serious ergot side effects include painful reddish discoloration of the skin over the shins and pleuropulmonary, retroperitoneal, and cardiac fibrosis.[9,30,35] Patients should be given warning information regarding the potential for ICDs and the dopamine dysregulation syndrome (DDS). DDS includes drug seeking and possibly complex stereotyped behavior (**punding**); ICDs manifest as gambling, compulsive shopping, compulsive sexual behavior, or binge eating. While these can occur with other PD drugs, the dopamine agonists are the most risky, particularly in older patients. Data show ICDs may occur in up to 40% of patients with dopamine agonists and are related to dose and duration.[30] Reducing or eliminating the agonist typically resolves these adverse effects.[39]

Dopamine agonists may cause excessive daytime sleepiness in PD patients including sudden sleep attacks that are potentially dangerous.[37,40]

▶ *Anticholinergics*

Ach (typically benztropine and trihexyphenidyl) minimize resting tremor and drooling but are not as effective as other agents for rigidity, bradykinesia, and gait problems. Because of their side effects including cognitive impairment, Ach are typically avoided in older patients, and tend to be used only early in therapy with younger patients.[28] Their inhibition of gastric motility may lead to erratic and decreased levodopa absorption. Lastly, they may worsen urinary retention or constipation.[1]

▶ *Amantadine*

Amantadine is an *N*-methyl-D-aspartate (NMDA)-receptor antagonist that blocks glutamate transmission, promotes dopamine release, and blocks acetylcholine.[35] It is likely effective as monotherapy and adjunct therapy for off time and for dyskinesias.[37,41] ER formulations are approved specifically for dyskinesias in PD making it the only FDA (Food and Drug

Administration)-approved option for this complication.[35,42] Side effects include nausea, dizziness, livedo reticularis, peripheral edema, orthostatic hypotension, hallucinations, restlessness, anticholinergic effects, and insomnia. Insomnia is minimized by taking the ER formulation at bedtime and the immediate release formulation earlier in the day. It should be avoided in the elderly who cannot tolerate its anticholinergic effects.[43]

▸ *Istradefylline*

Approved in the United States in 2019, the adenosine receptor antagonist istradefylline offers a nondopaminergic option for PD patients who experience off episodes. Initial studies found between one half and one hour increase in on time without dyskinesias when added to levodopa therapy. Dizziness, nausea, and hallucinations were among the most common adverse effects seen in clinical trials and concerns with dyskinesia are present with this drug similar to other PD therapies.[44]

▸ *Herbs and Supplements*

There is very little support for using herbals in PD. Patients should eat a balanced diet and monitor weight.[29] Because of osteoporosis and fall risk, consider providing a vitamin D supplement in patients with low concentrations.[24,28]

Treatment of Nonmotor Symptoms

KEY CONCEPT Treatment of nonmotor symptoms should be based on whether they are exacerbated by an off state or might be related to other neurotransmitter dysfunction.

Treatment of nonmotor symptoms includes both pharmacologic and nonpharmacologic approaches with goals of maintaining ADLs, a positive self-image, family communication, and a safe environment.

Psychological Symptoms

Psychological symptoms are common complaints in PD. When these are present, infections, metabolic changes, electrolyte disturbances, or toxic exposures are examined first to rule out other etiologies.

▸ *Depression*

Depression is common in patients with PD, affecting 35% or more of patients, and it often precedes the disease.[36] Although evidence supports efficacy of tricyclic antidepressants, their adverse effects are limiting. Alternatively, selective serotonin reuptake inhibitors may be considered because of their increased tolerability. Antidepressants are also useful for the treatment of anxiety disorders. Pramipexole has demonstrated to improve depression as well in patients with PD.[19,22] Because off periods can both precipitate anxiety and worsen depression, PD therapy should be adjusted to maximize on periods.[11,16]

▸ *Dementia*

Dementia occurs in approximately 80% of patients with PD 20 years after diagnosis. Rivastigmine is considered useful with the highest quality of evidence and is FDA approved for dementia in PD.[11,16,36,37]

Psychosis

Treating psychosis in PD can be difficult as most antipsychotics act as dopamine antagonists, mechanistically opposing PD drugs thus worsening motor symptoms. Additionally, all antipsychotics carry a black box warning of increased risk of death when used in patients with dementia.[35,36] Therefore, first treat any underlying medical causes for psychosis; then, gradually decrease and stop low-efficacy PD medications. If these strategies fail, antipsychotics may be considered.[18] Pimavanserin is the only antipsychotic specifically approved for PD psychosis and has the lowest risk of worsening motor symptoms. However, it is expensive, needs to be dispensed through a specialty pharmacy, interacts with CYP3A4 drugs, and can prolong QT interval.[18,35,45] Two other antipsychotics are recommended over others: clozapine is more effective, but traditionally, low-dose quetiapine has been preferred because clozapine requires monitoring for neutropenia (see Chapter 38). Neither is approved in PD but are preferred because of their weak dopamine antagonism and less frequent movement adverse effects.[11,45] While antipsychotics appear in the Beers criteria with a general recommendation to avoid in the elderly, these three drugs are listed as exceptions in PD patients.[46]

Sleep Problems

Sleep problems and fatigue are common in PD and may be due to medications, uncontrolled symptoms, or other causes such as nocturia, sleep attacks during the day, depression, SBD, or restless legs syndrome (RLS).[36,40] Amantadine and selegiline may worsen insomnia and some antidepressants and antipsychotics may worsen RLS; therefore, careful evaluation of drug regimens is necessary in patients with sleep complaints.

Reducing RLS may be achieved through PD medications. The rotigotine patch improves overall sleep quality as well as morning motor symptoms.[47] Iron supplementation for RLS may decrease levodopa absorption in addition to worsening constipation.[11,16] Improving nighttime motor symptoms, maximizing sleep hygiene, or implementing cognitive behavioral therapy may help as well.[16,47]

Many over-the-counter sleep aids have anticholinergic properties and should be used with caution in this population.

Autonomic and Other Problems

Drooling may accompany speech problems and dysphagia. Ach, botulinum toxin injections, and sublingual atropine can decrease drooling.[30,36]

Sexual dysfunction may respond with increased on time, removal of drugs that decrease sexual response, and pharmacologic therapy (eg, sildenafil).[15,16]

Patients with urinary frequency may find a bedside urinal and decreased evening fluid intake helpful. Improvement in PD symptoms can decrease urinary frequency, but symptoms may require catheterization or pharmacologic measures (eg, solifenacin).[19]

Constipation may improve with increased fluid intake, a fiber-rich diet, probiotics, and physical activity. Stool softeners or other laxatives may help including lubipristone.[15,16,19]

Treating orthostasis includes the removal of offending drugs, increasing carbidopa doses, increasing salt or fluids to the diet, and adding compression stockings or drugs (fludrocortisone, midodrine, and droxidopa). Droxidopa, a norepinephrine synthetic precursor, is approved for treating orthostatic hypotension associated with PD. It can cause supine hypertension, which may be mitigated with elevation of the head of the bed and requires monitoring of blood pressure with treatment. Patients should not take this within 3 hours of bedtime and should take it consistently with or without food.[19,35,37]

Table 34–3

Management of Motor Complications in Advanced PD[2,3,11,13,20,27,29]

I. Motor Fluctuations

Nonpharmacologic Approaches	Drugs to Alter Formulation or Dose	Drugs to Add
A. Suboptimal or delayed peak response		
Take Sinemet on an empty stomach Decrease dietary protein and fat around the delayed dose Minimize constipation Assess for *Helicobacter pylori* infection	Crush Sinemet or make liquid Sinemet Substitute standard Sinemet for some of the Sinemet CR Withdraw drugs with anticholinergic properties	Intermittent subcutaneous apomorphine
B. Optimal peak but early wearing off		
	Decrease dose and increase frequency of standard Sinemet Substitute Sinemet CR for some of the standard Sinemet	Dopamine agonist MAO-B inhibitor Amantadine COMT inhibitor
C. Optimal peak but unpredictable offs		
Adjust time of medications with meals and avoid high-protein meals or redistribute the amount of protein in diet Deep brain stimulation procedure	Substitute or add liquid Sinemet Switch to a different dopamine agonist if already on an agent Consider continuous infusion of levodopa or apomorphine	COMT inhibitor Dopamine agonist if not using one
D. Freezing		
Gait modifications (use visual cues such as walkover lines, tapping, rhythmic commands, rocking; use rolling walker) Physical therapy	Difficult to treat—adjust current medications based on other PD symptoms. Guide changes based on: On freezing, reduce dopamine medications, inject botulinum toxin Off freezing, increase Sinemet dose or add dopamine agonists	If present, treat anxiety with pharmacologic agents

II. Dyskinesias

Nonpharmacologic Approaches	Drugs to Alter Formulation or Dose	Drugs to Add
A. Chorea		
Deep brain stimulation	Decrease risk of occurrence by lowering Sinemet dose when adding other PD medications Evaluate the value of adjunctive PD medications and discontinue if motor complications outweigh benefit Adjust levodopa formulation, dose, or frequency	Amantadine Clozapine
B. Off period dystonia in the early morning		
No recommendations	Add or change short acting to long-acting formulations at bedtime if having nighttime off periods Change morning Sinemet CR dose to immediate-release with or without CR	Apomorphine
C. Diphasic dyskinesia		
Deep brain stimulation	Change CR preparations to immediate release; consider liquid Sinemet Increase Sinemet dose and frequency	Dopamine agonist Amantadine COMT inhibitor

COMT, catechol-*O*-methyl transferase; CR, controlled-release; MAO-B, monoamine oxidase B; PD, Parkinson disease

Treatment of Response Fluctuations

KEY CONCEPT As the disease progresses, most patients develop response fluctuations. Treatment capitalizes on the pharmacokinetic and pharmacodynamic properties of PD medications.

Treatment includes adjusting or adding medications to maximize the patient's on time, minimizing the time with dyskinesia, and minimizing off time (Table 34–3). Levodopa doses and intervals are adjusted for suboptimal or delayed peak levodopa concentrations. Longer acting formulations decrease wearing off periods. Adding or adjusting medications to combat unpredicted off periods and providing treatments that decrease freezing episodes may be necessary. Treatment plans also involve adjusting medication plans or surgery to decrease chorea, dystonia, diphasic dyskinesias, or akathisia.[3,11,14,29]

Patient Encounter Part 3: Follow-up Visit 6 Months Later

Six months have passed since the patient was last seen and her medication was altered. She is still complaining of depression, motor symptoms, and dizziness. Her UPDRS score is unchanged. Her husband has noticed that she is requesting early refills on her pramipexole and is demanding on taking them on time.

Create a problem list and provide an assessment of each problem.

Considering the goals of therapy, treatment options, and your assessment of each of the problems, create a care plan for each problem.

Patient Care Process

Collect Information:

- Review the physical examination and note the specific set of symptoms including their frequency and exacerbating factors.
- Collect diagnostic data such as the UPDRS and compare this to previous encounters.
- Obtain a complete medication list.

Assess the Information:

- Assess PD symptom impact on quality of life (QOL) and ADLs.
- Identify worsening of motor symptoms or disease progression.
- Determine if on time is maximized and whether medications require adjustment.
- Identify drug-induced dyskinesias and note specific times when these occur.
- Evaluate for the appropriate use of each medication including noting drugs, which may worsen PD symptoms as well as polypharmacy for PD.
- Assess if nonmotor symptoms are being adequately addressed.
- Assess the complete PD pharmacologic profile for drug or diet interactions, adverse drug reactions, adherence, and patient understanding of medication regimens.

Develop a Care Plan:

- Identify other specialists to engage in a complete health care team plan.
- Recommend a therapeutic regimen for motor symptoms that increases quality of life and daily functioning.
- Adjust dosages and timing of medications to maximize on time and reduce dyskinesia.
- Recommend drug therapy and other options for nonmotor symptoms that will not worsen motor symptoms.
- Develop a detailed medication administration schedule that is simple for the patient to follow, especially if medications with multiple daily dosing schedules are used.

Implement the Care Plan:

- Educate the patient about lifestyle modifications that will improve symptoms and sustain independence.
- Provide instruction on how to use medications including timing of doses with food.
- Educate the patient on how to adjust medications for fluctuations in response.
- Provide information to the patient and family and document about risks with dopaminergic drugs such as impulse control disorders, sudden sleep attacks, and psychosis.
- Refer the patient and family members to further information such as books and websites (http://www.parkinson.org). Provide information concerning local PD support groups when available.

Follow-up: Monitor and Evaluate:

- Instruct the patient to follow up for assessment of symptoms and disease progression.
- Follow up at least every 6 to 12 months, determine control of symptoms and if drug interactions or adverse reactions are present.
- Provide patient education on changes to medication regimens and nonpharmacologic options.

OUTCOME EVALUATION

KEY CONCEPT Patient monitoring involves a regular systematic evaluation of efficacy and adverse events of medication, referral to appropriate specialists, and patient education. Evaluate clinical outcomes over time by assessing the change in the UPDRS. Instruct patients to record the amount of on and off times daily to guide medication adjustment. Assess fall risk and implement safety measures to prevent falls. Scales assessing QOL, depression, anxiety, and sleep disorders are useful to track progression.

Abbreviations Introduced in This Chapter

Ach	Anticholinergics
ADL	Activities of daily living
COMT	Catechol-*O*-methyltransferase
CR	Controlled-release
DBS	Deep brain stimulation
DDS	Dopamine dysregulation syndrome
GI	Gastrointestinal
ICD	Impulse control disorder
MAO	Monoamine oxidase
NMDA	*N*-methyl-D-aspartate
PD	Parkinson disease
QOL	Quality of life
REM SBD	Rapid eye movement sleep behavior disorder
RLS	Restless legs syndrome
TRAP	Tremor, rigidity, akinesia/bradykinesia, postural/gait instability
UPDRS	Unified Parkinson Disease Rating Scale

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35

Pain Management

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Identify characteristics of the types of pain: nociceptive, inflammatory, neuropathic, and nociplastic.
2. Explain the mechanisms involved in pain transmission.
3. Select an appropriate method of pain assessment.
4. Recommend an appropriate choice of analgesic, dose, and monitoring plan for a patient based on type and severity of pain and other patient-specific parameters.
5. Perform calculations involving equianalgesic doses, conversion of one opioid to another, rescue doses, and conversion to a continuous infusion.
6. Educate patients and caregivers about effective pain management, dealing with chronic pain, and the use of nonpharmacologic measures.

INTRODUCTION

Pain is defined by the International Association for the Study of Pain (IASP) as "an unplesant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1] KEY CONCEPT Pain is an unpleasant subjective experience that is the net effect of a complex interaction of the ascending and descending neurons involving biochemical, physiologic, and psychological processes. Pain can affect all areas of a person's life including sleep, thought, emotion, and activities of daily living. There are no reliable objective markers for pain; thus, the patient is the only person who can describe the intensity and quality of their pain.

EPIDEMIOLOGY AND ETIOLOGY

Prevalence of Pain

Most people experience pain at some time in their lives, and pain is a symptom of a variety of diseases. Thus, identifying the exact prevalence of pain is a difficult task. Prevalence rates for a variety of different types of pain have been described (Table 35–1). Patients 65 years and older bear a significant burden of pain. The prevalence of pain in people older than 60 years is twice that in those younger than 60 years.[2] Studies suggest that 25% to 50% of community-dwelling elderly suffer pain. Pain is quite common among nursing home residents. It is estimated that 45% to 80% of nursing home patients and 25% of those with daily pain received neither analgesic medication nor nonpharmacologic treatment for their pain, contributing to functional impairment and a decreased quality of life.[2]

The financial impact of pain is considered to be significant. The total cost of pain in the United States has been estimated at $560 to $635 billion annually; about half of this cost is due to direct costs of health care while the other half is due to lost productivity.[3]

Challenges in Pain Management

Effective pain management should be balanced and multimodal, including, in some cases, the use of opioid analgesics. However, there is growing controversy over both the efficacy and the safety of opioid analgesics in managing patients with chronic pain. In 2011, the Institute of Medicine outlined several other important principles to guide the transformation of pain care, which included the following[4]:

- Effective pain management is a "moral imperative."
- Pain should be considered a disease with distinct pathology.
- There is a need for interdisciplinary treatment approaches.
- The effectiveness of pain treatment depends on a strong clinician–patient relationship.

Barriers to adequate pain management may be due to the fear of becoming addicted to opioids or cultural beliefs. Patients might not report pain for a variety of reasons including belief that pain is something they must live with, fear of consequences (eg, hospitalization, loss of independence), fear that the pain might be forecasting impending illness, the inability to understand terminology used by health care providers, or a belief that showing pain is unacceptable behavior.

Concerns about adequate pain management must be balanced with concerns about opioid misuse and diversion to achieve optimal pain management. Opioid use, misuse, and adverse effects have risen to epidemic proportions since the 1990s. While the United States has 4.4% of the global population, the country used 80% of the world's opioid supply.[5] Over the last 18 years, there has been an increase in deaths related to prescription opioids and increase in over doses due to illicit opioids.[6] Several recent guidelines have been published by the Centers for Disease Control and Prevention (CDC) and American Society of Interventional Pain

Table 35–1

Prevalence of Selected Pain Diagnoses[44–49]

Pain Diagnoses	Prevalence (%)
Back pain	74.7
Cancer	14–100
Chronic pain	10.4
Complex regional pain syndrome	1.2
Degenerative spine disease	63.6
Fibromyalgia	2
Limb pain	50
Migraine	12
Neuritis/radiculitis	52.8
Neuropathic pain	9.8

Physicians (ASIPP) to provide guidance for the use of opioids to ensure patients have access to safer, more effective chronic pain treatment while reducing the number of people who misuse or overdose from these drugs.[7,8] Risk assessment and monitoring of opioid use includes a clinical interview with special attention to the effects of opioids or illnesses suggestive of substance abuse, pain characteristics, and consequences, use of prescription drug monitoring program and risk assessment tools (ie, Opioid Risk Tool), initial urine drug screens, and screening for sleep disorders and mental health issues. Implementation of risk assessment and mitigation strategies along with a heightened awareness by clinicians of the potential deleterious effects of opioids has led to a plateau or decline in diversion and abuse of prescription opioids in recent years.[9]

PATHOPHYSIOLOGY

Types of Pain

Several distinct types of pain have been described, for example, nociceptive, inflammatory, neuropathic, and nociplastic.[1] Nociceptive pain is a transient pain in response to a noxious stimulus at nociceptors that are located in cutaneous tissue, bone, muscle, connective tissue, vessels, and viscera. Nociceptors are classified as thermal, chemical, or mechanical. The nociceptive system extends from the receptors in the periphery to the spinal cord, brainstem, and the cerebral cortex where pain sensation is perceived. This system is a key physiologic function that prevents further tissue damage due to the body's autonomic withdrawal reflex. When tissue damage occurs despite the nociceptive defense system, inflammatory pain ensues. The body now changes focus from protecting against painful stimuli to protecting the injured tissue. The inflammatory response contributes to pain hypersensitivity that serves to prevent contact or movement of the injured part until healing is complete, thus reducing further damage.

Neuropathic pain is defined as spontaneous pain and hypersensitivity to pain associated with damage to or pathologic changes in the peripheral or central nervous system (CNS).[1] Nociplastic pain, a relatively newer concept, is pain sensitivity due to an abnormal processing or functioning of the CNS in response to normal stimuli. Several conditions considered to have this abnormal sensitivity or hyperresponsiveness include fibromyalgia and irritable bowel syndrome.

Mechanisms of Pain

▶ *Pain Transmission*

The mechanisms of nociceptive pain are well defined and provide a foundation for the understanding of other types of pain.[10] Following nociceptor stimulation, tissue injury causes the release of substances (bradykinin, serotonin, potassium, histamine, prostaglandins, and substance P) that might further sensitize and/or activate nociceptors. Nociceptor activation produces action potentials (transduction) that are transmitted along myelinated Aδ-fibers and unmyelinated C-fibers to the spinal cord. The Aδ-fibers are responsible for first, fast, sharp pain, and release excitatory amino acids that activate α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors in the dorsal horn. The C-fibers produce second pain, which is described as dull, aching, burning, and diffuse. These nerve fibers synapse in the dorsal horn of the spinal cord, where several neurotransmitters are released including glutamate, substance P, and calcitonin gene-related peptide. Transmission of pain signals continues along the spinal cord to the thalamus, which serves as the pain relay center, and eventually to the cortical regions of the brain where pain is perceived.

▶ *Pain Modulation*

Modulation of pain (inhibition of nociceptive impulses) can occur by a number of processes. Based on the gate-control theory, pain modulation might occur at the level of the dorsal horn.[11] Because the brain can process only a limited number of signals at one time, other sensory stimuli at nociceptors might alter pain perception. This theory supports the effectiveness of counterirritants and transcutaneous electrical nerve stimulation (TENS) in pain management. Pain modulation can occur through several other complex processes. The endogenous opiate system consists of endorphins (enkephalins, dynorphins, and β-endorphins) that interact with μ-, δ-, and κ-receptors throughout the CNS to inhibit pain impulses and alter perception. The CNS also includes inhibitory descending pathways from the brain that can attenuate pain transmission in the dorsal horn. Neurotransmitters involved in this descending system include endogenous opioids, serotonin, norepinephrine, γ-aminobutyric acid (GABA), and neurotensin. The perception of pain involves not only nociceptive stimulation but also physiologic and emotional input. Consequently, cognitive behavioral treatments such as distraction, relaxation, and guided imagery can reduce pain perception by altering pain processing in the cortex.

▶ *Peripheral Sensitization, Central Sensitization, and Windup*

Under normal conditions, a balance generally exists between excitatory and inhibitory neurotransmission. Changes in this balance can occur both peripherally and centrally, resulting in exaggerated responses and sensitization, such as that observed in inflammatory, neuropathic, or nociplastic chronic pain. Pain in these settings might occur spontaneously without any stimulus or might be evoked by a stimulus. Evoked pain might arise from a stimulus that normally does not cause pain (allodynia) such as a light touch in neuropathic pain. Hyperalgesia, an exaggerated and/or prolonged pain response to a stimulus that normally causes pain, can also occur as a result of increased sensitivity in the CNS.

During normal pain transmission, the AMPA receptors are activated, but the *N*-methyl-ᴅ-aspartate (NMDA) receptor is blocked by magnesium.[10] Repeated nerve depolarization causes release of the magnesium block, allowing the influx of calcium and sodium, and results in excessive excitability and amplification of signals. Continued input from C-fibers and subsequent increases in substance P and glutamate causes the activation of the NMDA receptor, a process referred to as windup. Windup increases the number and responsiveness of neurons in the dorsal horn irrespective of the input from the periphery. Recruitment of neurons not normally involved in pain transmission or spread occurs, leading to allodynia, hyperalgesia, and spread to uninjured tissues.[12] The windup phenomenon supports the observation that untreated acute pain can lead to chronic pain and the belief that pain processes are plastic and not static.

CLINICAL PRESENTATION AND DIAGNOSIS

Classification of Pain

Pain has always been described as a symptom. However, recent advances in the understanding of neural mechanisms have demonstrated that unrelieved pain might lead to changes in the nervous system known as neural plasticity. Because these changes reflect a process that influences a physiologic response, pain, particularly chronic pain, might be considered a disease unto itself.

Pain can be divided into two broad categories: acute and chronic pain. Acute pain is also referred to as adaptive pain because it serves to protect the individual from further injury or promote healing.[11] However, chronic pain has been called maladaptive, a pathologic function of the nervous system or pain as a disease.

► *Acute Pain*

Acute pain is pain that occurs as a result of injury or surgery and usually self-limited, subsiding when the injury heals. Untreated acute pain can produce physiologic symptoms including tachypnea, tachycardia, and increased sympathetic nervous system activity, such as pallor, diaphoresis, and pupil dilation. Furthermore, poorly treated pain can cause psychological stress and compromise the immune system due to the release of endogenous corticosteroids. Somatic acute pain arises from injury to skin, bone, joint, muscle, and connective tissue, and it is generally localized to the site of injury. Visceral pain involves injury to nerves on internal organs (eg, intestines, liver) and can present as diffuse, poorly differentiated, and often referred pain. Acute pain should be treated aggressively, even before the diagnosis is established, except in conditions of head or abdominal injury where pain might assist in the differential diagnosis.

► *Chronic Pain*

Chronic pain persists beyond the expected normal time for healing and serves no useful physiologic purpose. Chronic pain might be nociceptive, inflammatory, neuropathic, or nociplastic in origin; however, all forms share some common characteristics. Chronic pain can be intermittent or persistent, or both. Physiologic responses observed in acute pain are often absent in chronic pain; however, other symptoms might predominate. The four main effects of chronic pain include (a) effects on the physical function, (b) psychological changes, (c) social consequences, and (d) societal consequences. Effects of chronic pain on physical function include impaired activities of daily living and sleep disturbances. Psychological components of chronic pain might include depression, anxiety, anger, and loss of self-esteem. As a result of physical and psychological changes, social consequences might ensue, such as changes in relationships with friends and family, intimacy, and isolation. Management of chronic pain should be multimodal and might involve cognitive interventions, physical manipulations, pharmacologic agents, surgical intervention, and regional or spinal anesthesia.

Chronic Malignant Pain Chronic malignant pain is associated with a progressive disease that is usually life-threatening such as cancer, acquired immunodeficiency syndrome (AIDS) AIDS, progressive neurologic diseases, end-stage organ failure, and dementia.[13] The goal is pain alleviation and prevention, often through a systematic and stepwise approach. Tolerance, dependence, and addiction are often not a concern due to the terminal nature of the illness.

Clinical Presentation and Diagnosis of Pain

General

Patients may be in acute distress (acute pain) or have no signs or symptoms of suffering (chronic pain).

Symptoms

Pain is described based on the following characteristics: onset, duration, location, quality, severity, and intensity. Other symptoms may include anxiety, depression, fatigue, anger, fear, and insomnia.

Signs

Acute pain may cause hypertension, tachycardia, diaphoresis, mydriasis, and pallor.

Diagnosis

The patient is the only person who can describe the intensity and quality of their pain. There are no laboratory tests that can diagnose pain.

Chronic Nonmalignant Pain Pain not associated with a life-threatening disease and lasting more than 6 months beyond the healing period is referred to as chronic nonmalignant pain. Pain associated with low back pain, osteoarthritis, previous bone fractures, peripheral vascular disease, genitourinary infection, rheumatoid arthritis, and coronary heart disease is considered nonmalignant. The numerous causes of this type of chronic pain make treatment complex and involves a multidisciplinary approach. Treatment is initially conservative utilizing a combination of nonpharmacologic and pharmacologic modalities such as acetaminophen, oral and topical nonsteroidal anti-inflammatory agents, and adjunctive treatment based on the cause of the pain. In cases of inadequate response to an adequate trial of initial therapy, the use of more potent analgesics including opiates may be considered with careful monitoring.[14]

Neuropathic Pain Neuropathic pain is considered to be a type of chronic nonmalignant pain involving disease of the central and peripheral nervous systems. Neuropathic pain might be broadly categorized as peripheral or central in nature. Examples of neuropathic pain include postherpetic neuralgia (PHN), which is pain associated with acute herpetic neuralgia or an acute shingles outbreak. Peripheral or polyneuropathic pain is associated with the distal polyneuropathies of diabetes, human immunodeficiency virus (HIV), and chemotherapeutic agents. Types of central pain include central stroke pain, trigeminal neuralgia, and a complex of syndromes known as complex regional pain syndrome (CRPS). CRPS includes both reflex sympathetic dystrophy and causalgia, both of which are neuropathic pain associated with abnormal functioning of the autonomic nervous system.

The symptoms of neuropathic pain are characterized as tingling, burning, shooting, stabbing, electric shock-like quality, or radiating pain. The patient might describe either a constant dull throbbing or burning pain, or an intermittent pain that is stabbing or shooting. Damage to the peripheral nerves might frequently be referred to the body region innervated by those nerves.

Pain Assessment

Effective pain management begins with a thorough and accurate assessment of the patient. Even though pain is a common presenting complaint, lack of regular assessment and reassessment of pain remains a problem and contributes to the mismanagement of pain.[15]

KEY CONCEPT Following initial assessment of pain, reassessment should be done as needed based on medication choice and the clinical situation.

▶ *Methods of Pain Assessment*

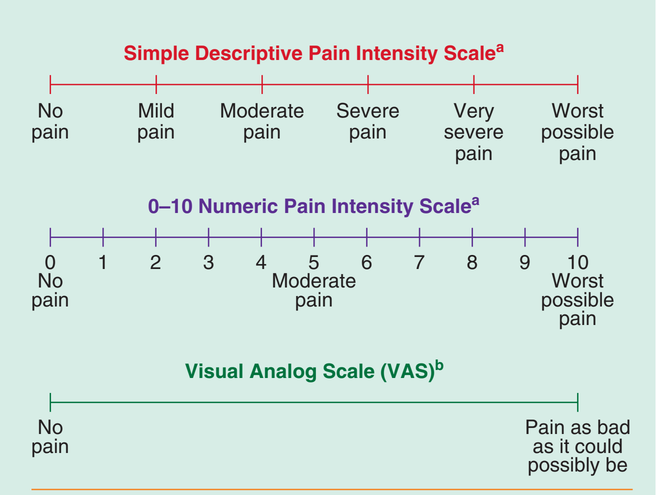
A patient-oriented approach to pain is essential, and methods do not differ greatly from those used in other medical conditions. A comprehensive history (medical, family, and psychological) and physical are necessary to evaluate underlying disease processes for the source of pain and other factors contributing to the pain.[12] A thorough assessment of the characteristics of the pain should be completed, including questions about the pain (onset, duration, location, quality, severity, and intensity), pain relief efforts, and efficacy and side effects of current and past treatments for pain. A common mnemonic for pain assessment is PQRST (Palliative/precipitating, Quality, Radiation, Severity, and Time).[16] Some clinicians have suggested the addition of U ("understanding how pain affects you") to this mnemonic.[17] During the interview, the impact of pain on the patient's functional status, behavior, and psychological status should also be assessed. Evaluation of psychological status is especially important in patients with chronic pain because depression and other affective disorders might be common comorbid conditions. A history of drug and alcohol use should be elicited due to the potential for addiction in patients who take opioids or other pain medications with a potential for misuse. Other conditions, such as renal or hepatic dysfunction, diabetes, and conditions that affect bowel function, can influence therapy choices and goals. A discussion of the patient's expectations and goals with respect to pain management (level of pain relief, functional status, and quality of life) should also be part of any pain interview.

▶ *Pain Assessment Tools*

Pain, particularly acute pain, might be accompanied by physiologic signs and symptoms, but there are no reliable objective markers for pain. Many tools have been designed for assessing the severity of pain including rating scales and multidimensional pain assessment tools.

Rating scales provide a simple way to classify the intensity of pain, and they should be selected based on the patient's ability to communicate (Figure 35–1).[18] Numeric scales are widely used and ask patients to rate their pain on a scale of 0 to 10, with 0 indicating no pain and 10 being the worst pain possible. Using this type of scale, 1 to 3 is considered mild pain, 4 to 6 is moderate pain, and 7 to 10 is severe pain. The visual analog scale (VAS) is similar to the numerical scale in that it requires patients to place a mark on a 10-cm line where one end is no pain, and the worst possible pain is on the other end. For patients who have difficulty assigning a number to their pain, a categorical scale might be an option to communicate the intensity of the pain experience. Examples of this include a simple descriptive list of words and the Wong–Baker FACES of Pain Rating Scale.[19]

Multidimensional assessment tools obtain information about the pain and impact on quality of life, but they are often more time-consuming to complete. Examples of these types of tools include the Initial Pain Assessment Tool, Brief Pain Inventory, McGill Pain Questionnaire, the Neuropathic Pain Scale, and the Oswestry Disability Index.[20–24] The Pain, Enjoyment of Life and General Activity (PEG) assessment tool is an ultrabrief pain assessment tool derived from the Brief Pain Inventory and recommended by the CDC.[25] The PEG score is the average of three individual scores.


Simple Descriptive Pain Intensity Scale[a]
No pain
Mild pain
Moderate pain
Severe pain
Very severe pain
Worst possible pain
0–10 Numeric Pain Intensity Scale[a]
0
1
2
3
4
5
6
7
8
9
10
No pain
Moderate pain
Worst possible pain
Visual Analog Scale (VAS)[b]
No pain
Pain as bad as it could possibly be

[a]If used as a graphic rating scale, a 10-cm baseline is recommended.
[b]A 10-cm baseline is recommended for VAS scales.

FIGURE 35–1. Pain rating scales. (From US Department of Health and Human Services, Agency for Health Care Policy and Research. Clinical practice guideline, cancer pain management. Rockville, MD: AHCPR; 1994 [cited 2014 Nov 6]. https://www.ncbi.nlm.nih.gov/books/NBK52300/#A19001. Cited July 16, 2021

▶ *Pain Assessment in Challenging Populations*

Children Pain interviews can be conducted with children as young as 3 or 4 years of age; however, communication might be limited by vocabulary.[26] Terms familiar to children such as "*hurt*", "*owie*", or "*boo boo*" might be used to describe pain. The VAS is best used with children older than 7 years. Other scales based on numbers of objects (eg, pokers chips), increasing color intensity,

Patient Encounter, Part 1

HPI: A 72-year-old woman with a tumor of the right fallopian tube is to undergo surgery to remove the tumor.

PMH: Hypothyroidism for 40 years; hypertension for 20 years; atrial fibrillation for 5 years; depression for 2 years.

FH: Mother had osteoporosis; father had diabetes

SH: Lives with husband; has four grown children

Meds: Metoprolol succinate ER 50 mg daily; rivaroxaban 20 mg daily; levothyroxine 150 mcg daily; polyethylene glycol 3350 17 g daily; lisinopril 2.5 mg daily; amiodarone 200 mg daily; sertraline 50 mg daily

Pain Assessment: Patient rates pain as 4 on a scale of 0 to 10

Based on the type of injury, what type of pain is this patient likely to experience?

What type of pain management regimen would you recommend in the postoperative period? Explain your answer.

or faces of pain might be helpful for children between 4 and 7 years of age. In children younger than 3 to 4 years, behavioral or physiologic measures, such as pulse or respiratory rate, might be more appropriate. Pain assessment in newborns and infants relies on behavioral observation for such clues as vocalizations (crying and fussing), facial expressions, body movements (flailing of limbs and pulling legs in), withdrawal, and change in eating and sleeping habits.[26] Preschool children experiencing pain might become clingy, lose motor and verbal skills, and start to deny pain because treatment might be linked to discomfort or punishment. School-aged children might exhibit aggressiveness, nightmares, anxiety, and withdrawal when in pain; adolescents might respond to pain with oppositional behavior and depression.

Elderly Most of the previously discussed pain scales can be used in older persons who are cognitively intact or with mild dementia. The pain thermometer and FACES of pain have been studied in older persons. In persons with moderate-to-severe dementia or those who are nonverbal, observation of pain behaviors, such as guarding or grimacing, provides an alternative for pain assessment. The Pain Assessment in Advanced Dementia (PAINAD) tool might be used to quantify signs of pain and involves observing the older adult for 15 minutes for breathing, negative vocalizations, facial expression, body language, and consolability.[27] Regardless of which pain assessment tool is used, the practitioner should first determine if the patient understands the concept of the scale to ensure reliability of the instrument.

TREATMENT

Desired Outcomes

Prevention, reduction, and/or elimination of pain are important goals for the treatment of acute pain. With chronic pain, elimination of pain might not be possible, and goals might focus on improvement or maintenance of functional capacity and quality of life.

General Approach to Treatment

KEY CONCEPT Effective treatment involves an evaluation of the cause, duration, and intensity of the pain and selection of an appropriate treatment modality for the pain situation. Depending on the type of pain, treatment might involve pharmacologic and nonpharmacologic therapy or both. General principles for the pharmacologic management of pain are listed in the section "Patient Care Process." Two common approaches to the selection of treatment are based on severity of pain and the mechanism responsible for the pain (Figure 35–2). Clinical practice guidelines for pain management are available from the American Pain Society (APS), the Agency for Healthcare Research and Quality (AHRQ), the American Geriatrics Society (AGS), and the American Society of Anesthesiologists (ASA).

▶ *Selection of Agent Based on Severity of Pain*

KEY CONCEPT Whenever possible, the least potent oral analgesic should be selected. Guidelines for the selection of therapeutic agents based on pain intensity are derived from the World Health Organization (WHO) analgesic ladder for the management of cancer pain (Table 35–2).[28] Mild-to-moderate pain is generally treated with nonopioid analgesics. Combinations of medium-potency opioids and acetaminophen (APAP) or nonsteroidal anti-inflammatory drugs (NSAIDs) are often used for moderate pain. Potent opioids are recommended for severe pain. Throughout this progression, adjuvant medications are added, as needed, to manage side effects and to augment analgesia. While these guidelines can be useful for initial therapy, the clinical situation (type of pain), cost, pharmacokinetic profile of available drugs,

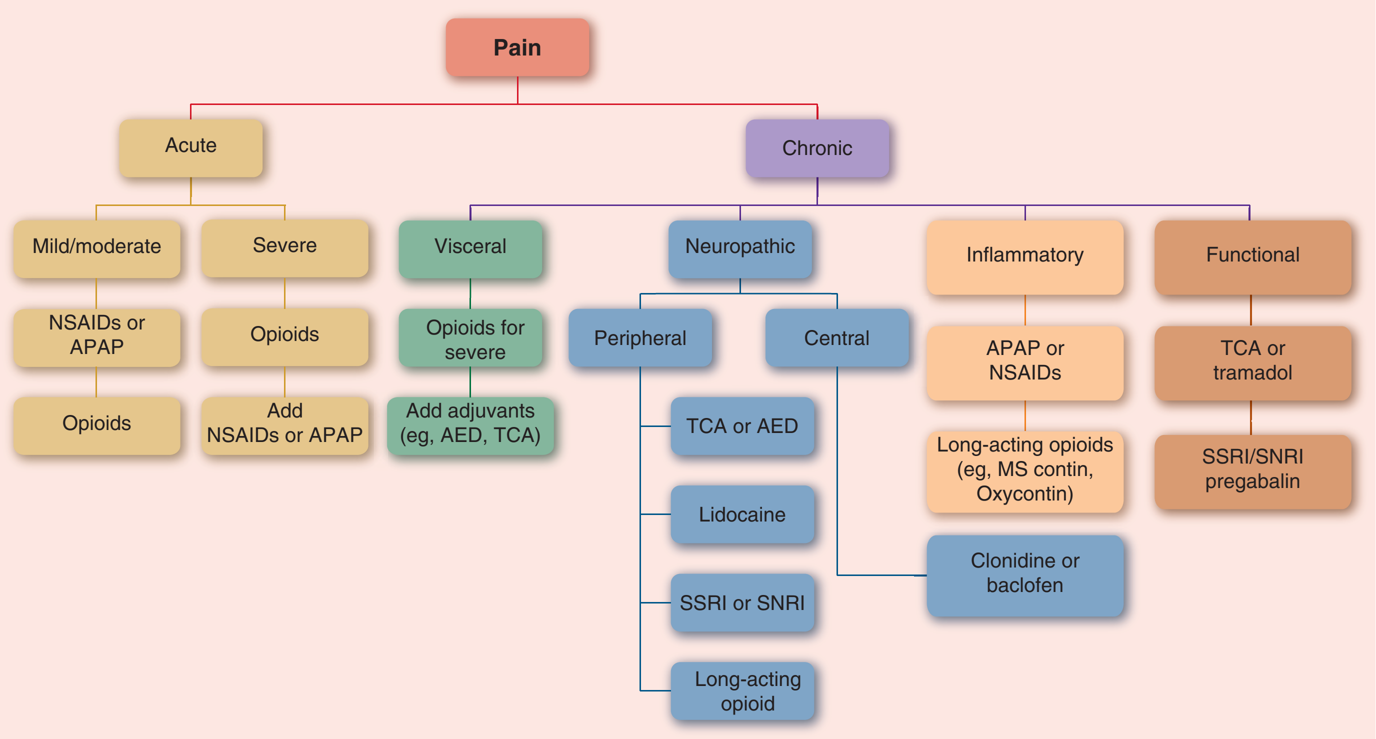


FIGURE 35–2. Pain algorithm. (AED, antiepileptic drugs; APAP, acetaminophen; MS, morphine sulfate; NSAIDs, nonsteroidal anti-inflammatory drugs; SNRI, serotonin norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants).

Table 35–2

Selection of Analgesics Based on Intensity of Pain[28,29,32]

Pain Intensity	Corresponding Numerical Rating	WHO Therapeutic Recommendations	Examples of Initial Therapy	Comments
Mild	1–3/10	Nonopioid analgesic; regular scheduled dosing	Acetaminophen 1000 mg every 6 hours; ibuprofen 600 mg every 6 hours	Consider adding an adjunct or using an alternate regimen if pain is not reduced in 1–2 days
Moderate	4–6/10	Add an opioid to the nonopioid for moderate pain; regular scheduled dosing	Acetaminophen 325 mg + codeine 60 mg every 4 hours; acetaminophen 325 mg + oxycodone 5 mg every 4 hours	Consider step-up therapy if pain is not relieved by two or more different drugs
Severe	7–10/10	Switch to a high-potency opioid; regular scheduled dosing	Morphine 10 mg every 4 hours; hydromorphone 4 mg every 4 hours	

and patient-specific factors (age, concomitant illnesses, previous response, and other medications) must also be considered. Pain medications might also be used in the absence of pain in anticipation of a painful event such as surgery to minimize peripheral and central sensitization.

▶ *Mechanistic Approach to Therapy*

Current analgesic therapy is aimed at controlling or blunting pain symptoms. However, diverse mechanisms contributing to various types of pain continue to be further elucidated. An understanding of these new mechanisms of pain transmission might lead to improvement in pain management as pharmacologic management of pain becomes more mechanism specific. Use of NSAIDs for inflammatory types of pain is an example of a mechanistic approach. Because several mechanisms of pain often coexist, a multimodal approach seems rational to target each mechanism.

Nonpharmacologic Therapy

Nonpharmacologic therapies (psychological interventions and physical therapy) might be used in both acute and chronic pain. Psychological interventions can reduce pain as well as the anxiety, depression, fear, and anger associated with pain. Psychological interventions helpful in management of acute pain are imagery (picturing oneself in a safe, peaceful place) and distraction (listening to music or focusing on breathing). Chronic pain patients might benefit from relaxation, biofeedback, cognitive behavioral therapy, psychotherapy, support groups, and spiritual counseling.

Physical therapy is an essential part of many types of pain situations. Treatment modalities include heat, cold, water, ultrasound therapy, TENS, massage, and therapeutic exercise. Heat and cold therapy are utilized in a variety of musculoskeletal conditions (muscle spasms, low back pain, fibromyalgia, sprains, and strains).

Pharmacologic Therapy

▶ *Nonopioid Analgesics*

Acetaminophen APAP, an analgesic and antipyretic, is often selected as initial therapy for mild-to-moderate pain and considered first line in several pain situations such as low back pain and osteoarthritis.[29] Mechanistically, APAP is believed to inhibit prostaglandin synthesis in the CNS and block pain impulses in the periphery. APAP is well tolerated at usual doses and has few clinically significant drug interactions except causing increased hypoprothrombinemic response to warfarin in patients receiving APAP doses of more than 2000 mg/day.[30] The maximum recommended dose for patients with normal renal and hepatic function is 4000 mg/day. Hepatotoxicity has been reported with excessive use and overdose, and the risk of this adverse effect increases in those with hepatitis or chronic alcohol use, as well as those who binge drink or are in a fasting state. Due to concerns of unintentional overuse and hepatoxicity, the FDA requires warning labels on over-the-counter (OTC) APAP products and limited the APAP component of narcotic analgesic combination to 325 mg per dosing unit. For these reasons, the maximum dose should be reduced by 50% to 75% in patients with renal dysfunction or hepatic disease and in those who engage in excessive alcohol use.

Aspirin and Other Salicylates Aspirin, nonacetylated salicylates, and other NSAIDs have analgesic, antipyretic, and anti-inflammatory actions. These agents inhibit cyclooxygenase (COX-1 and COX-2) enzymes, thereby preventing prostaglandin synthesis, which results in reduced nociceptor sensitization and an increased pain threshold.

Aspirin is effective for mild-to-moderate pain; however, the risk of gastrointestinal (GI) irritation and bleeding limits frequent use of this drug for pain management. Direct effects of aspirin on the GI mucosa and irreversible platelet inhibition contribute to this risk, which can occur even at low doses. Hypersensitivity reactions are also possible and might occur in 25% of patients with coexisting asthma, nasal polyps, or chronic urticaria. Of additional concern is the potential for cross-sensitivity of other NSAIDs in this group of patients. Nonacetylated salicylates (choline magnesium salicylate and sodium salicylate) have reduced risk of GI effects and platelet inhibition and might be used in aspirin-sensitive patients.

Nonsteroidal Anti-inflammatory Drugs NSAIDs are the preferred agents for mild-to-moderate pain in conditions that are mediated by prostaglandins (rheumatoid arthritis, menstrual cramps, and postsurgical pain) and in the management of pain from bony metastasis, but they are of minimal use in neuropathic pain. NSAIDs provide analgesia equal to or better than that of aspirin or APAP combined with codeine, and they are very effective for inflammatory pain and pain associated with bone metastasis.[10] These agents are classified by their chemical structures (fenamates, acetic acids, propionic acids, pyranocarboxylic acids, pyrrolizine carboxylic acids, and COX-2 inhibitors). Although only some members of this class have approval for treatment of pain, it is likely that all of them have similar analgesic effects. All members of this class appear to be equally effective, but there is great intrapatient variability in response. After an adequate trial of 2 to 3 weeks with a particular oral agent, it is reasonable to switch to another member of the class. Ketorolac and ibuprofen are available in parenteral and oral dosage forms; unlike other NSAIDs, ketorolac's duration of use is limited to 5 days due to risk of serious GI side effects. NSAIDs demonstrate a flat-dose response curve, with higher doses producing no greater efficacy than moderate doses but resulting in an increased incidence of adverse effects (GI irritation, hepatic dysfunction, renal insufficiency, platelet inhibition, sodium retention, and CNS dysfunction).

Patients at increased risk of NSAID-induced GI adverse effects (eg, dyspepsia, peptic ulcer formation, and bleeding) include the elderly, those with peptic ulcer disease, coagulopathy, and patients receiving high doses of concurrent corticosteroids. Nephrotoxicity is more common in the elderly, patients with creatinine clearance values less than 50 mL/min (0.83 mL/s), and those with volume depletion or on diuretic therapy. NSAIDs should be used with caution in patients with reduced cardiac output due to sodium retention and in patients receiving antihypertensives, warfarin, and lithium.

NSAIDs are classified as nonselective (they inhibit COX-1 and COX-2) or selective (inhibit only COX-2) based on degree of COX inhibition. COX-2 inhibition is responsible for anti-inflammatory effects, whereas COX-1 inhibition contributes to increase GI and renal toxicity associated with nonselective agents. Because the antiplatelet effect of nonselective NSAIDs is reversible, concurrent use might reduce the cardioprotective effect of aspirin due to competitive inhibition of COX-1. A boxed warning highlighting the potential for increased risk of cardiovascular events and GI bleeding is now required for all prescription nonselective NSAIDs and celecoxib. Stronger warnings about these adverse events are also required on nonprescription NSAIDs. When an NSAID is needed in a patient with cardiovascular risk, the benefits of therapy must outweigh the risks, and the lowest effective dose of the NSAID is recommended.[31]

▶ *Opioid Analgesics*

Opioids are considered the agents of choice for the treatment of severe acute pain and moderate-to-severe pain associated with cancer.[32] Opioids are classified by their activity at the receptor site, usual pain intensity treated, and duration of action (short acting versus long acting).

Selection and Dosing The opioids exert their analgesic efficacy by stimulating opioid receptors (μ, κ, and δ) in the CNS. There is a wide variety of potencies among the opioids, with some used for moderate pain (codeine, hydrocodone, tramadol, and partial agonists) and others reserved for severe pain (morphine and hydromorphone). Pure agonists (morphine) bind to μ-receptors to produce analgesia that increases with dose without a ceiling effect. Pure agonists are divided into three chemical classes: phenanthrenes or morphine-like, phenyl piperidine or meperidine-like, and diphenyl heptane or methadone-like. Partial agonists at the μ-receptor (ie, buprenorphine, butorphanol, and tramadol) cause less conformational change and receptor activation than full agonists. At low doses, both full and partial agonists may provide similar effects to their full agonist agents. However, when the dose of partial agonists increases, the analgesic activity will plateau, and further increases in doses will not provide additional relief but may increase the adverse effects. Mixed agonists/antagonists (ie, buprenorphine, butorphanol, nalbuphine, and pentazocine.) demonstrate varying activity depending on the opioid receptor but also varying on the dose. Partial agonists at the μ-receptor may cause reduced side effects but may precipitate withdrawal in patients who are dependent on pure agonists. Agents with high affinity for κ-receptors (pentazocine, nalbuphine, and butorphanol) are more likely to cause psychomimetic effects. Buprenorphine, a partial μ-agonist and κ antagonist, is indicated at high doses for opioid-use disorder while generally at lower doses to treat moderate-to-severe pain. Selection of the agent and route depend on individual patient-related factors including severity of pain, individual perceptions, weight, age, opioid tolerance, and concomitant disease (renal or hepatic dysfunction). Because pure agonists are pharmacologically similar, choice of agent might be also guided by pharmacokinetic parameters and other drug characteristics. Hepatic impairment can decrease the metabolism of most opioids, particularly methadone, meperidine, and pentazocine. Furthermore, the clearance of meperidine and morphine and their metabolites is reduced in renal dysfunction.

Table 35–3 provides a summary of opiate options, but several drugs warrant further discussion. Normeperidine, the active metabolite of meperidine, can produce tremors, myoclonus, delirium, and seizures. Due to the potential for accumulation of normeperidine, meperidine should not be used in the elderly, those with renal impairment, in patients using patient-controlled analgesia (PCA) devices, or for more than 1 to 2 days of intermittent dosing. Methadone is unique among the opioids because it has several mechanisms (μ-agonist, NMDA-receptor antagonist, and inhibition of reuptake of serotonin and norepinephrine). The long half-life of methadone (30 hours) permits extended dosing intervals; however, the potential for accumulation with repeated dosing often results in challenging dose conversion and concerns for respiratory depression. Another safety concern with methadone involves the risk of arrhythmia secondary to QT prolongation. Tramadol is a synthetic opioid with a dual mechanism of action (μ-agonist and inhibition of serotonin and norepinephrine reuptake) and efficacy and safety similar to that of codeine plus APAP. Tramadol has been evaluated in several types of neuropathic pain and might have a role in the treatment of chronic pain. Tramadol is associated with an increased risk of seizures in patients with a seizure disorder, those at risk for seizures, and

Table 35–3

Equianalgesic Doses of Selected Opioids[17,32,35,36]

	Dose Equianalgesic to 10 mg of Parenteral Morphine (mg)	
Opioid (Brand Name)	**Parenteral (mg)**	**Oral (mg)**
Mild-to-Moderate Pain		
Codeine (generic, various)	120	200
Hydrocodone (Vicodin, Lorcet)	N/A	30
Oxycodone (OxyContin, OxyFAST, Oxy IR)	N/A	20
Meperidine (Demerol)	100	400
Moderate-to-Severe Pain		
Morphine (Roxanol, MS Contin, Kadian, Avinza)	10	30
Hydromorphone (Dilaudid)	1.5	7.5
Oxymorphone (Opana, Opana SR, Numorphan)	1	N/A
Levorphanol (Levo-Dromoran)	2	4
Fentanyl (Duragesic)	0.1–0.2	N/A[a]
Methadone (Dolophine)	10[b]	3–5[b]

[a] Transdermal: 100 mcg/hour = 2–4 mg/hour of IV morphine.

[b] Dosage calculations when converting from morphine to methadone are not linear. The equianalgesic dose of methadone will decrease progressively as the morphine equivalents increase (Table 35–4).

IR, immediate release, MS, morphine sulfate, SR, sustained release.

those taking medications that can lower the seizure threshold. The use of tramadol with other serotonergic drugs (eg, selective serotonin reuptake inhibitors [SSRIs]) might precipitate serotonin syndrome. Although originally thought not to be habit forming, dependence can occur with tramadol.

About 70% of individuals will experience significant analgesia from 10 mg/70 kg of body weight of intravenous (IV) morphine or its equivalent.[10] For severe pain in opiate-naive patients, a usual starting dose is 5 to 10 mg of IV morphine every 4 hours. In the initial stages of severe pain, medications should be given around the clock. Rescue doses should be made available for breakthrough pain in doses equivalent to 10% to 20% of the total daily opioid requirement and administered every 2 to 6 hours if needed. Alternatively, one-sixth of the total daily dose or one-third of the 12-hourly dose might be used. Scheduled doses should be titrated based on the degree of pain. One method involves adjustment of the maintenance dose based on the total 24-hour rescue dose requirement. Alternatively, utilizing dose escalation, doses could be increased by 50% to 100% or 30% to 50% of the current dose, for those in severe and moderate pain, respectively. Once pain relief is achieved, and if treatment is necessary for more than a few days for cancer-related pain, conversion to a controlled-release or long-acting opioid may be made with an equal amount of agent. Several sustained-release products are available containing morphine, oxycodone, and fentanyl. Some clinicians will reduce the total daily dose of the long-acting dosage form by 25% when initiating a sustained-release product to reduce the likelihood of oversedation. The dose of a pure agonist is limited only by tolerability to side effects. Tolerance might develop to analgesic effects, necessitating increasing doses to achieve the same level of pain relief. Physical dependence will occur with the long-term use of opioids.[33]

Opioids are not first-line therapy for chronic pain. In response to the increase in opioid use and adverse events associated with such use, guidelines for the use of opioids in chronic pain have been recommended by the CDC.[8] The guidelines are not intended for patients receiving opioids for cancer treatment, palliative care, or in end-of-life. Table 35–4 provides a summary of these guidelines. In addition to these guidelines, the use of informed consent for chronic opioid therapy, medication management agreements, or pain contracts might be appropriate to monitor the use (prescribing and dispensing) of controlled substances.

Opioids are administered by a variety of routes, including oral (tablet and liquid), sublingual, rectal, transdermal, transmucosal, IV, subcutaneous (SC), and intraspinal. Although the oral and transdermal routes are most common, the method of administration is based on patient needs (severity of pain) and characteristics (swallowing difficulty and preference). Oral opioids have an onset of effect of 45 minutes, so IV or SC administration might be preferred if more rapid relief is desired. Intramuscular (IM)

Table 35–4

CDC Guidelines for Prescribing Opioids for Chronic Pain[8]

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.
4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥ 50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥ 90 MME/day or carefully justify a decision to titrate dosage to ≥ 90 MME/day.
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. 3 days or less will often be sufficient; more than 7 days will rarely be needed.
7. Clinicians should evaluate benefits and harms with patients within 1–4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.
8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥ 50 MME/day), or concurrent benzodiazepine use, are present.
9. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.
10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.
11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

ER, extended release; LA, long acting; MME, milligram morphine equivalent; PDMP, prescription drug monitoring program.

injections are not recommended because of pain at the injection site and wide fluctuations in drug absorption and peak plasma concentrations achieved. More invasive routes of administration such as PCA and intraspinal (epidural and intrathecal) are primarily used postoperatively but might also be used in refractory chronic pain situations. PCA delivers a self-administered dose via an infusion pump with a preprogrammed dose, minimum dosing interval, and a maximum hourly dose. Morphine, fentanyl, and hydromorphone are commonly administered via PCA pumps by the IV route but less frequently by the SC or epidural route.

Epidural analgesia is frequently used for lower extremity procedures and pain (eg, knee surgery, labor pain, and some abdominal procedures). Intermittent bolus or continuous infusion of preservative-free opioids (morphine, hydromorphone, or fentanyl) and local anesthetics (bupivacaine) might be used for epidural analgesia. Opiates given by this route might cause pruritus that is relieved by naloxone. Adverse effects including respiratory depression, hypotension, and urinary retention might occur. When epidural routes are used in narcotic-dependent patients, systemic analgesics must also be used to prevent withdrawal because the opioid is not absorbed and remains in the epidural space. Doses of opioids used in epidural analgesia are 10 times less than IV doses, and intrathecal doses are 10 times less than epidural doses (ie, 10 mg of IV morphine is equivalent to 1-mg epidural morphine and 0.1 mg of intrathecally administered morphine).[31]

Combination Analgesics Combinations of opioids and nonopioids often result in enhanced analgesia and lower dose of each. Combination analgesics are frequently used in moderate pain. However, in severe pain, the nonopioid component reaches maximum dosage, and thus, the usefulness of nonopioids in this situation is limited. Additionally, the combination products are short acting and often not suitable for chronic therapy. Single agents offer greater dosing flexibility than combination products.

Opioid Allergy True opioid allergies are rare and should not be confused with pruritus associated with opioid use. Cross-sensitivity between morphine-like, meperidine-like, and methadone-like agents is unlikely. Therefore, when an individual is allergic to one drug in a chemical class of opioids, it is reasonable to select an agent in another chemical class. For the purpose of drug selection in patients with allergies, mixed agonists/antagonists should be treated as morphine-like agents.

Tapering of Opioids Tapering of opioids should be considered in the following situations: painful situation has resolved; in those with prolonged opioid use; upon requests for dosage reduction; lack of clinically meaningful improvement in pain and function (eg, at least 30% improvement on the three-item PEG scale) dosages greater than 50 morphine milligram equivalents (MME)/day without benefit or opioids are combined with benzodiazepines; signs of substance use disorder (eg, work or family, problems related to opioid use, difficulty controlling use); overdose or other serious adverse event; or shows early warning signs for overdose risk such as confusion, sedation, or slurred speech. In these situations, the dose should be reduced by 10% per week to avoid withdrawal symptoms.

Managing Opioid Side Effects and Drug Interactions Side effects common to all opioids include sedation, hallucinations, constipation, nausea and vomiting, urinary retention, myoclonus, and respiratory depression. Table 35–5 shows management strategies for side effects. The most frequent side effects are sedation, nausea, and constipation. Sedation and nausea are common when initiating therapy and when increasing doses. Tolerance to respiratory depression develops rapidly with repeated doses, and respiratory depression is rarely a clinically significant problem in pain patients even those with respiratory impairment. Constipation is a significant adverse effect to which tolerance does not develop, and prophylaxis with stimulant laxatives (eg, senna or bisacodyl) and stool softeners such as docusate are recommended.

Codeine, hydrocodone, morphine, methadone, and oxycodone are substrates of the cytochrome P450 (CYP) enzyme, 2D6.[34] Inhibition of CYP2D6 results in decreased analgesia of codeine and hydrocodone due to decreased conversion to the active metabolites (eg, morphine and hydromorphone, respectively) and increased effects of morphine, methadone, and oxycodone. Methadone is a substrate of CYP3A4 and its metabolism is increased by phenytoin and decreased by cimetidine. CNS depressants might potentiate the sedative effects of opiates.

Patients with CYP450 pharmacogenetic variations may respond differently to opioids, ranging from drug unresponsiveness to toxicity with elevated serum levels.

Opioid Rotation Opioid rotation is the switch from one opioid to another to achieve a better balance between analgesia and treatment-limiting adverse effects. This practice is often used when escalating doses (> 1 g morphine/day) become ineffective.

Table 35–5

Managing Opioid Side Effects[18,32,35]

Adverse Effects	Drug Treatment/Management
Excessive sedation	Reduce dose by 25% or increase dosing interval
Constipation	Casanthranol-docusate one capsule at bedtime or twice daily; senna one to two tablets at bedtime or twice daily; bisacodyl 5–10 mg daily plus docusate 100 mg twice daily; polyethylene glycol 3350 17 g daily; methylnaltrexone 0.15 mg/kg SQ every other day; naloxegol 12.5–25 mg daily
Nausea and vomiting	Prevention: Hydroxyzine 25–100 mg (PO/IM) every 4–6 hours as needed; diphenhydramine 25–50 mg (PO/IM) every 6 hours as needed; ondansetron 4 mg IV or 16 mg PO Treatment: Prochlorperazine 5–10 mg (PO/IM) every 3–4 hours as needed or 25 mg PR twice daily; ondansetron 4–8 mg IV every 8 hours as needed
Gastroparesis	Metoclopramide 10 mg (PO/IV) every 6–8 hours (Caution: duration < 3 months)
Vertigo	Meclizine 12.5–25 mg PO every 6 hours as needed
Urticaria/ itching	Hydroxyzine 25–100 mg (PO/IM) every 4–6 hours as needed; diphenhydramine 25–50 mg (PO/IM) every 6 hours as needed
Respiratory depression	Mild: Reduce dose by 25% Moderate-to-severe: Naloxone 0.4–2 mg IV every 2–3 minutes (up to 10 mg) for complete reversal; 0.1–0.2 mg IV every 2–3 minutes until desired reversal for partial reversal; may need to repeat in 1–2 hours depending on narcotic half-life
CNS irritability	Discontinue opioid; treat with benzodiazepine

IM, intramuscular; IV, intravenous; PO, orally; PR, per rectum; SQ, subcutaneous, CNS, central nervous system.

In some settings, opioid rotation is used routinely to prevent the development of analgesic tolerance.[35]

Equianalgesic Dosing of Opioid Analgesics Conversion from one dosage form to another or from one opioid to another might be necessary in situations such as ineffective pain control, emergence of side effects, change in patient status, and in formulary restrictions. KEY CONCEPT Equianalgesic doses should be used when converting from one opioid to another. Clinicians should be familiar with the equianalgesic dosing and conversion strategies to avoid analgesic failure. Opioid potency is compared using a reference standard of 10-mg parenteral morphine. Switching from one dosage form to another of the same opioid (ie, IV to oral) is relatively simple. The current total daily dose is calculated and the total of the new dosage form is determined using a ratio of the equianalgesic doses. This result is then adjusted based on the usual dosing frequency of the new form. When converting to a sustained-release form of the same opioid, the oral dosage may be reduced by 25% to avoid initial sedation; however, the specific product literature should also be consulted.

The first step in an opioid conversion is to calculate the patient's total daily dose of opioid based on the regularly scheduled dose and the total amount of rescue dose needed in 24 hours. This total is then converted to morphine-dosing equivalents using equianalgesic doses (see Table 35–3). The total daily morphine dose is then used to calculate the daily dose of the new opioid using dosing equivalents from an equianalgesic table. Because cross-tolerance may not be complete between opioids, some references suggest that the calculated equianalgesic dose be reduced by 25% to 50%.[32] If the opioid switch is due to uncontrolled pain, a dosage reduction may not be needed. The calculated equianalgesic dose may need to be reduced more in the medically frail and when converting to methadone.[36,37] Methadone appears to be much more potent than once believed, and morphine-to-methadone ratios vary according to the total dose of morphine taken at the time of making the conversion to methadone (Table 35–6).[38,39] Conversion to methadone is a complex process, and several different strategies have been proposed including a switch of the entire dose in 1 day or a gradual conversion over 3 days.

Table 35–6

Methadone Dose Conversions[39]

Total Daily Dose of Oral Morphine	Morphine:Methadone Factor
< 100 mg	3:1 3-mg morphine:1-mg methadone
101–300 mg	5:1
301–600 mg	10:1
601–800 mg	12:1
801–1000 mg	15:1
> 1000 mg	20:1

Patient Encounter, Part 2

Following surgery, she was placed on morphine patient-controlled analgesia (PCA). She has been using 27 mg of morphine/24 hours with adequate pain control; however, she has developed redness and itching on her neck that is believed to be due to the morphine.

Current Meds: Morphine PCA; metoprolol succinate ER 50 mg daily; rivaroxaban 20 mg daily; levothyroxine 150 mcg daily; polyethylene glycol 3350 17 g daily; lisinopril 2.5 mg daily; amiodarone 200 mg daily; sertraline 50 mg daily. She will be discharged to a skilled nursing facility for rehabilitation therapy.

The physician would like to convert her to a combination preparation of hydrocodone and APAP.

What dosing regimen would you suggest?

Recommend a monitoring plan for this patient.

How would you assess pain response?

The patient is concerned about the redness and itching she developed while on morphine. What other interventions or education may be necessary at this time?

▶ *Adjuvant Agents for Chronic Pain*

The role of NSAIDs and opioids in chronic nonmalignant pain has been discussed; however, a review of adjuvant agents for chronic pain, particularly neuropathic pain, is warranted. Adjuvant analgesics are drugs that have indications other than pain but are useful as monotherapy or in combination with nonopioids and opioids. Common adjuvants include antiepileptic drugs (AEDs), antidepressants, antiarrhythmic drugs, local anesthetics, topical agents (eg, capsaicin), and a variety of other drugs (eg, NMDA antagonists, clonidine, and muscle relaxants).

Published guidelines have been suggested for the general management of neuropathic pain.[40] Suggestions for first-line therapy include gabapentin or pregabalin, transdermal lidocaine, or tricyclic antidepressants (TCAs) (Table 35–7).[40–43] Antidepressants, such as the SSRIs, have fewer side effects but appear to be less effective than the TCAs for neuropathic pain. However, serotonin-norepinephrine reuptake inhibitors (SNRIs) (eg, duloxetine and venlafaxine) have been used successfully for painful diabetic peripheral neuropathy (DPN). A stepwise approach is suggested

Patient Encounter, Part 3

She was discharged to a skilled nursing facility and is receiving physical therapy and occupational therapy 6 days each week.

Current Meds: Metoprolol succinate ER 50 mg daily; rivaroxaban 20 mg daily; levothyroxine 150 mcg daily; polyethylene glycol 3350 17 g daily; lisinopril 2.5 mg daily; amiodarone 200 mg daily; sertraline 50 mg daily, hydrocodone/acetaminophen 10/325 mg every 6 hours as needed for pain.

Pain Assessment: Patient reports pain of 7 out of 10; worse with movement. She complains of pain "everywhere, but my shoulder is really bothering me."

Physical therapy notes indicate patient is unable to complete therapy goals due to complaints of pain in her shoulder.

Based on this information, what would you recommend to optimize pain control?

Table 35–7

Selected Adjuvant Analgesics and Suggested Dosing[40–43]

Agent	Dosing Guidelines	FDA-Approved Indication
Amitriptyline (Elavil)	10–25 mg at bedtime with weekly increments to a target dose of 25–150 mg of amitriptyline or an equivalent dose of another TCA	
Duloxetine (Cymbalta)	DPN: 60 mg daily Fibromyalgia: 30 mg daily, may be increased to a target dose of 60 mg/day	DPN, fibromyalgia
Gabapentin (Neurontin)	Initially, 300 mg three times a day up to a maximum of 3600 mg daily, in divided doses[a]	PHN
Pregabalin (Lyrica)	DPN: Initially, 50 mg three times a day; may be increased to 100 mg three times a day within 1 week based on efficacy and tolerability[a] PHN: Initially 75 mg twice a day or 50 mg three times a day; may be increased to 100 mg three times a day within 1 week based on efficacy and tolerability[a] Fibromyalgia: Initially 75 mg twice a day, increase after 1 week to 300 mg to 450 mg/day (in divided doses every 12 hours)	DPN, PHN, and fibromyalgia
Lidocaine 5% (Lidoderm patch)	Up to three patches may be applied directly over the painful site once daily; patches are applied using a regimen of 12 hours on and 12 hours off	PHN

[a] Dosing for creatinine clearance of ≥ 60 mL/min (1.0 mL/s).

DPN, diabetic peripheral neuropathy; PHN, postherpetic neuralgia; TCA, tricyclic antidepressant.

for managing the patient with neuropathic pain beginning with the least invasive, effective therapeutic choice and proceeding to the rational use of multiple drug regimens (see Figure 35–2). Choice of agent might also depend on dosing frequency and comorbidities. Data on combination therapy are lacking, and the use of combined treatment is empirical based on the additive therapeutic benefit. Scheduled medication regimens instead of "as-needed" dosing should be used when treating chronic pain, and the effectiveness of therapy should be reassessed regularly. If patients are managed on a multiple drug regimen and changes are indicated, changing only one drug at a time is suggested. Topical agents (eg, capsaicin) might be added to a regimen to reduce the oral medication load, particularly if adverse effects are a problem or if pain is not relieved.

▶ *Complementary and Alternative Medicine*

Complementary and alternative medicine (CAM) is a term used to encompass a variety of therapies (eg, acupuncture, chiropractic, botanical and nonbotanical dietary supplements, and homeopathy). Painful conditions are among the most common reasons individuals seek relief from CAM. A variety of dietary supplements have been suggested for painful conditions such as S-adenosylmethionine (SAM-e), ginger, fish oil, feverfew, γ-linoleic acid, glucosamine, and chondroitin. Of these, glucosamine and chondroitin are the most popular and have the most evidence supporting their efficacy. Glucosamine in doses of 1500 mg/day has been shown to be effective in reducing the pain of osteoarthritis by fostering repair of cartilage, and it is recommended by the Osteoarthritis Research Society International (OARSI).[29]

Patient Encounter, Part 4

The patient has been at the skilled nursing facility for 2 weeks and is making progress toward rehabilitation goals; however, during a follow-up appointment to her surgeon, she learned that she has metastatic ovarian cancer.

She states that she has not been sleeping well and has lost 7 lb (3.2 kg) since admission. She also states that she hates waiting for her pain pills and requests something longer acting.

Pain Assessment: 8 out of 10

Current Meds: Metoprolol succinate ER 50 mg daily; rivaroxaban 20 mg daily; levothyroxine 150 mcg daily; polyethylene glycol 3350 17 g daily; lisinopril 2.5 mg daily; amiodarone 200 mg daily; sertraline 50 mg daily; diclofenac transdermal gel 1% to neck and left shoulder four times daily; hydrocodone/acetaminophen 10/325 mg every 4 hours as needed for pain (uses 6 doses per day).

What additional recommendations would you have at this time regarding pain management?

Are there any other therapeutic issues that should be addressed?

Patient Encounter, Part 5

The patient was discharged to her home, but 3 months after discharge was admitted to hospice service. She is no longer able to swallow her tablets and requires them to be crushed. The hospice nurse requests your advice on an equivalent regimen using transdermal fentanyl and oxycodone for breakthrough pain.

Pain Assessment: 8 out of 10

Current Meds: Metoprolol succinate ER 50 mg daily; rivaroxaban 20 mg daily; levothyroxine 150 mcg daily; polyethylene glycol 3350 17 g daily; lisinopril 2.5 mg daily; amiodarone 200 mg daily; diclofenac transdermal gel 1% to neck and left shoulder four times daily; morphine sulfate ER 30 mg twice daily; mirtazapine 15 mg at bedtime.

What additional recommendations would you have at this time regarding pain management?

Are there any other therapeutic issues that should be addressed?

Patient Care Process

Collect Information:

- Identify the source of pain.
- Assess the level of pain using a pain intensity scale.
- Review the medical and medication history.
- Determine if patient has insurance coverage for prescription medications.

Assess the Information:

- Determine if the patient is a candidate for pharmacotherapy.
- If patient is already receiving drug therapy, assess efficacy, side effects, adherence, and drug interactions.

Develop a Care Plan:

- Base the initial choice of analgesic on the severity and type of pain, as well as on the patient's medical condition and concurrent medications.
- Select the least potent oral analgesic that provides adequate pain relief and causes the fewest side effects.
- Avoid excessive sedation.
- Adjust the route of administration if the patient is unable to take oral medications.
- Use equianalgesic doses as a guide when switching opioids.
- Use a dosing schedule versus as-needed dosing.

Implement the Care Plan:

- Communicate the recommendations to the prescriber and members of the team.
- Communicate expectations of the therapy to the patient.

Follow-up: Monitor and Evaluate:

- Assess the patient for analgesic effectiveness and for side effects at each visit or more frequently, depending on the acuity of the patient's condition.
- Titrate the dose to one that achieves an adequate level of pain control.

OUTCOME EVALUATION

Routine pain assessment is essential for evaluating outcomes of therapy. For example, pain goals for acute pain might include "pain scale less than 3" or 30% reduction in PEG scale. Functional goals such as "be able to play a game with grandchildren," or "be able to knit again" may be appropriate for chronic pain. Assess patients periodically, depending on the method of analgesia and pain condition, for achievement of pain goals. Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions.

Abbreviations Introduced in This Chapter

AED	Antiepileptic drug
AGS	American Geriatrics Society
AHRQ	Agency for Healthcare Research and Quality
ASIPP	American Society of Interventional Pain Physicians
AIDS	Acquired immunodeficiency syndrome
AMPA	α-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid
APAP	Acetaminophen
APS	American Pain Society
ASA	American Society of Anesthesiologists
CAM	Complementary and alternative medicine
CDC	Centers for Disease Control and Prevention
CNS	Central nervous system
COX	Cyclooxygenase
CRPS	Complex regional pain syndrome
CYP	Cytochrome P450 enzyme
DPN	Diabetic peripheral neuropathy
GABA	γ-Aminobutyric acid
GI	Gastrointestinal
HIV	Human immunodeficiency virus
IASP	International Association for the Study of Pain
IM	Intramuscular
IV	Intravenous
MME	Morphine milligram equivalents
NMDA	*N*-methyl-D-aspartate
NSAID	Nonsteroidal anti-inflammatory drug
OARSI	Osteoarthritis Research Society International
PAINAD	Pain Assessment in Advanced Dementia (tool)
PEG	Pain intensity, Enjoyment of life, General activity Assessment Tool
PCA	Patient-controlled analgesia
PHN	Postherpetic neuralgia
PQRST	Palliative/precipitating, Quality, Radiation, Severity, and Time
SAM-e	*S*-adenosylmethionine
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TENS	Transcutaneous electrical nerve stimulation
VAS	Visual analog scale
WHO	World Health Organization

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Headache

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Differentiate types of headache syndromes based on clinical features.
2. Recommend nonpharmacologic measures for headache treatment and prevention.
3. Determine when the pharmacologic treatment of headache is indicated.
4. Construct individualized treatment regimens for the acute and chronic management of headache syndromes.
5. Monitor headache treatment to ensure its safety, tolerability, and efficacy.

INTRODUCTION

Headache is a common medical complaint with approximately 50% of the adult population experiencing at least one headache per year.[1] KEY CONCEPT Headaches can be considered primary or secondary conditions. Primary headaches, even when persistent or recurrent, are usually a benign condition. Secondary headaches are caused by an underlying medical disorder and may need medical emergencies. Primary headache syndromes are the focus of this chapter. KEY CONCEPT The International Headache Society (IHS) classifies primary headaches as migraine, tension-type, or cluster and other trigeminal autonomic cephalalgias.[2] Patients may seek headache care from multiple providers; so all clinicians should be familiar with the various types of headache; clinical indicators suggest the need for urgent medical attention or specialist referral, and nonpharmacologic and pharmacologic options for treatment.

EPIDEMIOLOGY OF HEADACHE DISORDERS

Migraine Headache

Migraine is a primary headache disorder with an estimated 3-month prevalence rate in the United States of 14.2% in adults over 18 years. Prevalence is higher in females at 19.1% compared to males at 9%. The highest prevalence is in women 18 to 44 years of age at 23.5%.[3] In pediatric patients, there is also a higher incidence in girls after the age of 10.[4] The difference in gender distribution is thought to be due to hormonal differences.

Tension-Type Headache

KEY CONCEPT Tension-type headache (TTH) is the most common primary headache disorder and can be further divided into episodic or chronic.[2] The term *TTH* is used to describe all headache syndromes in which sensitization to pericranial nociception, known as noxious stimuli, is the most significant factor in the pathogenesis of pain.[5] Overall reported prevalence of TTH is approximately 86%, and incidence is more common in women than men. Episodic TTH is the most common type, followed by frequent episodic TTH and chronic TTH. Incidence of TTH increases until approximately age 40, then incidence begins to slowly decline.[6] Environmental factors, as opposed to genetic predisposition, play a central role in the development of TTH. The mean frequency of attacks is 3 days per month in episodic disorders; episodic is defined as less than 15 attacks in a 1-month period with no pattern, and chronic TTH is defined as 15 or more attacks in a 1-month period for at least 6 months.[2]

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

Cluster headache disorders are severe primary headache syndromes and uncommon.[2] The lifetime prevalence is estimated to be 124 per 100,000.[7] Unlike migraine and TTH, cluster headaches are more frequently found in men. Onset most commonly occurs between 20 and 40 years.[2] A genetic predisposition is apparent, although affected individuals often present with additional risk factors, such as history of tobacco use, caffeine intake, and alcohol abuse.[7] Attacks consist of debilitating, unilateral head pains that occur in series lasting up to months at a time but may abate for extended periods, defined as remission, resulting in months or years between occurrences. In rare instances, cluster headache can be a chronic disorder without remission.[2]

ETIOLOGY AND PATHOPHYSIOLOGY OF HEADACHE DISORDERS

Migraine Headache

The exact mechanism by which migraines occur remains obscure, but the belief that only vascular changes are responsible for the pain is no longer accepted.[8] The vascular hypothesis suggested that intracerebral vasoconstriction has led to neural ischemia, which was followed by reflex extracranial vasodilation and pain. Negative neuroimaging evidence for such vascular changes, as well as the effectiveness of medications with no vascular properties, make this contention untenable.[5] A neuronal etiology has emerged as the leading mechanism for the development of migraine pain.[9] It is believed that depressed neuronal electrical activity spreads across the brain, producing transitory neural dysfunction.[8] Bioamine pathways projecting from the brain stem regulate activity within the trigeminovascular system. The pathogenesis of migraine is most likely due to an imbalance in the modulation of nociception and blood vessel tone by serotonergic and noradrenergic neurons.[9] Headache is likely due to compensatory overactivity in the trigeminovascular system of the brain. Activation of trigeminal sensory nerves leads to the release of vasoactive neuropeptides (eg, calcitonin gene–related peptide [CGRP], neurokinin A, substance P) that produce a sterile inflammatory response, which is triggered by a physical, chemical, or metabolic noxious stimuli around vascular structures in the brain, provoking the sensation of pain.[9] Continued sensitization of central nervous system (CNS) sensory neurons can potentiate and intensify headache as an attack progresses.[8]

Tension-Type Headache

The pathophysiologic mechanisms producing TTHs are not clearly understood and are likely multifactorial. However, central sensitization to peripheral nociceptive input arising from the pericranial myofascia is the leading hypothesis. The belief that sustained muscle contraction is solely responsible for generating the pain cannot be supported. Muscle tenderness is prominent in this syndrome, but it only reflects a heightened sensitivity to pain. TTH pain is believed to arise by disturbances in the muscles and tissues of the head being misinterpreted due to disordered CNS pain processing.[10]

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

Cluster headache is one of a group of disorders referred to as trigeminal autonomic cephalalgias.[11] This autonomic nervous system dysfunction is characterized by sympathetic underactivity coupled with parasympathetic activation. Similar to migraine, the pain of a cluster headache is believed to be the result of vasoactive neuropeptide release and neurogenic inflammation. The exact cause of trigeminal activation in this intermittently manifest syndrome is unclear.[11] One hypothesis is that hypothalamic dysfunction, occasioned by diurnal or seasonal changes in neurohormonal balance, is responsible for headache periodicity.[5] Serotonin affects neuronal activity in the hypothalamus and trigeminal system and may play a role in the pathophysiology of cluster headache. The precipitation of cluster headache by high-altitude exposure also implicates hypoxemia in the pathogenesis of trigeminal autonomic cephalalgias.[8]

CLINICAL PRESENTATION AND DIAGNOSIS OF HEADACHES

Migraine Headache

Migraine presents as a recurrent headache that is severe enough to interfere with daily functioning. KEY CONCEPT Migraine headaches are classified as migraine with aura and migraine without aura.[2] Aura is defined as a transient, focal neurologic symptom that can occur prior to or during an attack. These typically present as wavy lines or spots within the field of vision but can also present as a scotoma.[2] The IHS outlines diagnostic criteria that differentiate migraine with and without aura. Migraines can be triggered by changes in behavior, environment, diet, and hormone levels. Dietary intake of tyramine, aspartame, monosodium glutamate, and nitrites are known migraine triggers.[8] Migraines occurring 15 or more days per month for a 3-month period or longer, without the overuse of analgesic medications, are classified as chronic migraines.[2] Severe and debilitating migraine pain lasting more than 72 hours is termed status migrainosus.[2]

Clinical Presentation and Diagnosis of Migraine Without Aura

Patients experiencing "migraine without aura" may display the following headache symptoms and characteristics:

Two or more of the following are present:

1. Pain interrupts or worsens with physical activity
2. Unilateral pain
3. Pulsating pain
4. Moderate-to-severe pain intensity

One or more of the following are present during headache:

1. Nausea/vomiting
2. Photophobia and phonophobia

Duration: 4 to 72 hours (treated or not treated)

Criteria for diagnosis: Five or more attacks fulfilling above criteria are necessary

Laboratory assessments that may be helpful in excluding medical comorbidities: Complete blood count (CBC), complete chemistry panel, including liver function tests (LFTs), thyroid function tests (TFTs), and erythrocyte sedimentation rate (ESR)

Tension-Type Headache

TTH pain differs from migraine pain in that it is usually reported to be mild to moderate in severity, nonpulsating, and bilateral.[6] The pain is described by sufferers as a band-like tightness or pressure around the head. No transient neurologic deficits are noted, and systemic symptoms are rare.

Clinical Presentation and Diagnosis of Migraine with Aura

Patients experiencing "migraine with aura" may display the following headache symptoms and characteristics:

One or more of the following present with no motor weakness:

1. Visual (eg, flashes of light, blind spots)
2. Sensory (eg, sensitivity to light, sound, smell)
3. Speech and/or language (eg, speech or language difficulty)
4. Motor (eg, heaviness of limbs)
5. Brain stem (eg, vertigo, tinnitus)
6. Retinal (eg, change in vision or vision loss)

Two or more of the following:

1. At least one aura symptom that spreads gradually over at least 5 minutes
2. Individual aura symptoms lasting 5 to 60 minutes
3. At least one aura symptom is unilateral
4. The aura is accompanied or followed by a headache within 60 minutes

Criteria for diagnosis: Two or more attacks fulfilling above criteria are necessary

Clinical Presentation and Diagnosis of Tension-Type Headache

Patients experiencing TTH may display the following headache symptoms and characteristics:

Two or more of the following are present and are not aggravated by routine physical activity:

1. Bilateral pain
2. Nonpulsating pain
3. Mild or moderate pain intensity

Both of the following:

1. No nausea or vomiting (anorexia possible)
2. Either photophobia or phonophobia (not both)

Duration: 30 minutes to 7 days

Criteria for diagnosis: 10 or more attacks fulfilling above criteria occurring on average less than 1 day per month are necessary

TTHs occurring more than 15 days per month for more than 3 months, without evidence of medication overuse, would be classified as chronic TTH.[2]

Cluster Headache

Pain associated with cluster headache differs from migraine and TTH in that it is severe, intermittent, and short in duration.[5] Headaches typically occur at night, but attacks may occur multiple times per day.[11] The pain is usually unilateral, but, unlike migraine, it is not described as pulsatile.[5] Aura is not a feature, and pain intensity peaks early after onset, although it may persist for hours.[5] The headache is described as explosive, excruciating, and referred to as a "suicide headache." A constellation of features, ascribed to parasympathetic overactivity, can be seen, such as ipsilateral conjunctival injection as well as lacrimation, rhinorrhea, and sweating. Cluster headache patients tend to become excited and restless during attacks, rather than seeking quiet and solitude as in migraine.[11]

Clinical Presentation and Diagnosis of Cluster Headache

Patients experiencing cluster headaches may display the following headache symptoms and characteristics:

At least one or more of the following symptoms:

1. Lacrimation
2. Nasal congestion and/or rhinorrhea
3. Eyelid edema
4. Forehead or facial sweating/flushing
5. Sensation of fullness in the ear
6. Miosis and/or ptosis
7. Sense of restlessness or agitation

- Duration of pain: 15 to 180 minutes (untreated)
  - Frequency of attacks: One every other day and/or up to 8 per day for more than half the time the disorder is active (may have long periods when headaches are inactive)
  - Criteria for diagnosis: Five or more attacks fulfilling the above criteria

Patient Encounter, Part 1

A 29-year-old woman describes having mild-to-moderate headache that is bilateral and nonpulsating in nature. She denies nausea, vomiting, photophobia, and phonophobia. Her headaches typically last for 1 hour and occur three times per month. She reports using OTC pain relievers to help ease the pain, but she has not had any success thus far.

What type of headache is the patient most likely experiencing?

What characteristics of the headache support this diagnosis?

What are possible causes or triggers of headache in this patient?

What additional information is needed to formulate a treatment plan?

TREATMENT OF HEADACHE DISORDERS

Desired Outcomes

KEY CONCEPT The short-term treatment goal of migraine is to achieve rapid pain relief to allow the patient to resume normal activities. The long-term goal of therapy is to prevent headache recurrences and diminish headache severity.[12] Similarly, the goal of TTH care is to lessen headache, whereas the long-term goal is to avoid analgesic overuse and dependence.[8,13] The short-term therapeutic goal of cluster headache is to achieve rapid pain relief. Prophylactic therapy may be necessary to obtain the intermediate-term outcome of reducing the frequency and severity of headaches within a periodic cluster series as well as to achieve the long-term goal of delaying or eliminating recurrent periods.[14]

General Approach to Treatment

KEY CONCEPT Pharmacologic treatment of acute headache should be started early to abort the intensification of pain and improve response to therapy. First-line pharmacologic agents include nonsteroidal and opiate analgesics, as well as serotonin-receptor agonists (triptans).[12] The long-term management of headache syndromes focuses on lifestyle modification and other nonpharmacologic therapeutic options; if headaches are severe and frequent, prophylactic pharmacologic therapy is needed.[12] Nonpharmacologic therapies, which are important in the acute as well as preventive setting, include the following cognitive and behavioral treatment recommendations: relaxation timing, thermal biofeedback, acupuncture, cognitive behavioral therapy, and electrical nerve stimulation.[12] KEY CONCEPT Several clinical markers, so-called red flags, have been identified that warrant urgent physician referral and further diagnostic evaluation (Table 36–1).[15]

Nonpharmacologic Therapy

The successful management of headache disorders depends on comprehensive patient education. Recording headache frequency, duration, severity, possible triggers, and medication response in a "headache diary" provides beneficial information for the patient regarding headache precipitants and useful insights for

Table 36–1

Headache “Red Flags” Indicating Need for Urgent Medical Evaluation[8,15]

New-onset sudden and/or severe pain
Stereotyped pain pattern worsens
Systemic signs (eg, fever, weight loss, or accelerated hypertension)
Focal neurologic symptoms (ie, other than typical visual or sensory aura)
Papilledema
Cough-, exertion-, or Valsalva-triggered headache
Pregnancy or postpartum state
Patients with cancer, human immunodeficiency virus (HIV), and other infectious and immunodeficiency disorders
Seizures

the clinician selecting appropriate management strategies.[12] To prevent future occurrences, exposure to headache triggers (Table 36–2) should be limited.[14] In the acute setting, environmental control can lessen the severity of an attack, so patients may benefit from resting in a dark, quiet area. Behavioral interventions, such as biofeedback, relaxation therapy, and cognitive behavioral training, are effective and can be recommended for headache prevention. Headache sufferers may also benefit from stress management training.[8] Acupuncture has yielded inconsistent benefits in clinical trials.[16] Although the response is variable, headache patients should be advised to moderate alcohol use and curtail tobacco abuse.[14] All nonpharmacologic therapies may be useful in augmenting pharmacologic response.

Table 36–2

Migraine Triggers[8,44]

Behavioral

Emotional let down
Fatigue
Sleep excess or deficit
Stress
Vigorous physical activity

Environmental

Flickering lights
High altitude
Loud noises
Strong smells such as perfumes
Tobacco smoke
Weather changes

Food

Alcohol
Caffeine intake or withdrawal
Chocolate
Citrus fruits, bananas, figs, raisins, avocados
Dairy products
Fermented pickled products
Missing meals
Foods containing monosodium glutamate (MSG), Asian food, seasoned salt, nitrites (processed meats), saccharin/aspartame, diet soda or diet food, sulfites (shrimp), tyramine (cheese, wine, organ meats, yeast breads)

Medications

Cimetidine
Estrogen or oral contraceptives
Indomethacin
Nifedipine
Nitrates
Reserpine
Theophylline
Withdrawal due to the overuse of analgesics, benzodiazepines, decongestants, or ergotamines

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Normal childhood illnesses

FH: Father living, age 59 years: hypertension, diabetes mellitus; mother living, age 56 years: tension-type headaches; two sisters and one brother in good health

SH: Full-time pet groomer at a loud and strong-smelling veterinary clinic; two to three cups of coffee per day; enjoys two glasses of wine each night; has never smoked, but is married to a heavy smoker

Meds: Excedrin Extra Strength (acetaminophen 500 mg, aspirin 250 mg, caffeine 65 mg) two tablets orally every 6 hours as needed for headache

ROS: Headache, mild-moderate intensity, no sensitivity to light; no dizziness; no chest pain or palpitations; no shortness of breath with exertion; no weakness or joint discomfort

VS: BP 126/84, P 88, RR 19, T 37.0°C (98.6°F) oral

HEENT: No papilledema, neck tender without stiffness

CV: Regular rate and rhythm (RRR), normal S1, S2, S4 gallop, no murmur, rub

Chest: Clear to auscultation (CTA)

Abd: Benign, bowel sounds positive

Neuro: Nonfocal

Labs: CBC and complete chemistry panel within normal limits

What is your assessment of this patient’s condition?

What medical comorbidities or drug therapies may be contributing to her distress?

Identify treatment goals for this patient.

What nonpharmacologic options are needed at present, and what options are appropriate in the long term?

What pharmacologic therapy would you recommend in the acute setting?

Does this patient require long-term pharmacologic prophylaxis against recurrent headaches?

Pharmacologic Therapy

► *Migraine*

Analgesics, such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and combination products containing caffeine, with or without an opioid, are the initial pharmacologic option for the acute management of migraine headache, especially when severity is mild to moderate. Clinical trial evidence supports many NSAID medications in the acute treatment of migraines with and without aura. Acetaminophen alone or in proprietary combinations with aspirin, opioids, caffeine, or butalbital is also effective.[17] If these analgesics prove to be ineffective, and when headaches are severe, then migraine-specific medications, such as triptans, are administered. Early abortive treatment should be the rule. Larger doses of oral medications may be necessary for pain relief, due to the enteric stasis and poor drug absorption accompanying migraine attacks. Intranasal, parenteral, and rectal administration can circumvent this complication.[12]

Ergotamine derivatives produce salutary effects on serotonin receptors similar to triptans. They also impact adrenergic and dopaminergic receptors. This receptor binding can potentially lead to additional adverse effects. Ergotamine tartrate and dihydroergotamine (DHE) are the most commonly used agents.[12] Analgesic onset is within 4 hours, although additional dosing is required if an acceptable response is not achieved. When dosed parenterally, these drugs are usually provided with an antiemetic due to their potential to worsen nausea associated with migraine. The outpatient use of subcutaneous ergotamines is limited by the lack of a prefilled syringe form; the exception is intranasal DHE that can be self-administered to abort an attack.[12] The same cautions associated with triptan use are also applicable to ergot use in patients at risk for vascular events.

Triptans inhibit neurotransmission in the trigeminal complex and activate serotonin 1B/1D pathways in the brain stem, which modulate nociception. They also decrease the release of vasoactive neuropeptides leading to vascular reactivity and pain.[18] The triptans are available in intranasal, subcutaneous, and oral dosage forms, including tablets or orally dissolving tablets. The available agents differ in their dosing and pharmacokinetic properties, but all help in effective treatments to abort or diminish migraine headache (Table 36–3).[8,19–28] Patient responses can be variable; if a patient does not respond to one agent, another is selected before a patient is prematurely labeled as triptan unresponsive. The severity of headache correlates with symptomatic response; thus, administration should be prompt. Relief is usually experienced within 2 to 4 hours. Treatment delay may lead to decreased analgesia through the development of refractory central pain sensitization. Efficacy tends to be dose-related; however, adverse effects do not appear to increase in relation to dose. These medications are well tolerated; the most common side effects are dizziness, a sensation of warmth, chest fullness, nausea, and paresthesia. Rarely, ischemic vascular events may be precipitated by the potential vasoconstrictive nature of these drugs. An initial dose under direct practitioner supervision is indicated for patients at increased cardiovascular risk. Triptans are avoided in patients with migraine associated with neurologic focality, a history of previous stroke, poorly controlled HTN, or unstable angina. Triptans are relatively contraindicated for routine use in pregnancy.[29] Triptans should not be used with concurrent ergotamine administration with the wait time of at least 24 hours between use.[8]

The small molecule CGRP antagonists selectively block the receptor binding of this protein, a potent vasodilator and pain-signaling neurotransmitter, which is known to be increased during a migraine. Two products in this class have been FDA

Table 36–3

Comparison of Serotonin-Receptor Agonists (Triptans)[8,20–28]

Medication (Brand Name)	Dosage Forms	Strength (mg)	Usual Dosage (mg)	May Repeat (hours)	Hepatic and Renal Dosing Considerations (mg)	Potential Drug Interactions
Almotriptan (Axert)	Oral tablets	6.25 12.5	6.25–12.5	2	HI and severe RI: 6.25 starting dose and ≤ 12.5	Ergot derivatives substrate: CYP 3A4, CYP 2D6
Eletriptan (Relpax)	Oral tablets	20 40	20–40	2	Severe HI: not recommended	Ergot derivatives substrate: CYP 3A4, CYP 2D6
Frovatriptan (Frova)	Oral tablets	2.5	2.5	2	Severe HI: use caution	Ergot derivatives substrate: CYP 1A2
Naratriptan (Amerge)	Oral tablets	1 2.5	2.5	4	Mild–mod RI or HI: do not exceed 2.5; severe RI (< 15 mL/min [0.25 mL/s]): do not administer	Ergot derivatives substrate: CYP (various)
Rizatriptan (Maxalt and Maxalt MLT)	Oral tablets Disintegrating tablets	5 10	5–10	2	None identified	Ergot derivatives MAO-A inhibitors
Sumatriptan (Imitrex)	Oral tablets Subcutaneous injection	25, 50, 100 4,6	50 6	2 1	Mild–mod HI: oral dose not to exceed 50; severe HI: contraindicated	Ergot derivatives MAO-A inhibitors
Sumatriptan (Onzetra Xsail)	Nasal spray Nasal powder	5, 20/spray 11 mg/spray	5–20 22–44	2 2		
Sumatriptan/naproxen sodium (Treximet)	Oral tablets	85/500	85/500	2	RI (CrCl < 30 mL/min [0.50 mL/s]): not recommended; mild-to-severe HI: contraindicated	Ergot derivatives MAO-A inhibitors
Zolmitriptan (Zomig and Zomig-ZMT)	Oral tablets Disintegrating tablets Nasal spray	2.5, 5 2.5, 5 2.5, 5/spray	2.5 1.25–2.5 2.5	2 2 2	CrCl 5–25 mL/min (0.08–0.42 mL/s): clearance reduced by 25%, use caution; mod–severe HI: not recommended	Ergot derivatives MAO-A inhibitors substrate: CYP 1A2

CrCl, creatinine clearance; CYP, cytochrome P450 enzyme; HI, hepatic impairment; MAO-A, monoamine oxidase type A; RI, renal impairment.

approved for the acute treatment of migraine, ubrogepant in 2019 and rimegepant in 2020. Ubrogepant is available in tablet form and rimegepant is available as an oral-disintegrating tablet that can be taken upon symptom onset for migraines with or without aura. While CGRP antagonists are relatively well tolerated, with nausea as the most common side effect, there may be cost limitations of their use.[30]

The choice of initial therapy for acute migraine attacks is a subject of debate among specialists. Some believe that nonspecific analgesics should be used first line, whereas others believe migraine-specific drugs should be the choice for patients with severe pain or a history of significant disability. A stepped-care approach within attacks from less to more specific drugs is usually recommended. Once a history of headache refractory to common analgesics is established, triptans should be used as initial therapy.[12] Selection of initial headache treatment is important in reducing the incidence of medication overuse headache (MOH). This occurs when patients use ergotamines, triptans, opioids, or other combinations for more than 10 days per month. This can also be considered in patients who are using nonspecific analgesics for more than 15 days per month.[13] Status migrainosus is an especially severe and long-lasting form of migraine, lasting longer than 72 hours even with treatment. In patients who present to the hospital with intractable pain, IV metoclopramide supplemented with DHE may be needed. Intravenous valproic acid may be another option for therapy in these patients. Oral medications in this setting are not used because nausea and vomiting limit their bioavailability.[12] Migraine patients with frequent and severe attacks are candidates for prophylactic treatment.[31]

▶ *Tension-Type Headache*

Most individuals who experience episodic TTHs will not seek medical attention.[2] Instead, they will find relief with the use of widely available OTC analgesics. Acetaminophen products and NSAIDs are commonly utilized. An individual patient may benefit from topical analgesics (eg, ice packs) or physical manipulation (eg, massage) during an acute attack, but the evidence supporting nonpharmacologic therapies is inconsistent.[5] Relaxation techniques can often reduce headache frequency and severity. When pain is unrelieved, prescription-strength NSAID use is required, or the combination of acetaminophen with an opioid analgesic may be necessary. The frequent use of these more potent analgesics should be limited, so that the development of dependency is prevented. As described above, MOH can occur with the frequent use of analgesics for TTH. For patients experiencing frequent TTH, prophylactic treatment should be considered.[13]

▶ *Cluster Headache*

Cluster headaches respond to many of the treatment modalities used in acute migraine; however, a therapy specific to cluster headaches is the administration of high-flow-rate oxygen: 100% at 12 to 15 L/min by nonrebreather face mask for approximately 15 minutes.[32] If the pain is not aborted, retreatment is indicated. No long-term side effects are seen with short-term oxygen use. Initial prophylactic therapy is required to limit the frequency of recurrent headaches within a periodic series. If oxygen therapy is not wholly effective, drugs are useful adjunctive therapy. Drug therapy is also used when supplemental oxygen is not readily available. The triptan class is safe and effective. Intranasal or subcutaneous sumatriptan as well as intranasal zolmitriptan has demonstrated efficacy in decreasing cluster headache.[33] Oral triptans are also effective, but their delayed onset of action may limit their applicability in acute cluster headache treatment.[18] Cluster headache is rapid in onset and achieves peak intensity quickly, but it can be of short duration. Oral agents may have utility in limiting the recurrence of cluster attacks. Intranasal, intramuscular, or IV ergotamine agents are alternatives to triptan use.[5] Repeated dosing may break a cluster series. For those patients in whom triptans and ergotamine derivatives are contraindicated due to ischemic vascular disease, octreotide may be helpful to relieve pain.[34] Octreotide is a somatostatin analogue that has a short half-life and may be administered subcutaneously. Unlike the other abortive agents, it has no vasoconstrictive effects; the most prominent treatment emergent adverse effect is gastrointestinal (GI) upset. Glucocorticoids, provided IV and later tapered orally, are effective when cluster headache attacks are not satisfactorily controlled.[12]

Pharmacologic Therapy for Headache Prophylaxis

KEY CONCEPT Prophylaxis for headache disorders is indicated if headaches are frequent or severe, significant disability occurs, pain-relieving medications are used frequently, or adverse events occur with acute therapies.[12,31]

▶ *Migraine Prophylaxis*

Migraine headaches that are severe, frequent, or lead to significant disability require long-term medication therapy. Prophylactic therapy is also recommended for migraines associated with neurologic focality because it may prevent permanent disability.[12] Although multiple medication classes have garnered US Food and Drug Administration (FDA) labeling for migraine prevention, there is no consensus on the best initial therapy (Table 36–4).[31] **KEY CONCEPT** The choice of pharmacologic agent is individually tailored to patient tolerability and medical comorbidities.

The β-blockers have long been a mainstay in migraine prevention, and many have been proven to be effective in improving patient symptoms. Cautious dosage titration is advised for those patients who do not have other indications for β-blocker

Table 36–4

Oral Medications for Prophylaxis of Migraines[12,17]

Medication (Brand Name)	Usual Dosage (mg/day)	Main Adverse Effects
Antiepileptics		
Topiramate (Topamax)[a]	25–200	Paresthesias, dizziness, fatigue, nausea
Valproic acid (Depakene)[a]	500–1500	
Divalproex sodium (Depakote)[a]	500–1500	
β-Blockers		
Atenolol (Tenormin)[b]	25–200	
Metoprolol (Lopressor)[a]	50–200	Fatigue, exercise intolerance
Nadolol (Corgard)[b]	20–160	
Propranolol (Inderal)[a]	80–240	
Timolol (Blocadren)[a]	10–30	
Antidepressants		
Amitriptyline (Elavil)[a]	10–150	Weight gain, dry mouth, sedation
Venlafaxine (Effexor)[a]	37.5–150	

[a] Level A: Established efficacy.

[b] Level B: Probably effective.

use. Comorbid reactive airway disease is a relative contraindication to β-blocker prophylaxis, and patients with cardiac conduction disturbances should be closely monitored.[17] Patients should also be advised to take only 5 mg of rizatriptan (max 15 mg/day) when they are prescribed propranolol because propranolol may increase levels of rizatriptan significantly.[24] Calcium channel antagonists are often used when patients cannot tolerate β-blockers. None of the calcium channel blockers carry an FDA indication, and their efficacies are considered to be variable. Angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) have been evaluated for migraine prevention, but only two, lisinopril and candesartan, have shown possible efficacy.[17]

Low-dose amitriptyline or other tricyclic antidepressants (TCAs) have proven efficacy in migraine prevention.[17] Due to sedation, these medications are commonly administered at night. Secondary TCAs (eg, nortriptyline) or heterocyclic compounds (eg, trazodone) have fewer dose-limiting adverse effects than TCAs, especially anticholinergic effects (eg, dry mouth, constipation, and urinary retention), but efficacy has been variable with these agents. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been evaluated for migraine prevention, but thus far, only venlafaxine has demonstrated probable efficacy. The FDA has issued a controversial warning about using serotonergic antidepressants along with triptans due to the rare occurrence of serotonin syndrome.[35]

The antiseizure medications (ASM) valproic acid and topiramate are approved for migraine prophylaxis. In patients whose migraine headaches are believed to be related to trigeminal neuralgia, carbamazepine is used as prevention for both disorders.[17] Divalproex sodium doses are gradually titrated to 1000 mg/day; topiramate is titrated to a maximum of 100 mg twice per day. At these doses, serum drug level monitoring is infrequently needed.[17] Topiramate is especially useful in patients who have metabolic syndrome, diabetes, and dyslipidemia because it is unlikely to cause weight gain often seen with valproic acid. Topiramate has the potential for side effects such as paresthesia, fatigue, anorexia, nausea, and cognitive impairment. These side effects can be mitigated by a slow dosage titration and maintaining adequate hydration.[36]

Three injectable monoclonal antibodies targeting the CGRP were approved by the FDA for migraine prevention in 2018 and include erenumab-aooe, galcanezumab-gnlm, and fremanezumab-vfrm. They are all dosed as monthly injections with the exception of fremanezumab-vfrm that has an additional quarterly injection dosing option.[37–39] Later in 2020, Eptinezumab-jjmr was FDA approved as an intravenous infusion given over 30 minutes.[40] The most common side effects include injection site reactions and constipation. Further studies regarding long-term effectiveness and side effects are needed.

Methysergide is an ergotamine derivative that impacts central serotonin balance. Inflammatory fibrosis is a rare but serious adverse reaction associated with the prolonged use of methysergide. Retroperitoneal fibrosis, pulmonary fibrosis, or fibrosis in cardiac tissue can occur. These conditions may resolve upon drug withdrawal, but cardiac valvular damage can be irreversible. Some experts believe it is the best choice for refractory migraine with frequent attacks, but due to its significant adverse effect profile, it is not marketed in the United States.[41]

Given that migraines can be triggered by changes in hormonal balance, it is not surprising that some women have migraines around the time of menstruation. Often, these migraines can be prevented by starting NSAIDs prior to the beginning of menstruation. Triptans can be tried in patients unresponsive to NSAIDs. Three triptans have been shown to be effective in preventing menstrual migraines. Frovatriptan, naratriptan, and zolmitriptan can be considered and should be started 2 to 3 days prior to the beginning of menstruation.[31]

OnabotulinumtoxinA has received FDA approval for the treatment of chronic migraine, but the evidence supporting its use is conflicting. In 2008, the American Academy of Neurology conducted an evidence review and concluded that OnabotulinumtoxinA was probably ineffective for the prevention of migraines.[42] In the PREEMPT 1 and PREEMPT 2 trials, there was a statistically significant reduction in the number of headache days per month when compared to placebo, but the absolute difference between the two groups was only 1.8 days.[43,44]

While evidence is limited, some complementary alternative therapies can be considered for migraine prophylaxis. Petasites (butterbur) has been associated with a potential 60% reduction in the number of headaches experienced over a 1-month period when compared to placebo; however, the risk of liver toxicity associated primarily with the plant's root and allergic reactions in patients with asthma may limit its use. Studies for riboflavin have been mixed, with some older studies supporting its use for migraine prevention, but some newer studies have failed to show efficacy. Finally, MIG-99 (feverfew) has also shown possible efficacy with very limited trial evidence.[45]

▶ *Tension-Type Headache Prophylaxis*

The prevention of chronic TTHs uses the same pharmacologic strategies as for migraine prophylaxis. TCAs are the mainstay of chronic therapy. The efficacy of serotonergic agonists remains in question. Although there is a little need for muscle relaxants (eg, methocarbamol) in the treatment of acute TTH, they are often provided as a preventive intervention. Combination prophylactic therapies may be needed to wean patients from daily analgesic abuse. Stress reduction techniques may be particularly effective in this setting.[5]

▶ *Cluster Headache Prophylaxis*

The calcium channel blocker verapamil is the mainstay of cluster attack prevention and chronic prophylaxis.[5] It is dosed 240 to 360 mg/day within an attack period and may be dosed 120 to 240 mg/day for prevention during remission. Higher doses may be necessary to stave off recurrent cluster periods. Beneficial effects may be appreciated after 1 week of treatment, but 4 to 6 weeks is usually needed. Adverse effects include smooth muscle relaxation with the subsequent exacerbation of gastroesophageal reflux and the development of constipation. Caution should be exercised in patients with myocardial disease because verapamil is an inotropic and chronotropic cardiac suppressant.[5] Pharmacokinetic drug–drug interactions must be considered, as verapamil is a moderate inhibitor of oxidative metabolism through cytochrome P450 (CYP) enzyme 3A4. Eletriptan, a CYP 3A4 substrate, should be avoided concurrently with verapamil.[5,21] Lithium is another effective therapy to reduce headache frequency in a cluster series and limit recurrences.[12] The dose administered should be individualized to achieve a low serum concentration (0.4–0.8 mEq/L [mmol/L]). Dose adjustments in the setting of renal disease or congestive heart failure are required.[5] Lithium is contraindicated in patients concurrently prescribed thiazide diuretics, NSAIDs, ACEIs, or ARBs. Patient persistence with long-term lithium therapy may be hindered by the emergence of tremor, GI distress, and lethargy. Verapamil and lithium doses can be lowered when used in combination with ergotamine. If possible,

Patient Encounter Part 3: Creating a Care Plan

Based on the information presented, create a care plan for the acute and chronic management of this patient's headache. Your plan should include the following:

A statement of the drug-related needs and/or problems.

The goals of therapy.

A detailed, patient-specific therapeutic plan.

A monitoring plan to determine whether the goals have been achieved and adverse effects are avoided.

bedtime dosing is recommended, given the nocturnal predilection of cluster headache attacks.[11]

SPECIAL POPULATIONS

Migraine Headache in Children and Adolescents

Migraine headaches are common in children, and their prevalence increases in the adolescent years.[4] The diagnosis and evaluation of headaches are especially difficult in children, given their decreased ability to articulate symptoms. Treatment presents another challenge because medications used for headache management in adults have not been fully evaluated for efficacy and safety in children. Consensus panel recommendations identify ibuprofen as effective and acetaminophen as probably effective in the acute treatment of headache in patients older than 6 years.[41] Aspirin use is avoided due to the risk of precipitating Reye syndrome. The use of triptans in children and adolescents has not been shown to be more effective than placebo. Only rizatriptan is FDA approved for children over 6 and almotriptan for children over 12. The rest are approved for greater than 18 years of age.[20,24,45] Medication prophylaxis for migraines in children and adolescents is understudied with conflicting data.[46,47] Nonpharmacologic interventions and trigger identification and avoidance are advised.

Pregnancy

Headaches are common in pregnancy and are likely related to hormonal shifts. TTHs predominate; migraine attacks may increase in frequency, but more often, frequency decreases during pregnancy.[48] Recommendations for headache care during pregnancy are based on limited evidence and are largely anecdotal. Because headaches are not associated with fetal harm, reflexive pharmacologic therapy should be avoided and drug treatment choices carefully considered. Standard nonpharmacologic therapies are often sufficient. Acetaminophen is safe for the pregnant woman and her fetus.[49] NSAIDs are avoided late in the third trimester to prevent detrimental prostaglandin alterations leading to premature ductus arteriosus closure. Opioids are second-line agents and should not be used chronically. Opioids can lead to dependence in the mother and acute withdrawal in the infant after birth.[48] Centrally acting antiemetic agents are safe and may

Patient Care Process

KEY CONCEPT Individualized treatment regimens for headache disorders are based on headache type, pattern of occurrence, response to therapy, medication tolerability, and comorbid medical conditions.

Collect Information:

- Obtain a complete medical and social history to identify any potential drug–disease interaction or social factor that may influence treatment choices.
- Obtain a family medical history, focusing on headache or mental health disorders in first-degree relatives.
- Perform medication history, including prescription and nonprescription medications along with dietary supplements. Identify medication allergies.
- Complete a review of systems and physical examination to identify causes or complications of headache.
- Review medical records, including any laboratory assessment and radiographic finding.

Assess the Information:

- Based on information obtained for reviewing the patient's medical history, patient interview, review of systems, and physical examination, identify the type of headache.
- Determine if there are triggers for the patient's headaches.
- Assess laboratory assessments to determine renal function and liver function as these may affect medication choice.
- Based on patient history and family history, evaluate the patient's cardiovascular health especially if considering a triptan.
- If patient is already receiving pharmacotherapy, assess for appropriateness and efficacy.

Develop a Care Plan:

- Recommend appropriate pharmacologic therapy to abort headache based on type, patient characteristics, current medication profile, and comorbid conditions.
- When selecting new agents for acute management or prophylaxis, ensure that the medication is financially accessible.

Implement the Care Plan:

- Educate the patient on the administration, maximum dosage, and anticipated adverse effects of the prescribed medication and advise the patient when to seek emergency medical attention.
- Instruct the patient to keep a headache diary to assess therapeutic response.
- Educate on the potential for medication overuse headache.

Follow up: Monitor and Evaluate:

- Follow-up should be scheduled within 4 weeks of starting any new medication for headache to assess efficacy. As patient becomes more aware of headache symptoms and appropriate agents are on board for prevention and treatment of headache, follow-up can become less frequent (ie, 3–6 months).

be useful as adjunctive agents. Corticosteroids may be needed for intractable headache relief. Prednisone and methylprednisolone are preferred, as they are metabolized in the placenta and do not expose the fetus. In pregnant women with migraine headache, vasoconstrictive agents such as triptans are relatively contraindicated, even though maternal registry data reveal little teratogenicity. If triptans are considered for acute migraine treatment, sumatriptan, naratriptan, and rizatriptan have the greatest evidence of safety during pregnancy.[48] Ergot compounds are strictly avoided because they may precipitate uterine contractions and placental ischemia leading to hypoxemia in the fetus. Migraine prophylaxis is considered cautiously because β-blockers and calcium channel antagonists may lead to maternal hypotension and diminished placental blood flow or fetal bradycardia.[48] Use of antiseizure medications in this setting has not been sufficiently studied to allow definitive recommendations.

Outcome Evaluation

To ensure optimal headache management, in acute treatment and prophylactic therapy, monitor regimens both for therapeutic outcomes and adverse events, which may impact quality of life and medication adherence. In acute management, monitor patients for pain improvement within 2 hours of treatment initiation.[49] If pain control has not been achieved, additional therapy may be needed. With chronic management for headache prevention, patients are encouraged to track progress in a headache diary, and clinicians monitor overall headache status every several weeks to months for a 50% or greater reduction in headaches. A slow decrease in headache frequency is anticipated during this time. Monitoring for adverse effects is central to successful treatment. For acute management, monitor for GI effects from analgesics such as NSAIDs or octreotide, vasoconstrictive symptoms from triptans, and nausea and vascular problems from ergotamine derivatives. Monitor those taking β-blockers for reactive airway disease and cardiac conduction disturbances. Monitor those taking TCAs for sedation and anticholinergic effects such as dry mouth, constipation, and urinary retention. Monitor patients taking calcium channel blockers for gastroesophageal reflux symptoms and constipation, and monitor those taking lithium for tremor, GI distress, and lethargy.

Acknowledgments

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Abbreviations Introduced in This Chapter

ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
CBC	Complete blood count
CGRP	Calcitonin gene–related peptide
CNS	Central nervous system
CV	Cardiovascular
CYP	Cytochrome P450
DHE	Dihydroergotamine
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
GABA	γ-Aminobutyric acid
GI	Gastrointestinal
HI	Hepatic impairment
HIV	Human immunodeficiency virus
IHS	International Headache Society
MAO-A	Monoamine oxidase type A
MOH	Medication overuse headache
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over-the-counter
RI	Renal impairment
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TFT	Thyroid function test
TTH	Tension-type headache

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37

Substance-Related Disorders

Chris Paxos and Christian J. Teter

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Identify the prevalence of use for alcohol, opioids, central nervous system (CNS) stimulants, cannabinoids, and tobacco in the US population.
2. Explain the commonalities of action of substances on the reward system in the brain.
3. Determine when a patient meets criteria for substance use disorder.
4. Identify the typical signs and symptoms of intoxication and withdrawal associated with the use of alcohol, opioids, CNS stimulants, cannabinoids, and tobacco.
5. Determine the appropriate treatment measures to produce a desired outcome after episodes of intoxication and withdrawal.
6. Choose specific pharmacotherapeutic options based on patient-specific factors.
7. Recommend a comprehensive medication treatment and monitoring program to help maintain recovery and prevent relapse to substance use.

INTRODUCTION

Substance use disorders (SUDs) are highly prevalent worldwide. In the United States, patterns of substance use have been cyclical. For example, cocaine was first isolated from coca leaves in 1860. Its use was advocated by many in the medical establishment until the mid-1890s when it became evident that chronic use might be addictive in some individuals and could have deleterious physiologic effects. Its use decreased after prescribing and dispensing restrictions in the early 20th century. In the 1980s, a smokeable formulation (ie, crack) became available, and cocaine use again became epidemic. This historically cyclic nature of substance use is common to many substances with abuse potential.

KEY CONCEPT Pharmacotherapy has a role in treatment of some substance-related disorders, including intoxication, withdrawal, and/or long-term relapse prevention. These substances include alcohol, opioids, central nervous system (CNS) stimulants, cannabinoids, and tobacco. This chapter focuses on pharmacotherapy for these common substance-related disorders. Although other substances can be misused (eg, benzodiazepines), they are not the focus of this chapter.

EPIDEMIOLOGY AND ETIOLOGY

The National Survey on Drug Use and Health (NSDUH) uses a representative sample of individuals 12 years or older to determine the annual prevalence of licit and illicit substance use.[1] In 2018, 164.8 million Americans (60.2% of the population) used a substance, including alcohol, tobacco, or illicit substances in the past month. More than half (51.1%; 139.8 million) of Americans reported current (ie, past month) alcohol use. Nearly one in four Americans (24.5%; 67.1 million) reported binge drinking (ie, five or more drinks for men and four or more drinks for women), and 6.1% (16.6 million) reported heavy drinking (ie, binge drinking on five or more occasions) over the past month. Approximately one-fifth (21.5%; 58.8 million) of Americans reported current tobacco use. During the time frame of 2002 to 2018, cigarette use declined overall; however, this may be due in part to electronic cigarettes. Regarding illicit drug use, one in five Americans (19.4%; 53.2 million) reported past year use, with cannabis and prescription pain relievers being most common (Figure 37–1).[1] The NSDUH findings indicate that substance use is wide ranging and continues to be a major public health concern.

Reward Pathway

KEY CONCEPT Virtually all substances of abuse appear to activate the same brain reward pathway, which is highlighted by dopaminergic neurotransmission arising in the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NA) and prefrontal cortex (PFC). This pathway is also responsible for reinforcement of behaviors, focus, and learning.

Figure 37–2 depicts the mesocorticolimbic dopamine (DA) pathway. Key components are DA projections from the VTA to the NA and PFC.[2,3] Many studies support mesolimbic DA system involvement in natural rewards and reinforcement; however, there is also evidence that reinforcement exists independently of DA.[4,5] The initial pleasurable experiences secondary to substance use appear to be primarily attributable to activation of primary reward circuits in the brain. These same reward circuits operate under normal circumstances to reinforce activities that promote survival, such as food and water consumption, social affiliation, or sexual activity. In SUDs, these systems become disrupted, especially after repeated substance use in susceptible individuals. Therefore, SUDs may be viewed as a disease of disrupted reinforcement, where seeking and use of substances often supersedes natural rewards.

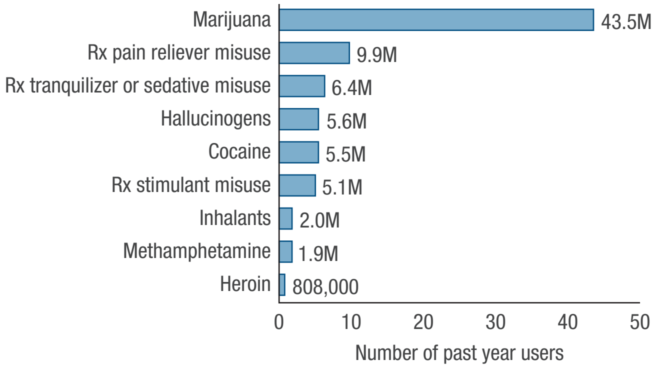

FIGURE 37–1. Past-year illicit drug use in the United States among individuals 12 years and older in 2018. (Data and figure in the public domain from Substance Abuse and Mental Health Services Administration. Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, 2019.)

Although most individuals experience pleasant effects, most persons that misuse these substances do not develop a disorder. Why some individuals develop SUDs while others do not relates to complex genetic, environmental, and cultural factors.

PATHOPHYSIOLOGY

Neuronal Adaptation

KEY CONCEPT Although activation of reward pathways explains the pleasurable sensations associated with acute substance use, chronic use (which may result in substance-related disorders) may be related to neuroadaptive effects within the brain.

While diagnostic criteria use SUD and related terminology, the term addiction continues to appear in the literature. Addiction is often described as a repeating cycle with three phases: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation (ie, craving).[5] The binge/intoxication phase is characterized by using a substance with abuse potential and experiencing its pleasurable or rewarding effects. Chronic use leads to neuroadaptations in the brain, including a generalized decrease in DA neurotransmission and increase in corticotropin-releasing factor (CRF). After a period of chronic use, an individual may experience the withdrawal/negative affect phase in the absence of the substance. Withdrawal symptoms can include negative emotions and physical symptoms. The preoccupation/anticipation phase, characterized by an individual craving the substance, may involve other neurotransmitters (ie, beyond DA). For example, elevated CRF, norepinephrine (NE), and glutamate may exist in the “extended amygdala” during prolonged abstinence. Perhaps these changes lead to a long-term need to use substances to relieve unpleasant symptoms, such as stress.[5] Multiple factors are associated with an increased risk of relapse, including substance availability, psychological stressors, and triggers such as seeing a white powder or returning to a location where substances were previously obtained. These factors may trigger residual adaptive changes (eg, elevated glutamatergic activity) that occurred during the period of addiction.

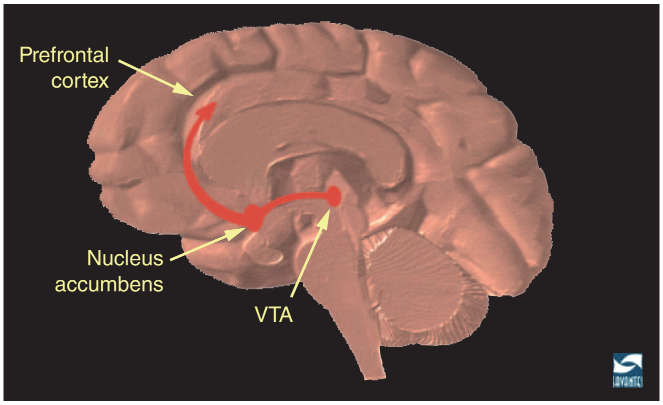

FIGURE 37–2. The mesocorticolimbic dopaminergic (ie, “reward”) pathway. (VTA, ventral tegmental area.) (Data available in the public domain from The National Institute on Drug Abuse [Internet]. https://www.drugabuse.gov/publications/teaching-addiction-science/understanding-drug-abuse-addiction-what-science-says.)

Patient Encounter 1

A 46-year-old man is admitted to inpatient psychiatry unit secondary to depressive symptoms. Past medical history includes major depressive disorder and alcohol use disorder, specifically, heavy episodic alcohol consumption. Home medications include sertraline and acamprosate, both of which he takes regularly. On examination, the patient reports that he does not drink consistently, but when he does consume alcohol, he tends to “overdo it” and that a typical drinking episode may “easily” involve 6 to 10 drinks. The patient appears to possess insight that his drinking is excessive and likely harmful to his health and well-being. The patient would like to reduce the number of drinks he consumes on a given occasion and “lessen the damage” he might be doing to himself.

What are the most immediate actions to be taken regarding this patient’s treatment?

What pharmacotherapy can help the patient maintain abstinence from alcohol?

CLINICAL PRESENTATION AND DIAGNOSIS

KEY CONCEPT Assess individuals for behaviors indicative of a substance use disorder, such as impaired control over substance use, risky use, and social impairment, as described in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).[6] Diagnostic criteria from the *DSM-5* are listed in Table 37–1. Consistent with the *DSM-5*, the remainder of this chapter is organized by pharmacologic class and discusses intoxication, withdrawal, and SUDs for each class (except tobacco, which does not have *DSM-5* intoxication criteria).

A variety of standardized instruments are available to screen for and assess the various stages of substance use and its consequences, such as withdrawal symptoms and functional impairment (Table 37–2).[7,8] The Addiction Severity Index (ASI) is the gold-standard instrument that assesses seven problem areas associated with substance use, such as medical and psychiatric status, in addition to measures of alcohol and drug use.[7] Many SUD instruments can be freely obtained from the Substance Abuse and Mental Health Services Administration (SAMHSA).

Table 37–1

***DSM-5* Criteria for Diagnosis of Substance Use Disorders**[6]

A problematic pattern of substance use leading to clinically significant impairment or distress; manifested by ≥ 2 of the following, occurring within a 12-month period:

1. Substance often taken in larger amounts or over longer period than intended.
2. Persistent desire or unsuccessful efforts to cut down or control substance use.
3. Great deal of time spent in activities necessary to obtain substance, use substance, or recover from its effects.
4. Craving, or a strong desire or urge to use the substance.
5. Recurrent substance use resulting in failure to fulfill major role obligations at work, school, or home.
6. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.
7. Important social, occupational, or recreational activities are given up or reduced because of substance use.
8. Recurrent substance use in situations in which it is physically hazardous.
9. Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem likely to have been caused or exacerbated by substance.
10. Tolerance, as defined by either of the following:
    a. Need for markedly increased amounts of substance to achieve intoxication or desired effect.
    b. Markedly diminished effect with continued use of same amount of substance.
11. Withdrawal, as manifested by either of the following:
    a. Characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the *DSM-5* criteria set for substance withdrawal).
    b. Substance (or closely related substance) is taken to relieve or avoid withdrawal symptoms.

Specify[a] current severity:
Mild: Presence of 2 to 3 symptoms.
Moderate: Presence of 4 to 5 symptoms.
Severe: Presence of ≥ 6 symptoms.

[a] Additional specifiers (eg, early vs sustained remission) and substance-specific notes (eg, taking opioid under medical supervision) are included in the *DSM-5*.

Intoxication Signs and Symptoms

Intoxication caused by most substances is described in the *DSM-5* as clinically significant, problematic behavioral or psychological changes to the individual, which are caused by the physiologic effects of the substance. These changes are observed during or shortly after use of the substance. Euphoria or experiencing a pleasurable sensation are initial effects of most substances with abuse potential.[9] Other signs and symptoms are specific to the particular substance or medication class involved. Table 37–3 lists the effects of intoxication from select substances.[6,10-13]

Withdrawal Signs and Symptoms

Although most substances with abuse potential can cause some degree of physical dependence, the severity of withdrawal varies considerably among them. Table 37–4 lists common withdrawal symptoms that emerge upon abstinence from substance use.[6,10-14] Typically, withdrawal symptoms are the opposite of the acute effects of the substance. For example, although alcohol is a CNS depressant, signs and symptoms of withdrawal encompass a hyperalert physiologic response.

Patient Encounter 2

A 27-year-old man reports the intention to quit his long-term cannabinoid use. Upon further discussion, it becomes clear that each time the patient attempts to quit cannabinoids, which he takes in many different forms, such as edibles and via his vaporizer, his anxiety becomes intolerable. This, in turn, also makes it very difficult for him to sleep through the night.

Are there medications that can be recommended to help the patient quit cannabinoid use?

Are there any limitations to these recommendations that should be disclosed?

TREATMENT OF SUBSTANCE USE DISORDER

Patients with SUDs require more than pharmacotherapy to achieve sustained remission. However, medications can sometimes alleviate the effects of intoxication, attenuate withdrawal symptoms, or somewhat decrease craving and likelihood of relapse. For example, pleasurable and intoxicating effects of opioids appear to be caused by their action as μ-opioid receptor agonists. Competitive μ-opioid receptor antagonists, such as naloxone, acutely reverse many opioid effects, including symptoms of intoxication. To date, specific antagonists for most other substances are unavailable. Similarly, reversal of withdrawal syndromes caused by substances with abuse potential is not always possible. Benzodiazepines are used for alcohol withdrawal because of cross tolerance with alcohol. For long-term medication management, patients with opioid use disorder can be maintained on a regimen of medically managed, US Food and Drug Administration (FDA)-approved opioid medications. Regardless of the pharmacotherapy chosen, medications should always be used as adjuncts to a comprehensive psychosocial approach.[10]

TREATMENT OF INTOXICATION SYNDROMES

KEY CONCEPT Treatment goals for acute intoxication of alcohol, opioids, CNS stimulants, and cannabinoids include (a) management of psychological/psychiatric manifestations of intoxication, such as aggression, hostility, and psychosis and (b) management of medical manifestations of intoxication, such as respiratory depression, hyperthermia, hypertension, cardiac arrhythmias, stroke, and seizures. In all cases of intoxication that require medical intervention, referral to and participation in treatment programs are desirable.

Alcohol Intoxication

Desired outcomes are appropriate management of medical problems, prevention of harmful behaviors, and stabilization of mood. Most cases of mild-to-moderate alcohol intoxication, including cases with blood alcohol concentrations (BACs) at lower limits of legal intoxication, do not require medical treatment. Providing a safe environment and reassurance until alcohol effects have dissipated is sufficient in most cases. Initially, BACs may continue to rise if gastrointestinal (GI) absorption is still occurring. Otherwise, BACs generally decrease at a rate of 15 to 20 mg/dL (0.015%–0.02% or 3.3–4.3 mmol/L) per hour. Table 37–3 lists the physiologic effects of alcohol at various BACs; however, individuals with tolerance to alcohol may not show the same level of symptoms at a given BAC as individuals without tolerance.

At more severe levels of intoxication, confusion, stupor, coma, and death may occur. Clinicians must rule out other causes of

Table 37–2

Commonly Used Instruments for Assessing Patients With Substance Use Disorders[7,8]

Instrument	Purpose	Values and Interpretation
Addiction Severity Index (ASI)	Assessment tool Semi-structured interview that addresses seven problem areas: medical status, employment and support, alcohol use, drug use, legal status, family and social status, and psychiatric status Questions include frequency, duration, and severity of problems in the past 30 days or lifetime for various substances Clinician- or technician-administered	200 items Patient and interviewer ratings included Interviewer severity ratings of "need for additional treatment" and composite scores to measure severity Composite score normative data from nationally representative sample of treatment programs is available for those seeking to compare a patient's ASI data with national data (www.tresearch.org); otherwise, comparisons with previous (eg, baseline) composite scores are useful
Alcohol Use Disorders Identification Test (AUDIT)	Screening tool Evaluates quantity and frequency of drinking, physiologic dependence on alcohol, and harmful use	10 items; maximum score = 40 Score of ≥ 8 identifies heavy drinking and those with possible alcohol use disorders
Alcohol Use Disorders Identification Test—Concise (AUDIT-C)	Clinician- or self-administered	AUDIT-C is an abbreviated 3-item version
CAGE Questionnaire	Screening tool Used to identify the presence of problematic drinking Clinician- or self-administered	4 items; maximum score = 4 Score of ≥ 2 is positive and suggests problem drinking Positive screen prompts the need for further assessment
Clinical Institute Withdrawal Assessment–Alcohol, Revised (CIWA-Ar)	Assessment tool Gold-standard alcohol withdrawal assessment; used as part of a symptom-triggered approach Clinician-administered	10 items; maximum score = 67 < 10: mild withdrawal 10–18: moderate withdrawal > 18: severe withdrawal Monitor scores over time; ≥ 8–10 (depending on institutional protocols or co-occurring conditions) indicates need for medication
Clinical Opiate Withdrawal Scale (COWS)	Assessment tool Used to follow the course of opioid withdrawal symptoms and effectiveness of medication regimens Clinician-administered	11 items Score of 0 (asymptomatic) to 4 or 5 (severely symptomatic) for each item based on intensity of signs and symptoms 5–12: mild withdrawal 13–24: moderate withdrawal 25–36: moderately severe withdrawal > 36: severe withdrawal Monitor scores over time; higher scores may indicate need for medication; no standard cut-off exists
Fagerström Test for Nicotine Dependence	Assesses extent of nicotine tolerance, dependence, and craving	6 items Higher scores may predict greater difficulty quitting 0–2: very low 3–4: low 5: moderate 6–7: high 8–10: very high

these serious adverse events because patients may combine alcohol with other substances, sustain head or other injuries, or have vitamin deficiencies and electrolyte abnormalities. If consciousness is impaired, give thiamine by the intravenous (IV) or intramuscular (IM) route at 100 mg/day for at least 3 days. If hypoglycemia is suspected, administer thiamine before glucose-containing fluids to prevent precipitation of acute Wernicke syndrome (see Alcohol Withdrawal section). Interactions between alcohol and medications may also occur. Table 37–5 details drug–drug interactions associated with medications used to treat SUDs.[15]

Behaviorally, patients may insist on driving, become aggressive and agitated, or otherwise be a danger to themselves or others. Indeed, most suicidal behaviors among those misusing alcohol occur during intoxication. Antipsychotics lower the seizure threshold and are best avoided. However, in some instances, agitation may require antipsychotic treatment. Haloperidol has been proposed as a potential option for agitation in the presence of alcohol intoxication.[16] Sedation with benzodiazepines has been used but, in the presence of alcohol, respiratory depression can be dangerous or even fatal.

Opioid Intoxication

The word *opioid* refers to medications and substances that exert their action through the opioid system. Opioids encompass a wide range of substances, including naturally occurring (eg, morphine) and synthetic (eg, oxycodone).

Patients with acute intoxication usually present with miosis, euphoria, slow breathing, slow heart rate, and low blood pressure. Seizures may occur with certain agents, such as meperidine.

Table 37–3

Signs and Symptoms of Drug Intoxication for Select Substances[6,10-13]

Drug	Behavioral Effects	Physiologic Effects
Alcohol	Disinhibition, euphoria, dysphoria, inappropriate aggressive or sexual behavior, impaired judgment; possibly progressing to somnolence and coma as the blood level increases	Blood levels 0.02%–0.1% (20–100 mg/dL or 4.3–21.7 mmol/L): Slight impairment (eg, reaction time) Blood levels 0.1%–0.2% (100–200 mg/dL or 21.7–43.4 mmol/L): Significant impairment (eg, balance, speech, vision) Blood levels 0.2%–0.3% (200–300 mg/dL or 43.4–65.1 mmol/L): Marked ataxia, mental confusion, nausea, vomiting Blood levels 0.3%–0.4% (300–400 mg/dL or 65.1–86.8 mmol/L): Severe dysarthria, amnesia, hypothermia Blood levels > 0.4% (400 mg/dL or 86.8 mmol/L): Coma, decreased respiration or respiratory arrest, aspiration of gastric contents, airway obstruction by flaccid tongue, drop in blood pressure and body temperature
Opioids	Drowsiness, sedation, slurred speech, impaired memory and attention, psychomotor retardation	Nausea, vomiting, respiratory depression (dose-related), stupor, coma, itching, miosis, hypothermia, bradycardia
CNS stimulants	Elated mood, anxiety, panic, impaired judgment, violent behavior, paranoia, delusions, hallucinations (tactile or auditory, rarely visual), increased motor activity, compulsive or stereotyped behavior (eg, skin picking)	Neurologic/neuromuscular: mydriasis, headache, tremor, hyperreflexia, muscle twitching, flushing, hyperthermia or cold sweats, rhabdomyolysis (possibly resulting in renal failure), dyskinesias, seizures, coma Cardiovascular: tachycardia, hypertension, vasoconstriction, arrhythmias, myocardial infarction, cerebral hemorrhage GI: nausea, vomiting, weight loss
Cannabinoids	Anxiety, euphoria, paranoia, impaired judgment, social withdrawal	Impaired motor coordination, tachycardia, xerostomia, conjunctival injection, increased appetite

CNS, central nervous system; GI, gastrointestinal.

Monitor patients carefully to avoid cardiac and respiratory depression and death from overdose. One strategy is to reverse intoxication using naloxone 0.4 to 2 mg IV every 2 to 3 minutes up to 10 mg; the IM, subcutaneous, or intranasal (IN) route may be used if IV access is unavailable. Naloxone is shorter-acting than many opioids and may require readministration at periodic intervals; otherwise, patients could lapse into cardiopulmonary arrest after a symptom-free interval of reversed intoxication. In addition, naloxone can induce withdrawal symptoms in patients with physical dependence to opioids, so patients may awaken feeling distressed and agitated. Buprenorphine intoxication may be more difficult to reverse.[17]

Table 37–4

Signs and Symptoms of Drug Withdrawal for Select Substances[6,10-14]

Drug	Timeline	Symptoms
Alcohol	As levels decrease:	
	Early symptoms	Tremor, nausea, vomiting, tachycardia (> 110 beats/min), hypertension (> 140/90 mm Hg), headache, insomnia
	Peak (24 hours)	Seizure activity (usually 1 or 2 generalized tonic-clonic seizures, but can be numerous and possibly fatal)
	72–96 hours	Delirium tremens
	Onset at any time	Hallucinations (usually visual)
Opioids	For shorter-acting opioids (eg, heroin, morphine) withdrawal may begin 6–24 hours after last dose and last for about 1 week; with longer-acting opioids (eg, methadone) may take up to 2–4 days for withdrawal to emerge and will last longer	EENT: lacrimation, mydriasis, rhinorrhea GI: nausea, vomiting, diarrhea Cardiovascular: increased heart rate and blood pressure CNS: irritability, restlessness, yawning Musculoskeletal: increased body temperature, piloerection
CNS stimulants	Stage 1: immediately following binge	Craving, intense dysphoria, depression, anxiety, agitation
	Stage 2: within 1–4 hours	Dysphoria, desire for sleep
	Stage 3: 3–4 days	Hypersomnia, increased appetite, craving may dissipate but return later
Cannabinoids	Withdrawal symptom onset typically within 24–72 hours; peaks within 1 week	Severity reflects degree and duration of cannabinoid use; symptoms include irritability, anxiety, sleep abnormalities, depressed mood, headache, tremors, sweating, chills
Tobacco	Begins within 24 hours of cessation; peaks within 1–2 weeks; may persist for months	Severity reflects degree and duration of nicotine use; symptoms include irritability, anxiety, frustration, craving, difficulty concentrating, decreased heart rate, increased appetite

CNS, central nervous system; EENT, ears, eyes, nose, and throat; GI, gastrointestinal.

Table 37–5

Clinically Relevant Drug Interactions With Substances or Medications Used to Treat Substance Use Disorders[15]

Drug	Interacting Drug	Type of Interaction
Amphetamines	MAOIs	Combination of amphetamines and MAOIs may result in hypertensive reactions; AVOID combination
	Sodium bicarbonate	Sodium bicarbonate increases renal tubular reabsorption of amphetamine, resulting in prolonged amphetamine elimination half-life; closely monitor
Buprenorphine	Atazanavir	Combination of buprenorphine and atazanavir (without ritonavir) results in both lower atazanavir levels and higher buprenorphine levels; AVOID combination
	CYP3A4 inhibitors	May raise buprenorphine levels; monitor for greater than expected effects
Bupropion	MAOIs	Combination of bupropion and MAOIs may result in hypertensive reactions; AVOID combination
	Substances that lower seizure threshold	Use caution when initiating other medications that lower the seizure threshold; AVOID bupropion in patients at risk for experiencing alcohol withdrawal
Cigarette smoking	CYP1A2 substrates	Cigarette smoking (but not NRT) induces CYP1A2, increasing metabolism of CYP1A2 substrates (eg, theophylline, olanzapine, clozapine); may need to increase substrate dose when patient begins to smoke or decrease substrate dose if smoking is stopped
Disulfiram	Alcohol-containing solutions	Disulfiram reaction; AVOID combination
	Metronidazole	Combination has led to CNS effects (eg, psychosis); AVOID combination
	Benzodiazepines	Disulfiram (weakly) inhibits CYP1A2, 2C9, and 3A4; many benzodiazepines are metabolized via these pathways and doses may need to be lowered; lorazepam and oxazepam undergo conjugation and are alternatives
	Cocaine	Disulfiram decreases clearance of cocaine; may have increased or prolonged cocaine effects with combination
	Phenytoin	Disulfiram decreases metabolism of phenytoin, resulting in higher phenytoin levels; phenytoin dose may need to be reduced; because phenytoin undergoes nonlinear metabolism, it is difficult to predict magnitude of increase in blood levels; AVOID combination if possible
Alcohol	Acetaminophen	Chronic alcohol use increases hepatotoxicity risk when acetaminophen is used in high doses
	Bupropion	Abrupt discontinuation of alcohol with bupropion use may lower seizure threshold; AVOID bupropion in patients at risk for experiencing alcohol withdrawal
	Cefotetan or metronidazole	Disulfiram-type reaction may occur when these anti-infectives are combined with alcohol; AVOID combination
	CNS depressants	Alcohol may potentiate the effects of CNS depressant medications; advise patients to AVOID combination
	Methotrexate	Risk of hepatotoxicity may be increased in those who chronically drink large amounts of alcohol; AVOID methotrexate in this population if possible; otherwise, monitor LFTs
	MAOIs	Alcohol DOES NOT interact with MAOIs; however, tyramine may be a component of aged alcoholic drinks, such as red wines or tap beers
	Tapentadol	Alcohol may result in higher maximum serum levels of extended-release tapentadol; AVOID combination
Methadone	CYP3A4 inducers	Methadone is primarily metabolized via CYP3A4; if used together, may need to increase methadone dose to avoid withdrawal
	CYP3A4 inhibitors	May result in higher methadone levels; methadone dose adjustment should be based on clinical judgment, but a dose decrease may be necessary
	Didanosine	Methadone decreases oral absorption of didanosine; monitor the therapeutic effects of didanosine as a dose increase may be necessary
	Efavirenz	Efavirenz is a CYP3A4 inducer; efavirenz decreases methadone levels and has precipitated methadone withdrawal; may need to increase methadone dose
	MAOIs	Potential serotonin syndrome when MAOIs are combined with methadone; AVOID combination
	Nevirapine	Nevirapine is a CYP3A4 inducer and may decrease methadone levels, resulting in withdrawal complaints; may need to increase methadone dose
	QTc-prolonging medications	Medications that prolong the QT interval (eg, ziprasidone) should be AVOIDED with methadone when possible due to additive QT-prolonging effects
	Zidovudine	Methadone increases zidovudine levels, likely via methadone inhibition of both metabolic and renal clearance of zidovudine; may need to decrease zidovudine dose to avoid toxicity

CNS, central nervous system; CYP, cytochrome P450; LFT, liver function test; MAOI, monoamine oxidase inhibitor; NRT, nicotine replacement therapy.

Secure the airway and ensure breathing in cases of opioid overdose. In some cases, intubation and manual or mechanical ventilation may be required to avoid oxygen desaturation leading to brain hypoxia or anoxia and brain damage or death.

New opportunities for "take-home" naloxone have emerged in an effort to prevent overdose deaths. Many states allow naloxone distribution to family members or friends who can administer it if a patient is experiencing opioid intoxication. The FDA has approved a naloxone autoinjector and IN naloxone for this purpose.[15,17] The IN naloxone is commonly used in nonmedical settings due to ease of use. Educate patients and caregivers on naloxone, including when to use, how to assemble, proper administration, and notifying emergency services.[8]

Stimulant (Cocaine and Amphetamines) Intoxication

Desired outcomes of stimulant intoxication treatment are appropriate management of medical and psychiatric complications. Medical problems include hyperthermia, hypertension, arrhythmias, chest pain, stroke, seizures, and rhabdomyolysis. Some problems are related to route of administration, such as nosebleeds or infections with IN or IV administration, respectively. Psychiatric effects include anxiety, aggression, and psychosis.[13]

Pharmacotherapy for stimulant intoxication in acute settings may include benzodiazepines, aspirin, nitroglycerin, nitroprusside, and phentolamine.[13] The American Heart Association guidelines indicate that acute use of β-blockers is not recommended and may worsen cocaine-related chest pain and hypertension secondary to unopposed α-receptor–mediated vasoconstriction.[18] Rhabdomyolysis management includes administration of IV fluids to enhance renal perfusion.[13]

Cocaine is short-acting, and a single benzodiazepine may provide sufficient treatment for anxiety reactions. Depending on benzodiazepine half-life, multiple doses may be required for longer-acting amphetamine intoxication. Antipsychotics can manage psychosis, and psychotic symptoms usually respond rapidly in the absence of other co-occurring psychiatric disorders.[13]

Cannabinoid Intoxication

No established treatment recommendations exist for cannabinoid intoxication. Symptoms may include tachycardia, anxiety, and paranoia. Symptomatic treatment is commonly used. Synthetic cannabinoids are more likely than cannabis to produce serious psychiatric disturbances and may require aggressive benzodiazepine treatment for intense symptoms of anxiety or psychosis. These intense psychiatric symptoms are theorized to result from potent full-agonist activity and the lack of cannabidiol in synthetic products.[13] Cannabidiol has been associated with diminishing anxious and psychotic symptoms and behaviors.[19]

TREATMENT OF WITHDRAWAL SYNDROMES

KEY CONCEPT Treatment goals for withdrawal from alcohol, opioids, CNS stimulants, and cannabinoids include (a) a determination if pharmacologic treatment of withdrawal symptoms is necessary, (b) management of other medical manifestations, and (c) referral to the appropriate program for long-term treatment. Desired outcomes in the treatment of withdrawal syndromes are to ensure patient safety, comfort, and successful transition to longer-term maintenance treatment. Referral to specialized SUD treatment is strongly recommended after treatment of withdrawal. Rapid referral can introduce patients to the concept of recovery while they still vividly recall the negative consequences from using substances. Achieving a drug-free state by detoxification and then rehabilitation with a focus on total abstinence, or a reduction in substance use for some individuals, is the ideal outcome.

Alcohol Withdrawal

Alcohol withdrawal is characterized as either uncomplicated or complicated. Each differs in terms of pharmacologic treatment.

▶ *Uncomplicated Alcohol Withdrawal*

Uncomplicated alcohol withdrawal is the more commonly observed syndrome and is not complicated by seizures, **delirium tremens** (DTs), or hallucinosis. Symptoms are typically rated using a validated scale, such as the Clinical Institute Withdrawal Assessment–Alcohol, Revised (CIWA-Ar) (Table 37–2). There is some evidence for "kindling" during successive episodes of alcohol withdrawal, such that symptom severity and complications increase with additional withdrawal episodes.[11,20,21]

Benzodiazepines are the treatment of choice for uncomplicated alcohol withdrawal.[10] Anticonvulsants, such as carbamazepine, sodium valproate, and gabapentin, have also been evaluated. Commonly used benzodiazepines include lorazepam, diazepam, and chlordiazepoxide. They differ by routes of administration and by pharmacokinetic properties, such as the rapidity of onset due to the rate of GI absorption and the rate of crossing the blood–brain barrier. Benzodiazepines are given using a symptom-triggered approach or loading dose strategy. Adjunctive "as needed" medications are typically used, as well.[11]

Benzodiazepines can be administered for signs and symptoms of alcohol withdrawal using a symptom-triggered approach with the CIWA-Ar scale.[22] The recommended CIWA-Ar threshold score for treating uncomplicated alcohol withdrawal with medications is 8. When the CIWA-Ar score is 8 or greater, this "triggers" benzodiazepine administration. For example, lorazepam is given at a dose of 1 to 2 mg. The CIWA-Ar is then repeated hourly after each administration during the first 24 hours until the patient's withdrawal symptoms are minimized. Risks of not treating patients with high CIWA-Ar scores with medication are seizures and DTs, and those with a prior history of seizures or DTs have an increased risk for subsequent episodes.

An alternative to the symptom-triggered approach is the loading dose strategy. Longer-acting agents, such as diazepam and chlordiazepoxide, are given in large doses initially, then followed by a 3- to 5-day taper. Their long half-lives and active metabolites usually provide a natural taper without further medication administration. Diazepam may be preferred to chlordiazepoxide secondary to its faster onset (ie, quicker GI absorption and rapid CNS entry due to high lipophilicity). However, a faster onset of action may be associated with euphoria and is a treatment disadvantage. This approach may be accompanied by "as needed" short-acting benzodiazepine doses for breakthrough alcohol withdrawal symptoms.

Special Dosing Considerations Unlike chlordiazepoxide and diazepam, lorazepam is not metabolized into active compounds. It is excreted by the kidneys after glucuronidation. This is important because many patients with alcohol use disorder have compromised liver function. Therefore, when treatment is initiated before results of liver function tests (LFTs) are known, lorazepam may be preferred. Patients with liver disease may still be treated with diazepam or chlordiazepoxide at lower doses.[11]

American Psychiatric Association (APA) guidelines recommend thiamine for patients being treated for moderate-to-severe alcohol use disorders to prevent or treat adverse neurologic symptoms.[10] However, there are inadequate data with regard to the most efficacious thiamine dose, frequency, and route of administration to prevent or treat Wernicke syndrome associated with alcohol use disorders.[23] The APA guidelines recommend thiamine 50 to 100 mg/day given IV or IM, although other guidelines recommend higher doses (eg, thiamine 300 mg/day).[10,24] Administration of thiamine, essential for proper energy utilization by the CNS, must precede glucose-containing IV fluid administration, which can help prevent an acute exacerbation of Wernicke syndrome.

▶ *Complicated Alcohol Withdrawal*

Alcohol Withdrawal Seizures Alcohol withdrawal seizures, a medical emergency, should be treated in an inpatient setting. Withdrawal seizures are usually generalized tonic-clonic convulsions. Although binge drinking and alcohol withdrawal can lead to status epilepticus, the occurrence of focal seizures or status epilepticus may also suggest another etiology. Management consists of keeping the airway open and preventing self-injury during convulsions. Benzodiazepines are the treatment of choice. Give diazepam 5 to 10 mg IV to terminate a seizure if IV access is available. Repeat dose in 5 minutes if seizures persist. Alternatively, lorazepam 4 mg IM may be given, followed by insertion of an IV line after convulsive movements subside. In the event of a recurrent seizure, lorazepam 2 mg IV may be administered if the patient received IM lorazepam. Avoid IM diazepam or chlordiazepoxide because of erratic absorption that complicates the timing of subsequent doses and can result in delayed oversedation. Intravenous benzodiazepines may depress respiration; therefore, administer only if advanced cardiopulmonary support is available. When the patient can take oral medications, treatment may continue using either the symptom-triggered or loading dose strategy. Electrolyte imbalances can contribute to seizures and should be corrected.[21,25] Avoid phenytoin for preventing or treating alcohol-related seizures.[20] Alcohol withdrawal seizures result from γ-aminobutyric acid (GABA) and glutamate abnormalities secondary to chronic alcohol intake. Phenytoin affects sodium channels rather than directly affecting GABA or glutamate and is ineffective for alcohol-related seizures.

Alcohol Withdrawal Delirium (DTs) DTs is a medical emergency necessitating hospitalization. Signs and symptoms include hallucinations, delirium, severe agitation, fever, increased blood pressure and heart rate, and possible cardiac arrhythmias. Benzodiazepines are the treatment of choice.[22] Reserve haloperidol for severe agitation unresponsive to benzodiazepines. Evidence does not support antipsychotic monotherapy; in addition, antipsychotics may prolong the QT interval and lower the seizure threshold.[25] Administer thiamine according to the previously described guidelines.

Opioid Withdrawal

Withdrawal from opioids is extremely uncomfortable. Opioid withdrawal is commonly described as feeling “sick,” because it resembles a bad case of the flu. Symptoms include muscle, bone, and joint pain, nausea, vomiting, diarrhea, anxiety, headaches, mydriasis, rhinorrhea, lacrimation, piloerection, yawning, fever, increased heart rate, and hypertension.[12] Following initial withdrawal symptoms, patients can experience protracted withdrawal symptoms of dysphoria, craving, and hyperalgesia that can remain for weeks or months.[8] Therefore, the general approach is to manage acute symptoms, stabilize medical issues, and facilitate entry into an opioid use disorder treatment program.[10]

Clinical withdrawal scales (Table 37–2), such as the Clinical Opiate Withdrawal Scale (COWS), provide interrater reliability and clinical utility given their objective measurement of withdrawal severity. The baseline score assists in deciding whether to treat pharmacologically or to observe. As COWS scores increase (eg, 5 or greater), treatment of symptoms is indicated. In severe withdrawal, either buprenorphine (ie, partial μ-opioid receptor agonist) or methadone (ie, full μ-opioid receptor agonist) are recommended for medically supervised withdrawal (detoxification). Methadone is the gold standard for treating opioid use disorders but, under current US law, medically supervised withdrawal with methadone requires referral to a federally approved program. Pharmacotherapy for opioid withdrawal treatment in regular clinical settings is with a symptoms-based approach or buprenorphine.[26]

▶ *Medically Supervised Withdrawal*

Medically supervised withdrawal entails using μ-opioid receptor agonists (buprenorphine or methadone) in tapering doses to manage opioid withdrawal symptoms and assist patients in discontinuing opioids. On its own, short-term medically supervised withdrawal is associated with high rates of patients returning to illicit opioid use; therefore, consider transitioning to maintenance treatment with methadone, buprenorphine, or naltrexone.[8] As methadone is only available for use in federally approved opioid treatment programs (OTPs), this chapter will focus on buprenorphine. Refer to Chapter 35 for additional information on methadone.

Buprenorphine is a partial μ-opioid receptor agonist and is available in multiple formulations with varying pharmacokinetic profiles. For example, buprenorphine in combination with naloxone is available as a sublingual tablet, sublingual film, and buccal film.[15] Certain formulations (eg, sublingual film) may have greater buprenorphine bioavailability, and hence lower dosage requirements than other formulations (eg, sublingual tablets). Naloxone is poorly absorbed via the sublingual and buccal routes but is added to buprenorphine formulations to block opioid receptors if the medication is injected. Thus, naloxone has negligible effects when used appropriately while discouraging inappropriate IV use. Therefore, buprenorphine plus naloxone is the recommended formulation (vs buprenorphine alone) unless the patient is pregnant or hypersensitive to naloxone. Opioid antagonists, such as naloxone, have been associated with severe negative outcomes among pregnant women (eg, spontaneous abortion) and should be avoided.[26]

To initiate buprenorphine, a patient with physical dependence to opioids should be displaying signs of opioid withdrawal. Otherwise, buprenorphine will likely induce withdrawal because it has high affinity for μ-opioid receptors, displacing other full μ-opioid agonists, and is a partial rather than full agonist. Table 37–6 provides an example protocol for initiating buprenorphine.[8] Once the final dose is established, it is tapered and discontinued within 1 to 2 weeks (eg, 25% reduction per day as a general rule of thumb) or continued as a maintenance dose.

▶ *Symptoms-Based Treatment*

Symptomatic treatment focuses on minimizing withdrawal symptoms to increase patient comfort. Examples of symptom-specific medications are listed in Table 37–7.

▶ *General Patient Guidelines for Outpatient Opioid Detoxification*

Patient safety is the highest priority. The first step is to educate patients about the course of withdrawal. Symptoms generally peak at 5 to 7 days and may last up to 2 weeks, depending on the

Table 37–6

Sample Regimen[a] for Buprenorphine Induction Treatment of Opioid Withdrawal and Long-Term Relapse Prevention[8]

Day	Buprenorphine Sublingual/Buccal Dosage
1	2–4 mg every 2 hours (maximum, 8 mg on first day)
2	Start with total day 1 dose; additional 2–4 mg every 2 hours (maximum, 16 mg)
3	Start with total day 2 dose; additional 2–4 mg every 2 hours (maximum, 32 mg)
4–5	Maintain on dose required to alleviate withdrawal symptoms[b]

[a] For withdrawal from any opioid.

[b] Patient will likely be transitioned to long-term maintenance dose indefinitely.

half-life of the opioid used. Educate patients on the side effects of medications used for medically supervised withdrawal. Balance the risk of adverse events with the potential benefits. Buprenorphine side effects include constipation, sedation, and headaches. Potential for serious overdose exists when buprenorphine is combined with benzodiazepines or other sedative–hypnotics.

Risk of developing physiologic tolerance to buprenorphine is high if used for prolonged periods. In this case, buprenorphine requires a slow taper to discontinuation. Withdrawal from buprenorphine is generally easier and less severe than withdrawal from a full agonist, such as methadone.[8] However, there is concern regarding a subset of patients who have difficulty discontinuing buprenorphine. The duration of buprenorphine treatment is specific to each patient's needs and resources, and difficulty in tapering the medication to discontinuation complicates this decision further.

Following medically supervised withdrawal, rehabilitation and acquiring recovery skills are tied to positive outcomes. This goal can be accomplished by either achieving medically supervised withdrawal on-site during rehabilitation or by quick and seamless transition from detoxification to a rehabilitation program. The more time that elapses between the two modalities, the greater the likelihood of treatment failure and relapse.

Stimulant (Cocaine, Amphetamines) Withdrawal

Cocaine and amphetamine withdrawal are grouped together because their symptom profiles as described in *DSM-5* are similar, and the physiologic basis of their withdrawal syndromes involves the DA neurotransmitter system.[6,13] This group of stimulants includes methylphenidate, but not nicotine and caffeine, which have different neurophysiologic mechanisms of action. Major adverse complications of stimulant withdrawal are profound depression with suicidal thoughts, and the primary treatment goal is suicide prevention. Therefore, unless suicidality warrants hospitalization, stimulant withdrawal can be treated in outpatient setting with psychological support and reassurance with an emphasis on patient safety. Medications have been studied to alleviate withdrawal symptoms and cravings, but inconsistent results preclude any recommendations for their routine use. Refer patients with stimulant use disorder for treatment because of the high risk for continued use either during or immediately following stimulant withdrawal.

Table 37–7

Symptoms-Based Treatment Approach for Opioid Withdrawal[8,10,27]

The following are examples of medications for withdrawal symptoms that cause distress:

1. Insomnia: trazodone 75–200 mg at bedtime
2. Headache, muscle aches, or pain: acetaminophen 500–1000 mg every 6 hours
3. Noradrenergic hyperactivity: clonidine 0.1–0.2 mg every 6–8 hours (not to exceed 1.2 mg in 24 hours) lofexidine 0.54–0.72 mg every 6 hours (not to exceed 2.88 mg in 24 hours)
4. Abdominal cramps: dicyclomine 10–20 mg every 6 hours
5. Diarrhea: loperamide 2 mg every 6 hours

Cannabinoid Withdrawal

Symptoms of cannabinoid withdrawal are primarily behavioral. For example, significant anxiety may accompany cannabinoid withdrawal, which can lead many individuals to resume substance use. This is particularly problematic following heavy and prolonged use. Pharmacotherapy aimed at improving anxiety or sleep difficulties (eg, buspirone, gabapentin) shows promise for the management of cannabinoid withdrawal.[28] Currently, no medications are FDA approved to specifically target cannabinoid withdrawal.

GENERAL APPROACH TO THE TREATMENT OF SUBSTANCE USE DISORDERS

KEY CONCEPT A multimodal and comprehensive approach is preferred when treating patients with SUDs given the heterogeneous nature of addiction. Pharmacologic treatment is always adjunctive to psychosocial therapy. Steps to be taken in the management of SUDs are similar for all substances and are highlighted in the Patient Care Process.[10]

Address comorbid psychiatric conditions such as anxiety, depression, insomnia, and pain. These conditions increase risk of relapse to substance use. Although complete abstinence may be desirable, harm reduction may be sufficient in certain cases. **Harm reduction** involves strategies that seek to reduce negative consequences associated with substance use. Examples include **medication-assisted treatment**, naloxone deregulation, needle syringe programs, and medically supervised injection sites.[29]

Nonpharmacologic Therapy

Although pharmacologic agents may help prevent relapse, psychotherapy is the core therapeutic intervention. Psychotherapy typically addresses one or more of the following:

- Motivation enhancement to stop or reduce substance use
- Coping skills education
- Providing alternative reinforcement
- Managing painful affect (eg, dysphoria)
- Enhancing social support and interpersonal functioning

A thorough review of psychosocial approaches is beyond the scope of this chapter and are available elsewhere.[10] However, a few of the commonly used techniques are cognitive-behavioral therapy, motivational-enhancement therapy, and other behavioral therapies (eg, community reinforcement).

Pharmacologic Therapy

▶ *Maintenance Treatment*

KEY CONCEPT Certain pharmacologic agents are helpful for long-term maintenance in patients with SUDs. Typically, these medications exert their effects by one of the following theorized mechanisms: (a) substitution therapy with an agonist, (b) blocking effects with an antagonist, and (c) miscellaneous relapse prevention medications with indirect mechanisms of action. Medications from each of these categories are discussed in greater detail for alcohol, opioid, cannabinoid, stimulant, and tobacco use disorders.

▶ *Alcohol Use Disorder*

The FDA-approved medications for alcohol use disorder are naltrexone (oral and depot), acamprosate, and disulfiram. Practice guidelines recommend naltrexone and acamprosate as first-line agents.[24,30] However, in motivated patients or with supervised administration to ensure adherence, disulfiram is another option.[31] More recently, APA guidelines have strengthened their recommendations for the use of topiramate or gabapentin as potential medication management options. The following sections discuss FDA-approved medications; however, novel approaches, such as gabapentin and topiramate, may also be considered for alcohol use disorder.

Naltrexone Is a competitive opioid receptor antagonist that decreases alcohol intake, craving for alcohol, and alcohol-induced euphoria (ie, reduces positive reinforcement of drinking).[3] Naltrexone is more efficacious than placebo for a variety of drinking measures.[30] According to a meta-analysis, it significantly improves abstinence rates, decreases relapse rates, and has a safety profile similar to placebo.[32] Predictors of naltrexone efficacy may include family history of alcohol use disorder and a specific μ-opioid receptor gene polymorphism.[33] In the landmark COMBINE study, which assessed the efficacy of behavioral intervention, medical management, medications, and their combinations for treatment of alcohol use disorder, naltrexone with medical management was associated with a higher percent of days abstinent than other interventions.[34] An oversimplified interpretation of this complex study suggests that naltrexone is effective (eg, higher percent of days abstinent), but acamprosate offers no discernable advantage.[34]

Naltrexone is available as a tablet and long-acting IM injection. Naltrexone is dosed 50 mg once daily, with a range from 25 to 100 mg. A 25-mg test dose can be given, then increased to 50 mg/day as tolerated. While specific dosage adjustments are not provided in the package insert, caution is warranted in patients with severe hepatic or renal impairment.[15] Adherence to naltrexone strongly affects drinking outcomes; therefore, a long-acting IM formulation is available. Administered as 380 mg once monthly, it results in significantly greater reductions in heavy drinking days compared with placebo injection.[35]

Common side effects include nausea, headache, insomnia, and nervousness. Injectable naltrexone is associated with injection site reactions. Because naltrexone can precipitate withdrawal in patients with physical dependence to opioids, withhold the first dose for 7 to 10 days after last opioid use (10–14 days for long-acting opioids) and give only when the urine drug screen for opioids is negative. Naltrexone can be hepatotoxic, albeit typically not at oral doses less than 250 mg/day or at the recommended injectable dose. Baseline and periodic LFTs are recommended.[15]

Naltrexone can block effects of opioid receptor agonists, rendering them therapeutically ineffective. Given that opioid agonists are a mainstay of pain management, alternatives to opioids may be required in patients requiring pain relief.

Educate patients taking naltrexone to carry a pocket warning card or wear a medical bracelet. In the event that emergency pain management is needed, the patient will be insensitive to opioid analgesia unless potentially toxic doses are administered. Warn patients of the potential for opioid overdose under two conditions. First, dosing with opioids to reverse opioid insensitivity (ie, naltrexone's competitive blockade of opioid receptors) requires high doses of opioids that can cause respiratory depression and death. Second, following chronic opioid receptor antagonist therapy, patients are likely to have reduced tolerance to opioids, thereby increasing risk of respiratory depression and death when previously tolerated doses of opioids are taken.[15]

Acamprosate AR appears to be a glutamatergic *N*-methyl-D-aspartate receptor antagonist and may affect GABA.[3] Alcohol acutely inhibits glutamatergic function. During acute and post-acute alcohol withdrawal, increased activity of the glutamate system is caused by upregulation of receptors combined with absence of alcohol-related inhibition. Thus, acamprosate may correct glutamate/GABA imbalances that occur following chronic alcohol use (eg, reduce negative reinforcement associated with craving and withdrawal).[3,15]

Generally, trials assessing efficacy of acamprosate have shown mixed results. This may be partly attributable to differences in research methodologies, such as varying levels of abstinence required in trials before acamprosate initiation.[30] Notably, in the aforementioned COMBINE study, acamprosate appeared to offer no treatment advantage,[34] but more recent data suggest it is more efficacious than placebo.[36] A meta-analysis suggests that acamprosate may be more effective at maintaining abstinence, whereas naltrexone may more effectively reduce heavy drinking and craving.[37]

The dose of acamprosate is 666 mg orally three times daily. It is not metabolized by the liver and is excreted unchanged by the kidneys. Consequently, it is contraindicated in patients with severe renal impairment (creatinine clearance 30 mL/min [0.50 mL/s] or less), and dose reduction is necessary when creatinine clearance is between 30 and 50 mL/min (0.50 and 0.83 mL/s). Monitor renal function in older adult patients to ensure proper dosing. Common side effects are nausea, diarrhea, and CNS effects, including insomnia, anxiety, and depressive symptoms.[15]

Disulfiram Irreversibly blocks the enzyme aldehyde dehydrogenase, a step in the metabolism of alcohol.[15] This results in increased blood levels of the toxic metabolite, acetaldehyde. As acetaldehyde levels increase, patients experience the disulfiram reaction consisting of the following symptoms: decreased blood pressure, increased heart rate, chest pain, palpitations, dizziness, flushing, sweating, weakness, nausea, vomiting, shortness of breath, blurred vision, and syncope. Symptom severity increases with amount of alcohol consumed, and emergency treatment may be warranted. Psychologically, disulfiram works to deter drinking due to the knowledge that the disulfiram reaction occurs if alcohol is consumed.[31] Efficacy directly depends on medication adherence and can be effective when procedures for enhancing adherence are used.[31,38]

The usual starting dose of disulfiram is 250 mg once daily. It can be started at 500 mg once daily for the first 1 to 2 weeks, and the range is 125 to 500 mg/day.[15] Compared with 250 mg, the larger dose is recommended if a patient does not experience a disulfiram reaction after alcohol consumption. The smaller dose is given when intolerable side effects are experienced at higher doses or for older adult patients. Use disulfiram with caution in patients with renal or hepatic impairment. Dosing begins only after the BAC reaches zero (ie, 12–24 hours after the last drink) and after the patient is educated on the consequences of drinking with disulfiram.

Contraindications include cardiovascular or cerebrovascular disease, hypersensitivity to thiuram derivatives, and metronidazole. Common side effects are rash, drowsiness, and metallic or garlic-like taste. Less common, but concerning, adverse effects include neuropathies, psychosis, and hepatotoxicity.[15] Given the serious nature of these adverse events, baseline and periodic monitoring is recommended. If LFT values are greater than three times the upper limit of normal, withhold disulfiram and repeat testing every 1 to 2 weeks. When LFTs return to normal, they may be repeated every 1 to 6 months.[39] Although elevated LFTs may signal disulfiram-induced hepatotoxicity, it may also indicate the patient was not taking disulfiram and resumed alcohol consumption. Psychosis has been reported with doses exceeding 500 mg/day and may be related to disulfiram's inhibition of DA β-hydroxylase, resulting in increased DA activity. Nevertheless, patients with schizophrenia or other co-occurring psychiatric disorders have received disulfiram at usual doses without difficulties.[40]

The disulfiram–alcohol interaction serves as disulfiram's mechanism of action. Depending on the dose of disulfiram, sensitivity to disulfiram, amount of alcohol consumed, and metabolism, patients may be at risk for an adverse interaction with alcohol for 2 to 14 days after stopping disulfiram (5 days on average) and should be educated accordingly. Table 37–5 lists relevant disulfiram interactions.

Universally accepted treatment algorithms for alcohol use disorder treatment are lacking. Table 37–8 lists patient-specific factors that can guide medication selection.[39]

▶ *Opioid Use Disorder*

After conclusion of withdrawal, patients may not feel their usual selves for some time and could relapse to using opioids, just to "feel normal." Long-term use of opioids results in neuroadaptations, and the brain might not readily return to its prior homeostasis. The goal of treatment is to encourage stability, both in the body and in the patient's life. If an individual is not successful in quitting opioids (eg, because of withdrawal symptoms or postacute craving), then maintenance treatment should be considered.

Methadone, buprenorphine, and long-acting naltrexone are used for maintenance treatment, also called medication-assisted treatment, of opioid use disorder. Methadone is a full μ-opioid receptor agonist and widely used to treat women during pregnancy. Methadone maintenance treatment can only be provided in federally approved OTPs.[26] Naltrexone, an opioid receptor antagonist, is administered as a once-monthly IM injection. Administer naltrexone 7 to 10 days after last opioid use (10–14 days for long-acting opioids) to avoid precipitating withdrawal in a patient with physical dependence to opioids. The final medication for maintenance treatment, which will be the focus of this section, is buprenorphine.

The more widely available office-based opioid treatment (OBOT) exclusively uses buprenorphine, a partial μ-opioid receptor agonist, typically in oral formulations also containing naloxone.[8] Two long-acting buprenorphine formulations are also available: a subcutaneous injection and subdermal implants.[15] Under the Drug Addiction Treatment Act of 2000 and the Comprehensive Addiction and Recovery Act of 2016, clinicians may prescribe buprenorphine in the outpatient office-based setting once requirements (eg, training) are met. When these criteria are met, qualified providers obtain a separate "X" Drug Enforcement Administration number.[8]

Patients receiving buprenorphine maintenance should sign a treatment contract requiring full adherence, financial responsibility for treatment, adherence to office policies, and agreement to provide random urine samples for drug screens. Instruct patients to bring their prescribed medication for pill counts at every visit. In the event of OBOT failure, the alternative to buprenorphine maintenance is referral to an OTP for methadone administration. Methadone may offer an advantage over buprenorphine for select outcomes (eg, retention in treatment).[41] Therefore, there are circumstances under which referral to methadone maintenance remains the preferred treatment option.

Although there are no treatment algorithms to guide medication selection, there are protocols for some medications that assist with dosing and titration. The effective maintenance dose of buprenorphine (with or without naloxone) is usually between 8 and 24 mg/day.[15] Initiate buprenorphine at the low end of the

Table 37–8

Alcohol Use Disorder Medication Decision Grid[39]

Pretreatment Indicator	Acamprosate	Disulfiram	Oral Naltrexone	Injectable Naltrexone
Renal failure	X	A	A	A
Significant liver disease	A	C	C	C
Coronary artery disease	A	C	A	A
Chronic pain	A	A	C	C
Current opioid use	A	A	X	X
Psychosis	A	C	A	A
Unwilling or unable to sustain total abstinence	A	X	A	A
Risk factors for poor medication adherence	C	C	C	A
Diabetes	A	C	A	A
Obesity that precludes intramuscular injection	A	A	A	X
Family history of alcohol use disorders	A	A	+	+
Bleeding or other coagulation disorders	A	A	A	C
High level of craving	A	A	+	+
Opioid use disorder in remission	A	A	+	+
History of postacute withdrawal syndrome	+	A	A	A
Cognitive impairment	A	X	A	A

+, particularly appropriate; A, appropriate to use; C, use with caution; X, contraindicated.

Patient Encounter 3

A 42-year-old woman presents to the pharmacy to pick up a prescription. She is diagnosed with epilepsy and seasonal allergies and takes the following: levetiracetam 1000 mg twice daily and over-the-counter loratadine 10 mg once daily. While at the pharmacy counter, the patient expresses interest in tobacco cessation pharmacotherapies. The patient smokes approximately 1 pack of cigarettes per day and denies alcohol or illicit substance use.

Is the patient a candidate for all first-line tobacco cessation pharmacotherapies?

Can the patient take a combination of tobacco cessation pharmacotherapies?

dosing range for older adult patients. Reduce initial and titration doses for patients with hepatic impairment and monitor for signs of toxicity or overdose.[15] The subcutaneous injection is given as 300 mg once monthly for 2 months, then 100 mg once monthly thereafter. The dose can be increased to 300 mg once monthly if needed. In patients stabilized on 100 mg once monthly, a dose of 300 mg to cover a 2-month duration may be given in select circumstances (eg, extended travel). The subdermal implants deliver buprenorphine continuously for up to 6 months.

▶ *Stimulant Use Disorder*

There are no FDA-approved pharmacotherapies for treatment of stimulant use disorder. Combine medications with psychosocial approaches. The APA guidelines suggest three medications as possible treatment options: topiramate, disulfiram, and modafinil.[10,42] Disulfiram shows promise, possibly due to its inhibition of DA β-hydroxylase, which converts DA to NE. The resulting increase in DA may counter DA deficiency states that are believed to underlie cocaine withdrawal and craving.[42] Consistent with the APA guidelines, a more recent systematic review also cited the potential of topiramate for the treatment of stimulant use disorders. However, it should be noted that the authors considered the evidence for topiramate to be of "low strength," and therefore the findings must be interpreted with caution.[43]

▶ *Cannabinoid Use Disorder*

There are no proven pharmacotherapies for treatment of cannabinoid use disorder. As previously described for cannabinoid withdrawal, promising medication management approaches for cannabinoid use disorders target symptoms of anxiety or sleep difficulties that complicate cessation of cannabinoid use.[28] Pharmacotherapy trials have emerged in the literature, but universally accepted medication treatment strategies have yet to emerge.

▶ *Tobacco Cessation*

Nonpharmacologic Behavioral treatment increases abstinence rates. The five As model below can be used by all clinicians.[14]

- Ask about tobacco use.
- Advise to quit.
- Assess willingness to make a quit attempt.
- Assist in quit attempt.
- Arrange follow-up.

Provide tobacco cessation education to all patients who use tobacco, and assist those interested to achieve cessation. Screen for tobacco use, provide all patients who use tobacco with brief advice and assistance with appropriate medications to quit, and provide referral to specialized services when needed.[14]

Electronic cigarette use has grown considerably in recent years. Preliminary evidence suggests they may be useful for smoking cessation; however, long-term safety is unknown.[44-47] Studies are investigating the harmful constituents that individuals are exposed to with electronic cigarettes.[44] The FDA recently gained regulatory authority over electronic cigarettes, allowing them to restrict sales to minors and ensure products contain proper health warnings.

Pharmacologic According to practice guidelines, first-line medications for tobacco use disorder are nicotine replacement therapy (NRT), bupropion sustained-release (SR), and varenicline (Table 37–9).[14]

Maintenance treatment for tobacco use disorders is achieved with any single or combination of the currently available NRTs.[14] Similar to opioid receptor agonists, NRTs act as substitution therapy as safer alternatives to tobacco use. While NRTs are generally considered safe, their use in pregnancy is made on a case-by-case basis.[48] Given the various products available, choice of NRT formulation depends on various factors, including patient preference.[10]

Two non-NRT medications are FDA approved for the treatment of tobacco use disorders: bupropion SR and varenicline. Bupropion is an antidepressant that blocks reuptake of DA and NE; in addition, it appears that one of its metabolites is a nicotinic antagonist. These mechanisms may help explain how bupropion reduces nicotine reinforcement, withdrawal, and craving.[3] Bupropion is contraindicated in patients with seizure disorders, eating disorders, and patients withdrawing from alcohol or sedative–hypnotics.[15] Varenicline is an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist. Varenicline decreases withdrawal and craving and prevents reinforcing effects of nicotine if the patient relapses.[3] Warnings include seizures and cardiovascular adverse events (eg, angina).[15] Both bupropion SR and varenicline have been associated with psychiatric disturbances (eg, depression, anxiety, psychosis) when used for smoking cessation.[15]

As shown in Table 37–10, various NRTs, bupropion SR, and varenicline increase abstinence rates at 6 months compared to placebo.[49] Combining NRTs (eg, nicotine patch and "as needed" gum) is common. A meta-analysis concluded that NRT, bupropion SR, and varenicline all improve smoking cessation rates. Varenicline was more effective than single NRT or bupropion SR, but varenicline and combination NRT were equally effective.[50]

OUTCOME EVALUATION

KEY CONCEPT A major component of successful SUD treatment is to monitor use of medications and identify a mechanism for long-term support of sobriety that might be appropriate for a specific patient such as Alcoholics Anonymous, Narcotics Anonymous, or recovery programs for healthcare professionals.

To determine immediate treatment outcomes for patients with intoxication and withdrawal syndromes, evaluate parameters such as blood pressure, heart rate, respirations, body temperature, and mental status. Select validated and standardized instruments to monitor the responsiveness of withdrawal syndromes to

Table 37–9

First-Line Medications for Treatment of Tobacco Use Disorder[14,15]

Medication	Dosing and Administration[a]	Adverse Effects, Warnings, and Precautions[b]
Nicotine patch (7, 14, and 21 mg)	Apply 1 patch/day to nonhairy area on the upper body; rotate application sites Use 21 mg for 4–6 weeks, 14 mg for 2 weeks, then 7 mg for 2 weeks if > 10 cigarettes/day Use 14 mg for 6 weeks, then 7 mg for 2 weeks if ≤ 10 cigarettes/day Duration: 8–12 weeks	Skin irritation, insomnia, vivid dreams Remove patch at bedtime if sleep disturbances occur and apply new patch in the morning
Nicotine gum (2 and 4 mg)	Chew slowly until gum tingles, then "park" in cheek until tingle is gone; repeat Avoid eating or drinking for 15 minutes before or during use Use 4 mg if first cigarette is smoked within 30 minutes of waking; otherwise, use 2-mg dose Use 1 piece every 1–2 hours for 1–6 weeks, then 1 piece every 2–4 hours for 7–9 weeks, then 1 piece every 4–8 hours for 10–12 weeks Maximum: 24 pieces of gum/day Duration: 12 weeks (or as needed)	Sore mouth, hiccups, dyspepsia, insomnia Limit swallowing excess saliva to avoid GI irritation
Nicotine lozenge (2 and 4 mg)	Avoid chewing; occasionally move lozenge around mouth until completely dissolved Avoid eating or drinking for 15 minutes before or during use Use 4 mg if first cigarette is smoked within 30 minutes of waking; otherwise, use 2-mg dose Use 1 piece every 1–2 hours for 1–6 weeks, then 1 piece every 2–4 hours for 7–9 weeks, and 1 piece every 4–8 hours for 10–12 weeks Maximum: 20 lozenges/day Duration: 3–6 months	Hiccups, cough, heartburn, nausea, insomnia Limit swallowing excess saliva to avoid GI irritation
Nicotine nasal spray (0.5 mg delivered to each nostril)	Do not inhale during administration 1 dose = 1 spray in each nostril Use 1–2 doses/hour Maximum: 5 doses/hour; 40 doses/day Duration: 3–6 months; taper	Nasal irritation or congestion, changes in smell Avoid in patients with reactive airway disease Dependence risk is higher than other formulations
Nicotine inhaler (4 mg in each cartridge)	Inhale ("puff") lightly 80 times/cartridge Cold temperature decreases nicotine delivery; store in warm area (eg, pocket) Avoid eating or drinking for 15 minutes before or during use Use 6–16 cartridges/day Maximum: 16 cartridges/day Duration: Up to 6 months; taper	Mouth and throat irritation (improves with use), cough, rhinitis, sneezing
Bupropion sustained-release	Dosing: 150 mg once daily for 3 days, then 150 mg twice daily Start 1–2 weeks before quit date	Neuropsychiatric events (eg, mood disturbances) when used for smoking cessation
Varenicline	Dosing: 0.5 mg once daily for 1–3 days, then 0.5 mg twice daily for 4–7 day, then 1 mg twice day on day 8 and after Renal dosing (CrCl < 30 mL/min [< 0.50 mL/s]): 0.5 mg once daily with a maximum of 0.5 mg twice daily Start 1 week before quit date	CNS: insomnia, abnormal dreams, neuropsychiatric events (eg, depression, suicidal thoughts) GI: dose-related nausea

[a] NRT dosage adjustments for renal or hepatic impairment are not established. Severe impairment may affect nicotine clearance.

[b] Avoid NRT in patients with recent myocardial infarction, arrhythmias, or unstable angina.

CNS, central nervous system; CrCl, creatinine clearance; GI, gastrointestinal; NRT, nicotine replacement therapy.

medical treatment. To determine the overall effectiveness of your health system for the treatment of substance-related disorders, monitor outcomes using sentinel events such as the rates of cardiopulmonary arrest, seizures, discharges against medical advice, patient violence, and use of physical restraints. The ultimate goal is to enable the transition of patients to formal substance use treatment when indicated.

Important outcome indicators to evaluate postintoxication and/or postwithdrawal treatment can be divided into three major groups: decreased consumption of substances, decreased problems associated with substance use, and improved psychosocial functioning. When complete abstinence has not been achieved, quantify the consumption of substances using quantity–frequency measures, rates of abstinence, and time to first relapse as determined by interviews, self-report, and biological markers such as urine and blood tests. The ASI (Table 37–2) assesses alcohol and substance-related problems in various domains and provides a more comprehensive picture of the patient's life.

KEY CONCEPT Clinicians must be familiar with "essential" resources, many of which are in the public domain. Table 37–11 provides a list of these resources that provide useful information for clinical management, research, teaching, and policy development purposes.

Table 37–10

Six-Month Postquit Smoking Abstinence Rates and Associated Odds Ratios[49]

Medication	Abstinence Rate (%)	Odds Ratio (95% CI)
Placebo	13.8	1.0
NRTs		
Nicotine gum (6–14 weeks)	19.0	1.5 (1.2–1.7)
Nicotine patch (6–14 weeks)	23.4	1.9 (1.7–2.2)
Nicotine gum (> 14 weeks)	26.1	2.2 (1.5–3.2)
Nicotine patch (> 14 weeks)	23.7	1.9 (1.7–2.3)
Non-NRTs		
Bupropion SR	24.2	2.0 (1.8–2.2)
Varenicline (1 mg/day)	25.4	2.1 (1.5–3.0)
Varenicline (2 mg/day)	33.2	3.1 (2.5–3.8)
Combination Strategies		
Nicotine patch (> 14 weeks) + ad lib gum or spray	36.5	3.6 (2.5–5.2)
Nicotine patch + bupropion SR	28.9	2.5 (1.9–3.4)

CI, confidence interval; NRT, nicotine replacement therapy; SR, sustained-release.

Table 37–11

Essential Substance Use Disorder Treatment Resources

Source	Website	Example Highlight
American Psychiatric Association	www.psych.org	Clinical practice guidelines
American Society of Addiction Medicine	www.asam.org	Principles of Addiction Medicine textbook
National Institute on Alcohol Abuse and Alcoholism	www.niaaa.nih.gov	Alcohol Research & Health journal
National Institute on Drug Abuse	www.drugabuse.gov	Education resources
Substance Abuse and Mental Health Services Administration	www.samhsa.gov	National Survey on Drug Use and Health Treatment Improvement Protocols

Patient Care Process

Collect Information:

- Conduct a medication history for prescription, nonprescription, herbal, and dietary supplement use. Identify medication allergies and associated reactions.
- Retrieve a state prescription drug-monitoring program report.
- Document medical history, family history (eg, SUDs, psychiatric disorders), social history (eg, alcohol, tobacco, and illicit substance use), physical assessment, and mental status examination findings.
- Document other factors (eg, transportation, employment) that may impact treatment.
- Determine the patient's preferences, beliefs, and functional goals.
- Consider the use of screening and assessment instruments (Table 37–2).
- Assess the patient's readiness to change.

Assess the Information:

- Assess medication appropriateness, efficacy, safety, and adherence.
- Review laboratory tests (eg, electrolytes, liver and renal function, drug screen, human immunodeficiency virus [HIV] test).
- Assess previous periods of abstinence and factors that worked to achieve this.

Develop a Care Plan:

- Substance *intoxication*: Management is typically supportive. The most important goal is to maintain cardiopulmonary function. If consciousness is impaired, obtain blood chemistries to help identify causative substance and rule out other etiologies. Observe patient until intoxication has resolved.
- Substance *withdrawal*: Select instrument to monitor withdrawal symptoms and guide medication use (Table 37–4). Severe symptoms (eg, seizures) require inpatient treatment.
- Medication management is an adjunct to psychosocial approaches for achieving recovery.
- Align treatment (eg, medically supervised withdrawal vs longer-term treatment) with patient goals.

Implement the Care Plan:

- Educate the patient and the patient's support system about SUDs, medications, adverse effects, and adverse effect management. Ensure the patient has access to medications.
- Discuss the importance of medication adherence and psychosocial treatment approaches.
- Provide referrals for the treatment of co-occurring medical conditions or complications.
- Reduce stress and risk factors for relapse and improve attitude toward wellness.

Follow-up: Monitor and Evaluate:

- Assess treatment effectiveness, safety, and adherence regularly. Make changes as needed.
- Evaluate progress toward treatment goals (eg, improved coping skills, functioning, and relapse prevention).
- Continuously monitor for triggers, cravings, substance use, and relapse. Provide support.

Abbreviations Introduced in This Chapter

APA	American Psychiatric Association
ASI	Addiction Severity Index
AUDIT	Alcohol Use Disorders Identification Test
BAC	Blood alcohol concentration
CAGE	Cut down, angry/annoyed, guilty, eye opener
CIWA-Ar	Clinical Institute Withdrawal Assessment–Alcohol, Revised
CNS	Central nervous system
COWS	Clinical Opiate Withdrawal Scale
CRF	Corticotropin-releasing factor
DA	Dopamine
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition
DTs	Delirium tremens
FDA	US Food and Drug Administration
GABA	γ-Aminobutyric acid
GI	Gastrointestinal
IM	Intramuscular
IN	Intranasal
IV	Intravenous
LFT	Liver function test
NA	Nucleus accumbens
NE	Norepinephrine
NRT	Nicotine replacement therapy
NSDUH	National Survey on Drug Use and Health
OBOT	Office-based opioid treatment
OTP	Opioid treatment program
PFC	Prefrontal cortex
SAMHSA	Substance Abuse and Mental Health Services Administration
SR	Sustained-release
SUD	Substance use disorder
VTA	Ventral tegmental area

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38

Schizophrenia

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Recognize signs and symptoms of schizophrenia and be able to distinguish among positive, negative, and cognitive impairments associated with the illness.
2. Explain potential pathophysiologic mechanisms that are thought to underlie schizophrenia.
3. Identify treatment goals for a patient with schizophrenia.
4. Recommend appropriate antipsychotic medications based on patient-specific data.
5. Compare side effect profiles of individual antipsychotics.
6. Educate patients and families about schizophrenia, treatments, and the importance of adherence to antipsychotic treatment.
7. Describe components of a monitoring plan to assess the effectiveness and safety of antipsychotic medications.

INTRODUCTION

Schizophrenia is a challenging disorder often requiring lifelong treatment. The disorder may have many pathophysiologic pathways that ultimately manifest with psychotic symptoms, including positive symptoms such as hallucinations and delusions, as well as disordered thinking. Commonly, these symptoms are accompanied by cognitive impairment (abnormalities in thinking, reasoning, attention, memory, and perception), impaired insight and judgment, and negative symptoms including loss of motivation (**avolition**), loss of emotional range (restricted affect), and a decrease in spontaneous speech (poverty of speech). Cognitive impairments and negative symptoms account for much of the poor social and functional outcomes. Schizophrenia is the fourth leading cause of disability among adults and is associated with substantially lower rates of employment, marriage, and independent living compared with population norms. Persons with schizophrenia have a higher mortality rate as compared with the general population, likely due to numerous factors such as physical comorbidities, insufficient health services, poor diet, lack of exercise, substance use (including tobacco), stigma about mental illness, and low socioeconomic status. However, earlier diagnosis, treatment, advances in research, and newer treatment developments have led to better outcomes with the potential for remission and recovery.

EPIDEMIOLOGY AND ETIOLOGY

Approximately 0.7% of the world population suffers from schizophrenia, with symptoms typically presenting in late adolescence or early adulthood.[1] Prevalence is equal in men and women, but symptoms appear earlier in men with first hospitalization typically occurring at 15 to 24 years compared to 25 to 34 years in women.

The etiology of schizophrenia remains unknown. A genetic basis is supported by the fact that first-degree relatives of patients with schizophrenia carry a 10% risk of developing the disorder, and when both parents have the diagnosis, the risk to their offspring is 40%. For monozygotic twins, the concordance rate is about 50%. Many genes have been weakly associated with the development of schizophrenia; however, there is probably no single "schizophrenia gene." Research continues to explore candidate genes, loci, and copy number variants, hoping to better understand the genetic contribution.[2] Possibly, when a genetic liability is present, environmental stimuli may trigger expression of the illness. These risk factors may include intrauterine exposure to significant stress, viral or bacterial infections. Also, emerging data suggest that certain drugs of abuse during childhood or adolescence, such as marijuana, may be one of those "triggers" in susceptible individuals. More research is needed on the role of these factors in the development of schizophrenia.

PATHOPHYSIOLOGY

The dopamine hypothesis, the oldest pathophysiologic theory, proposes that psychosis is caused by excessive dopamine in the brain. This hypothesis followed the discovery that chlorpromazine, the first antipsychotic medication, was a postsynaptic dopamine antagonist. Drugs that cause an increase in dopamine (eg, cocaine and amphetamines) worsen or cause psychotic symptoms, and medications that decrease dopamine (eg, antipsychotics) improve psychotic symptoms. However, data reveal a more complicated picture with both hyperdopaminergic and hypodopaminergic brain regions in schizophrenia. Hyperdopaminergic activity in the **mesolimbic pathway** contributes to positive symptoms of psychosis, while hypoactivity of the **mesocortical pathway** in the prefrontal cortex may contribute to negative symptoms. Thus, a more modern reworking of the dopamine hypothesis is the "dysregulation hypothesis," which takes these findings into account and also focuses primarily on presynaptic dopamine.[3] It is possible, however, that the hypothesized dopamine abnormalities may

Patient Encounter, Part 1

A 22-year-old woman was brought to the emergency department (ED) at a local hospital by the police after she was found wandering her neighborhood. The neighbors saw her peering in the windows and trying to open the doors of their homes and called the police. In the ED, her appearance was disheveled and her hair was long and tangled. She was easily distracted and irritable and when asked what she was doing wandering the neighborhood, she stated "I left my home because they are plotting to kill me there. It is dangerous there and I had to leave". During her interview with the psychiatry resident, she frequently looked over her shoulder, and her eyes darted around the room. Then she asked the resident, "Do you even understand me? I need to get out of here. It is not safe for me here and they are looking for me. There is nothing wrong with me. I am really hungry; do you have something for me to eat?"

Her attention seemed to be focused on something else and then she blurted out "my dad is my other half and he will protect me." When asked to explain, she said "I tell the voices my dad is my other half. They tell me I am terrible and that I should die." The patient's mother was called to the ED to see her daughter and provide more information.

She was admitted to the inpatient psychiatric unit for further evaluation.

What diagnoses are suggested by this presentation?

What additional information would clarify the diagnosis, and why?

Should the patient's mother be involved in her care?

represent changes occurring secondary to other pathophysiologic abnormalities. Other implicated neurotransmitter systems include a combined dysfunction of the dopamine and glutamate neurotransmitter systems. It is hypothesized that glutamate, possibly through malfunctioning *N*-methyl-D-aspartate (NMDA) receptors, impacts dopaminergic activity in the mesolimbic and mesocortical pathways. NMDA antagonists such as phencyclidine (PCP) and ketamine can elicit a state resembling schizophrenia, including positive and negative symptoms and cognitive impairments.[3] There is evidence for the serotonergic system in schizophrenia as evidenced by serotonin-induced hallucinations and serotonin modulation of second-generation antipsychotics (SGAs).[4] It is notable that, to date, antipsychotics without any primary or secondary dopamine-modulating properties have been ineffective for the treatment of positive symptoms of schizophrenia.

CLINICAL PRESENTATION AND DIAGNOSIS

In addition to the positive, negative, and cognitive symptoms of schizophrenia, people with schizophrenia may sometimes be uncooperative, suspicious, hostile, anxious, or aggressive. Psychotic and depressive symptoms may lead to poor hygiene and impaired self-care. Sleep and appetite disturbances may be present, and people with schizophrenia may have difficulty living independently, forming close relationships with others, and initiating or maintaining employment. Co-occurring medical and substance use disorders are common with cigarette smoking and illicit drug use about four to five times more prevalent than the general population.[5,6]

KEY CONCEPT A diagnosis of schizophrenia is made clinically because there are no psychological assessments, brain imaging, or laboratory examinations that confirm the diagnosis.

The diagnosis is made by ruling out other causes of psychotic symptoms and meeting specified diagnostic criteria. When present, a family history of mental illness supports the diagnosis. The commonly accepted diagnostic criteria for schizophrenia are from the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-5*)[7] (Table 38–1).

KEY CONCEPT Patients presenting with odd behaviors, illogical thought processes, fixed false beliefs, and hallucinations should be comprehensively assessed to rule out other diagnoses or contributing factors.[8]

At minimum, patients with psychotic symptoms should have a medical workup at the time of admission to rule out other diagnoses or contributing factors, such as medical illnesses, infections,

Table 38–1

Diagnostic Criteria for Schizophrenia

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be 1, 2, or 3:
   1. Delusions
   2. Hallucinations
   3. Disorganized speech (eg, frequent derailment or incoherence)
   4. Grossly disorganized or catatonic behavior
   5. Negative symptoms (ie, diminished emotional expression or avolition)

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved before onset (or when onset is in childhood or adolescence, there is a failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meets Criterion A (ie, active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (eg, odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (a) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms or (b) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiologic effects of a substance (eg, drug of abuse or medication) or another medical condition.

F. If there is a history of autism spectrum disorder or communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

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or other psychiatric or substance use disorders. Often, people with psychosis are poor historians and the gathering of collateral information about symptoms and medical history from family/friends is necessary. When considering delusional symptoms, cultural beliefs and norms should be explored. Co-occurring substance abuse, medical illnesses, and psychosocial stressors often confound the diagnosis.

COURSE AND PROGNOSIS

Treatment of schizophrenia has been associated with poor long-term outcomes in the past; however, with earlier treatment and better care, many people can achieve remission, and recovery is possible. Without early intervention, there are traditionally intermittent acute psychotic episodes with a downward decline in psychosocial functioning. Though many of the more dramatic and acute symptoms may fade with time, severe residual symptoms may persist. Involvement with law enforcement is common for vagrancy, loitering, and disturbing the peace. Life expectancy is shortened primarily because of suicide, cardiovascular disease, accidents, and compromised self-care. Lifetime risk of suicide for people with schizophrenia is 5% to 10%, and it is estimated that suicide risk in this population exceeds that in the general population more than eightfold.[9] Persistent adherence with a tolerable medication regimen improves prognosis, while relapse without antipsychotic medication exceeds 50% in the year following discontinuation of antipsychotic treatment.

The onset of schizophrenia can be rapid with acute psychosis presenting as the first symptom, or can be insidious with negative symptoms and social impairments predating psychosis by many years. Whether insidious or acute, the period around the diagnosis is difficult for patients, families, and clinicians. Patients may hide symptoms from family and friends and isolate themselves from social support networks. Gradual development of psychosis and the misunderstanding of symptoms can delay diagnosis and treatment. Recent data suggest that people treated early in their illness may have a better prognosis. Therefore, the first challenge of optimal therapy is to initiate treatment closer to the onset of psychosis.

Clinical Presentation of Schizophrenia

General

Schizophrenia is a chronic disorder of thought and affect, causing significantly impaired vocational and interpersonal function. Onset is usually preceded by gradual social withdrawal, diminished interests, changes in appearance and hygiene, changes in cognition, and bizarre or odd behaviors incongruent with cultural beliefs and norms. The clinical presentation of a person with schizophrenia is extremely varied.

Symptoms

Psychotic symptoms (positive symptoms):

- Hallucinations (distortions or exaggeration of perception).
  - Most frequently auditory, can also be visual, olfactory, gustatory, and tactile.
  - Can be voices or thoughts that feel distinct from the person's mind.
  - Voices may be threatening or commanding (eg, commanding the person to perform a particular action).
- Delusions (fixed false beliefs).
  - Beliefs despite invalidating evidence.
  - May be bizarre in nature.
  - Often paranoid in nature which may cause suspiciousness.
- Thought disorder (illogical thought and speech).
  - Loosening of associations.
  - **Tangentiality**.
  - **Thought blocking**.
  - **Concreteness**.
  - Circumstantiality.
  - Perseveration.
  - Thinking and speech may be incomprehensible and illogical.

Negative symptoms:

- Impoverished speech and thinking.
- Lack of social drive (avolition).
- Flatness of emotional expression.
- Apathy.
- May be primary or occur secondarily to medication side effects, mood disorder, environmental understimulation, or demoralization.
- The best strategy for differentiating primary from secondary negative symptoms is to observe for their persistence over time despite efforts at resolving the other causes.

Cognitive impairments (diminished function in the following):

- Attention.
- Processing speed.
- Verbal, visual memory, and working memory.
- Problem solving.
- Loss of, on average, one standard deviation of preillness IQ, with the average IQ between 80 and 84.

Laboratory and Other Diagnostic Assessments

An initial psychotic workup includes a thorough neurologic, medical, and laboratory evaluation to rule out other causes:

- Electrolytes.
- Blood urea nitrogen.
- Serum creatinine.
- Urinalysis.
- Liver and thyroid function profile.
- Syphilis serology.
- Serum pregnancy test.
- Urine toxicology.

If warranted, neuroimaging and/or electroencephalogram (EEG).

TREATMENT

Desired Outcomes

KEY CONCEPT The goals of treatment are to reduce symptomatology and psychotic relapses and to improve functional and social outcomes.[10] Patients should receive comprehensive treatment as early as possible, and earlier treatment can lead to better outcomes.[11] In the past, the primary treatment goal was to decrease positive symptoms and associated hostile and aggressive behaviors. Newer approaches also focus on functional and social outcomes. Though antipsychotic medications may improve combativeness, hostility, sleep, and appetite, other aspects of the illness are less responsive to treatment. Improvements in negative symptoms, cognitive functioning, social skills, and judgment generally require adjunctive treatments and a longer period to improve.

General Approach to Treatment

The concept of recovery has become an increasingly prominent treatment goal. Treatment planning increasingly includes providing recovery-oriented services to people with schizophrenia. A range of nonpharmacologic interventions are now part of the long-term strategy to improve functioning. Implementation of evidence-based practice and prescribing behaviors has led to the use of interventions that promote a remission or recovery attitude, and new data suggest that one in seven people with schizophrenia can achieve full recovery.[12,13] Moreover, recent attempts to improve and measure patient satisfaction and to include shared decision making have fostered patient empowerment and hope.

KEY CONCEPT The cornerstone of treatment is antipsychotic medication, and most patients with schizophrenia relapse when not medicated. Treatment with antipsychotic medications should begin as soon as psychotic symptoms are recognized. Many patients are on lifelong antipsychotic medication because nonadherence and discontinuation are associated with high relapse rates. Often, adjunctive medications may also be necessary for specific symptoms or comorbid diagnoses. If other symptoms are present, such as depression and anxiety, these symptoms should be aggressively treated. Nonpharmacologic and psychosocial treatments should also play an important role in treatment.

Nonpharmacologic Therapy

▶ *Psychosocial Treatment*

As previously discussed, antipsychotic medications are the cornerstone of schizophrenia treatment plans; however, KEY CONCEPT psychosocial support helps improve functional outcomes. Residual symptoms often persist such as avolition, isolation, and impaired social functioning, limiting participation in social, vocational, and educational endeavors. Psychosocial interventions, as adjuncts to pharmacotherapy, help people with

Patient Encounter, Part 2

PPH: This is her first admission to a psychiatric hospital. Her mother reports that her daughter changed during her first year away at college and did not return for her second year. She lived at home and became reclusive, no longer spending time with her family or friends. The family could often hear her talking loudly in her room, but she could not tell them who she was talking to. The patient stopped taking care of herself and would wear the same clothes several days in a row. She would wander away from home for days and then suddenly return but could not tell anyone where she had been. She was often found on the streets with dangerous people who exploited her. The patient occasionally was aggressive and threatening toward her mother.

PMH: She does not have any other medical illnesses including seizures or history of head trauma.

SH: The patient did well in grade school and graduated from high school. She was active in the band and theater. She attended her first year of college away from home, but after the first year, she did not return. The only job she has had was as a cashier at a local convenience store when she was 20, but she was let go after 3 months for wandering away during her shift.

FH: The patient grew up with her parents and one brother who is 2 years older than her. Her mother is an elementary school teacher, has a history of major depression, and has a good relationship with her daughter but does not understand why she is behaving this way. The patient's father recently passed away from cancer, and she had been very close to him. Her brother recently graduated from college with a degree in business as an accountant and accepted his first job out of town. There is no history of schizophrenia in the family. The patient's mother states that her mother (the patient's grandmother) had a psychiatric diagnosis and remembers her being hospitalized for periods of time but does not know what the diagnosis was.

Mental Status Examination

Appearance: Appears disheveled, dressed in dirty clothes, and hair is long, tangled, and looks like it has not been washed for several days. No abnormal movements. Poor eye contact. She is distracted and is looking around the room and over her shoulder.

Speech: Speech is loud, but normal rate.

Mood: Says she feels "normal but agitated." Denies feeling depressed.

Affect: Guarded with restricted range. She denies feeling sad, guilty, hopeless, or helpless.

Thought content: She is not a reliable historian and cannot explain where she goes when she leaves home or how she ends up on the street with strangers. She endorses hearing voices and states that they tell her she is terrible and should die. She has passing thoughts of suicide but no plan. She denies homicidal thoughts.

Thought processes: Irritable, vague, and paranoid.

Cognition: Grossly intact.

Insight and judgment: Insight and judgment are poor. She does not believe she has a mental illness.

Given this additional information, how has your differential diagnosis changed?

What medications would you consider to be first-line options, and why?

What are the goals of treatment for this patient?

schizophrenia cope with challenging aspects of their illness and set goals as medication alone is typically not sufficient for remission and recovery. In the United States, psychosocial treatments are less frequently used than in Europe, but their use is increasing, and current guidelines recommend nonpharmacologic strategies in conjunction with antipsychotic treatment. There are much data to support family education in decreasing relapse rates and vocational support to improve vocational outcomes. A few of the best-supported and most promising approaches to psychosocial rehabilitation are social skills training (SST), cognitive behavioral therapy for psychosis (CBTp), and cognitive remediation (CR). In addition, psychoeducation, supported employment, Assertive Community Treatment (ACT), and Medical Home care models have improved outcomes.[12,14]

Pharmacologic Therapy

▶ *Antipsychotic Treatment*

In the United States, we have two general classes of antipsychotic medications, the first-generation antipsychotics (FGAs; typical antipsychotics) and the second-generation antipsychotics (SGAs) (atypical antipsychotics). The SGAs include risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, lurasidone, brexpiprazole, cariprazine, lumateperone, and clozapine. Clozapine, the prototype SGA, is the recommended treatment for treatment-resistant schizophrenia (TRS) as it has superior efficacy in this population. However, it has some additional monitoring and a unique side effect profile (see below). Antipsychotic medications share a common mechanism of dopamine antagonism, although there is significant variation in receptor binding among the agents as some also act as dopamine partial agonists. Dopaminergic antagonism is important in symptom treatment but also contributes to some medication-induced side effects. Of the four main dopaminergic pathways in the brain, positive symptoms are thought to be associated with hyperdopaminergic activity in the mesolimbic pathway, so blockade in this area is thought to reduce psychotic symptoms. However, blockade of dopamine activity in the other three main pathways may worsen some symptoms or lead to side effects. For example, hypodopaminergic activity in the mesocortical pathway may be associated with negative symptoms and cognitive impairments, and further reducing dopamine activity could exacerbate these issues. Blockade of dopaminergic activity in the **nigrostriatal** pathway can lead to motor-related side effects, and blockade of dopaminergic activity in the **tuberoinfundibular** pathway may lead to prolactin elevation and related side effects.[3] Differences in dopaminergic and nondopaminergic receptor antagonism and receptor affinity across the antipsychotic agents and classes lead to differing potential for dopamine-related side effects.

KEY CONCEPT Compared with the FGAs, the SGAs are associated with a lower risk of motor side effects (tremor, stiffness, restlessness, and dyskinesia).

With the introduction of SGAs in the 1990s, the use of FGAs has progressively decreased, and FGAs have less than 10% market share of the antipsychotics used for schizophrenia. This decline occurred because of the touted better side effect profile and other possible benefits of SGAs in nonpsychotic domains of the illness. However, a large landmark study (the Clinical Antipsychotics Trials of Intervention Effectiveness [CATIE trial]; $n > 1400$) examined the effectiveness of SGAs relative to a midpotency FGA, perphenazine. The study revealed that the FGA was equal to the SGAs for the primary endpoint of time to discontinuation of medication.[15] SGAs have historically been much more expensive than the FGAs; however, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, and clozapine are now available in generic formulations. When selecting an antipsychotic, the risk-to-benefit profile becomes fundamental and the varying side effect profiles must be considered.

Second-Generation (Atypical) Antipsychotics

FGAs exert most of their effects through dopamine receptor blockade at the dopamine$_2$ (D_2) receptor. SGAs may have different receptor binding profiles that contribute to their "atypicality." This possibly includes greater serotonin to dopamine antagonism, dopamine antagonism with rapid dissociation, partial dopamine antagonism and serotonin$_{1A}$ (5-HT$_{1A}$) partial agonism. Despite heterogeneous receptor binding, the efficacy for positive symptoms among the SGAs is similar.[15] Several long-acting injectable (LAI) formulations are now available and will be discussed below. However, due to differences in specific receptor binding affinity, side effect risks may vary between these agents. Additionally, recent data for SGAs and lower doses of FGAs document similar overall efficacy with an effect size for acute treatment of 0.30 to 0.60 for most antipsychotics.[16] These findings have led to a modest resurgence of FGA use. Only clozapine, however, has demonstrated superior efficacy in treatment-resistant patients. An important distinction of the SGAs is their lower propensity to cause acute as well as long-term **extrapyramidal symptoms** (EPSs) including **tardive dyskinesia** (TD). TD risk with SGAs is 1.5% annually in adults (< 54 years of age) compared to approximately a 5% annual risk with FGA treatment.[17] However, side effects such as weight gain, the potential for glucose dysregulation, and lipid abnormalities may be caused by treatment with these agents. Weight gain may be caused by a combination of lifestyle and medication interaction with neurotransmitter systems that may increase appetite and food intake (serotonergic, histaminergic, and dopaminergic), and, although all antipsychotics may be associated with weight gain, certain SGAs such as clozapine, olanzapine, quetiapine, and risperidone may offer greater risk. Similarly, risk of lipid abnormalities mirrors the risk for weight gain. Risk for glucose dysregulation or new-onset diabetes generally follows the risk of agents with most weight gain potential, although it is important to note that clozapine and olanzapine have been associated with diabetic ketoacidosis in the absence of significant weight gain in isolated cases. Sexual side effects as a result of prolactin elevation may occur due to dopamine antagonism at the tuberoinfundibular tract. SGAs have differing potentials to cause these side effects, which may include gynecomastia, galactorrhea, oligomenorrhea, or amenorrhea.

KEY CONCEPT The SGAs are heterogeneous with regard to side effect profiles. Many SGAs carry an increased risk for weight gain and for the development of glucose and lipid abnormalities; therefore, careful monitoring is essential. Dosing and comparative side effects of SGA are shown in Tables 38–2 and 38–3.

▶ *Risperidone*

Risperidone, a benzisoxazole derivative, was the initial first-line oral SGA to become available generically. It has high binding affinity to both serotonin 2$_A$ (5-HT$_{2A}$) and D_2 receptors and binds to α_1 and α_2 receptors, with very little blockade of cholinergic receptors.[18] At doses less than or equal to 6 mg/day, EPSs are low, although higher doses are associated with a greater incidence of EPS. Risperidone is often associated with elevated prolactin to a greater extent than most other SGAs and FGAs. Elevated prolactin levels can, but do not always, lead to amenorrhea, galactorrhea, gynecomastia, and sexual dysfunction. Mild-to-moderate

Table 38–2

Second-Generation (Atypical) Antipsychotics

Second-Generation Antipsychotic	Usual Oral Starting and Target Dose (mg/day) (Schizophrenia)	Maximum Oral Dose Likely to Be Beneficial (mg/day)	Available Dosage Forms
Aripiprazole (Abilify; Abilify MyCite; Aristada [aripiprazole lauroxil injection])	Initial: 10–15 Target: 15–30	30	• 2-, 5-, 10-, 15-, 20-, and 30-mg tablets • MyCite available as 2, 5, 10, 15, 20, and 30-mg tablets with Ingestible Event Marker (IEM) sensor to track drug ingestion (adults) • 1-mg/mL oral solution • 10- and 15-mg orally disintegrating tablets • Abilify Maintena extended-release 300- and 400-mg vial powder for suspension or prefilled syringe long-acting injection • Aristada extended-release 441, 662, 882, and 1064-mg prefilled syringes • Aristada Initio, including 675-mg long-acting injection and 30-mg oral dose
Asenapine (Saphris; Secuado [patch])	Initial: 5 twice daily Target: 10–20 total daily dose	10–20	• 2.5-, 5-, and 10-mg sublingual tablets • Secuado (asenapine) transdermal system for once-daily administration; 3.8 mg/24 hours initial dosing; available as 3.8 mg/24 hours, 5.7 mg/24 hours, and 7.6 mg/ 24 hours
Brexpiprazole (Rexulti)	Initial: 1 Target: 2–4	4	• 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets
Cariprazine (Vraylar)	Initial: 1.5 Target: 1.5–6	6	• 1.5-, 3-, 4.5-, and 6-mg capsules
Clozapine (Clozaril, FazaClo, Versacloz, also available generically)	Initial: 12.5–25 Target: 300–450	500–800	• 12.5-, 25-, 50-, 100-, and 200-mg tablets • FazaClo (orally disintegrating tablets) 12.5, 25, 100, 150, and 200 mg • Versacloz (oral suspension) 50 mg/mL
Iloperidone (Fanapt)	Initial: 1 twice daily Target: 12–24 total daily dose	24	• 1-, 2-, 4-, 6-, 8-, 10-, and 12-mg tablets
Lumateperone (Caplyta)	Initial and target: 42 mg daily with food	42	• 42-mg capsule
Lurasidone (Latuda)	Initial: 40 Target: 40–160	160	• 20-, 40-, 60-, 80-, and 120-mg tablets
Olanzapine (Zyprexa, also available generically)	Initial: 5–10 Target: 10–20	30–40[a]	• 2.5-, 5-, 7.5-, 10-, 15-, and 20-mg tablets • Orally disintegrating tablets: 5, 10, 15, and 20 mg • IM 10-mg vial (after reconstitution, ˜5 mg/mL) • Zyprexa Relprevv 210-, 300-, and 405-mg/vial powder for suspension long-acting injection
Paliperidone (Invega)	Initial: 6 Target: 3–12	12	• 1.5-, 3-, 6-, and 9-mg tablets • Invega Sustenna 39-, 78-, 117-, 156-, and 234-mg prefilled syringes for long-acting injection • Invega Trinza 273-, 410, 546-, or 819 mg for long-acting injection
Quetiapine (Seroquel, also available generically)	Regular release Initial: 25 twice daily Target: 300–750 Extended release Initial: 300 Target 400–800	800	• 25-, 50-, 100-, 200-, 300-, and 400-mg tablets • Seroquel XR (extended-release tablets) 50-, 150-, 200-, 300-, and 400-mg tablets
Risperidone (Risperdal, also available generically)	Initial: 1–2 Target: 4–6	6–8	• 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets • 1 mg/mL (30-mL) solution • Orally disintegrating tablets: 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets • Risperdal Consta long-acting injectable 12.5-, 25-, 37.5-, and 50-mg vial/kit • Perseris long-acting subcutaneous injection; 90- and 120-mg kits
Ziprasidone (Geodon, also available generically)	Initial: 20 twice daily Target: 120–160 total daily dose	160–240[a]	• 20-, 40-, 60-, and 80-mg capsules • IM 20 mg/mL

[a] Outside product labeling guidelines.

IM, intramuscular.

Table 38–3

Comparative Side Effects Among the SGAs and Haloperidol

Side Effect	Cloz	Risp[a]	Olan	Quet	Zip	Ari	Ilo	Asen	Lur	Brex	Carip	Lum[b]	Hal
Anticholinergic side effects	+++	±	++ (Higher doses)	+	±	±	±	+	±	±	±	±	±
EPS at clinical doses	+	+	±	±	±	+	+	+	+	±	+	±	++
Dose-dependent EPS	0	++	+	0	+	+	+	+	+	+	+	0	+++
Orthostatic hypotension	+++	++	+	++	+	+	++	+	+	±	±	±	++
Prolactin elevation	0	+++	+	±	+	0	+	±	±	±	0	±	+
QTc prolongation	+	±	±	+	+	±	+	+	+	±	±	0	±
Sedation	+++	+	+	++	+	+	++	+	+	+	+	+++	+
Seizures	++	±	±	±	±	±	±	±	±	±	±	±	±
Weight gain	+++	++	+++	++	+	+	+	+	+	+	±	0	±
Glucose dysregulation	++	+	++	+	±	±	±	±	±	±	±	0	±
Lipid abnormalities	+++	+	+++	++	±	±	±	±	±	±	±	0	±

[a] Side effects similar for paliperidone.

[b] Based on 4 weeks of exposure; long-term effects not known. Long-term study in progress. No comparative data available.

0, absent; ±, minimal; +, mild or low risk; ++, moderate; +++, severe; SGA, second-generation antipsychotic; EPS, extra-pyramidal symptoms.

Cloz, clozapine; Risp, risperidone; Olan, olanzapine; Quet, quetiapine; Zip, ziprasidone; Ari, aripiprazole; Ilo, iloperidone; Asen, asenapine; Lur, lurasidone; Brex, brexpiprazole; Carip, cariprazine; Lum, lumateperone; Hal, haloperidol.

weight gain and mild elevations in serum lipids and glucose may occur.

▶ *Olanzapine*

Olanzapine has greater affinity for 5-HT$_{2A}$ than for D$_2$ receptors. It also has affinity at the binding sites of D$_4$, D$_3$, 5-HT$_3$, 5-HT$_6$, α_1-adrenergic, muscarinic$_{1-5}$ (M$_{1-5}$), and histamine$_1$ (H$_1$) receptors.[19] In the CATIE trial, olanzapine was associated with the longest time to treatment discontinuation,[15] suggesting it may differ from the other SGAs in effectiveness. Olanzapine has a low rate of EPS and causes slight, transient prolactin elevations. Olanzapine causes significant weight gain across the dosage range, similar to that seen with clozapine and greater than that observed with the other SGAs. Olanzapine is also associated with hypertriglyceridemia, increased fasting glucose, and new-onset type 2 diabetes (ie, metabolic syndrome). Among the first-line SGAs, it is associated with the greatest elevations in these metabolic parameters.[15]

▶ *Quetiapine*

Quetiapine, structurally related to clozapine and olanzapine, has high affinity for 5-HT$_{2A}$ receptors and lower affinity for D$_2$ and D$_1$ receptors. It has some affinity for α_1, α_2, and H$_1$ receptors but very little for muscarinic receptors. Quetiapine may be beneficial for anxiety and depression. Motor side effects and prolactin elevations are uncommon. Orthostasis occurred in 4% of subjects in clinical trials. Sedation is common, but generally transient. Quetiapine is sometimes used for insomnia, though this practice is off label and not considered an appropriate use. Weight gain and elevations in triglycerides can occur. Use of quetiapine with agents that can prolong the QTc interval or in patients with prolonged QTc should be avoided. Quetiapine has been associated with some dose-related decreases in thyroid hormones.

▶ *Ziprasidone*

Ziprasidone was developed to block D$_2$ receptors but also to bind with greater affinity to central 5-HT$_{2A}$ receptors. It has a binding affinity ratio of 11:1 for 5-HT$_{2A}$:D$_2$ receptors. It has a relatively high affinity for 5-HT$_{2C}$, 5-HT$_{1D}$, α_1-adrenergic, and D$_1$ receptors.[20] It should be taken with food (at least 500 calories [2100 J]), as this results in absorption levels twice that of fasting administration. Liability for EPS, weight gain, and lipid elevations is low but does occur. Ziprasidone causes some prolongation of the QTc interval in adults. However, overdose data and pharmacokinetic interaction data show little evidence that significant QTc prolongation occurs. Use of ziprasidone with agents that can prolong the QTc interval or in patients with existing diseases associated with prolonged QTc should be avoided. Drug reaction with eosinophilia and systemic symptoms (DRESS) has occurred rarely.

▶ *Aripiprazole*

Aripiprazole has both antagonist and partial agonist activity at the D$_2$ receptor. Aripiprazole is also a partial agonist at 5-HT$_{1A}$ receptors, an antagonist at 5-HT$_{2A}$ receptors, and has affinity for D$_3$ receptors. Additionally, it has moderate affinity for α_1 and H$_1$ receptors with no appreciable affinity for the M1 receptor.[21] In CYP2D6 poor metabolizers, start dosing with one-half the usual dose with adjustment to clinical efficacy. Sedation, nausea, and vomiting are the most often seen side effects. Elevations in weight, lipids, and glucose are generally negligible, and aripiprazole is not associated with elevations in serum prolactin. In fact, patients switched to aripiprazole from other antipsychotic agents may experience decreases in prolactin.

▶ *Paliperidone*

Paliperidone is the 9-hydroxy (9-OH) metabolite of risperidone. The efficacy of risperidone and paliperidone is similar. Receptor binding affinity is also similar between the two agents, with paliperidone having a greater affinity at 5-HT$_{2A}$ compared with D$_2$ receptors. Unlike many other antipsychotic medications, paliperidone is mostly excreted unchanged, a potential advantage in patients with liver impairment, although adjustment may need to be made in renal impairment. Patients should be told to expect to see the shell of the tablet in the stool because it may not dissolve in the digestive tract.[22] Side effects of paliperidone are expected to be similar to those of risperidone, including the potential for dose-related EPS and prolactin elevation.[22]

▶ Iloperidone

Iloperidone exhibits high affinity for 5-HT_{2A}, dopamine D_2, and D_3 receptors and acts as an antagonist at these, as well as at the 5-HT_{1A} and norepinephrine α_1/α_{2C} receptors. Doses must be titrated because of the risk of orthostatic hypotension, and dosing should be reduced by half in CYP2D6 poor metabolizers. Common adverse reactions include dizziness, dry mouth, fatigue, orthostatic hypotension, tachycardia, and weight gain. Dizziness, tachycardia, and weight gain were twice as common with higher dose (20–24 mg total daily dose) versus lower doses (10–16 mg total daily dose).[23] Use of iloperidone with agents that can prolong the QTc interval or in patients with diseases that are associated with prolonged QTc should be avoided.

▶ Asenapine

Asenapine's mechanism of action is thought to be its antagonistic activity at 5-HT_{2A} and D_2 receptors. It also exhibits a high affinity for other serotonergic and dopaminergic receptors, as well as α_1- and α_2-adrenergic receptors and H_1 receptors. Asenapine tablets must be placed under the tongue and allowed to dissolve completely; tablets should not be chewed or swallowed. Patients should not drink or eat for 10 minutes after administration. No added benefit was seen with doses above 10 mg twice daily, but adverse effects increase. Common adverse effects include somnolence, dizziness, and akathisia. It has shown little effect on metabolic parameters and weight change. Labeling for asenapine was modified to address rare occurrence of hypersensitivity reactions, including anaphylaxis and angioedema.[24] A transdermal formulation of asenapine has been marketed as a once-daily (every 24 hours) formulation.

▶ Lurasidone

Lurasidone antagonizes D_2 and 5-HT_{2A} receptors. It also has moderate affinity as an antagonist at α_{2C}, is a partial agonist at 5-HT_{1A}, and is an antagonist at α_{2A} receptors. Lurasidone should be taken with caloric intake of at least 350 calories (1500 J) for maximal absorption. Adverse reactions reported in at least 5% of patients (and at least twice the placebo rate) include somnolence, akathisia, nausea, parkinsonism, and agitation. Lurasidone has shown only a small effect on body weight and causes minimal changes in other metabolic parameters.[24]

▶ Brexpiprazole

Brexpiprazole is a partial agonist at 5-HT_{1A}, D_2 and D_3 receptors. It is also an antagonist of 5-HT_{2A}, 5-HT_{2B}, 5-HT7, α_{1A}, α_{1B}, α_{1D}, α_{2C}, and H_1 receptors. It has negligible affinity for muscarinic receptors. In CYP2D6 poor metabolizers, usual dosage should be reduced by one-half. This medication is slightly less stimulating and has less akathisia than aripiprazole. The most commonly occurring side effects are weight gain and akathisia.[25]

▶ Cariprazine

Cariprazine is a dopamine D_3-preferring D_2/D_3 receptor partial agonist. It also acts as a partial agonist of 5-HT_{1A} and as an antagonist of 5-HT_{2A} receptors. It is given once daily and has a long half-life; thus, side effects should be monitored for several weeks after initiation or a dose change. Most common side effects are akathisia, EPS, nausea, vomiting, somnolence, and restlessness. Those having a known hypersensitivity reaction to cariprazine should not be treated with the medication.[26]

▶ Lumateperone

Lumateperone is a 5-HT_{2A} and D_2 receptor antagonist with higher affinity for 5-HT_{2A} compared with D_2, and lower affinities for α_1 and H_1 receptors. It also works as a presynaptic dopamine partial agonist, serotonin reuptake inhibitor, and an indirect modulator of glutamatergic systems. Due to gastrointestinal adverse effects in clinical trials, it is recommended to administer lumateperone with food. Only one dose (42 mg) is currently approved due to lack of efficacy of varying doses. Dose titration or adjustment is not required. Use of lumateperone was not associated with increased EPS risk as compared with placebo in pooled safety analyses of three clinical studies. Sedation/somnolence and dry mouth were associated with occurrence greater than twice the rate of placebo or at least 5% of patients exposed to lumateperone. Rates of EPS-related side effects and mean change in weight were less for lumateperone and placebo compared with risperidone.[27]

First-Generation (Typical) Antipsychotics

The FGAs are high-affinity D_2 receptor antagonists. During chronic treatment, they block 65% to 80% of D_2 receptors in the striatum and other dopamine tracts in the brain.[25] Clinical

Patient Encounter, Part 3

The patient started treatment with haloperidol 5 mg/day in the hospital. After a couple of days, the dose of haloperidol was increased to 10 mg/day. Over several days, the patient started to feel less paranoid and the voices began to dissipate. She began participating in group activities on the unit and interacting with her peers. She was discharged from the hospital after 2 weeks. Her mother agreed to have her return home.

The patient had a follow-up appointment 2 weeks after discharge. At the appointment, she expressed feeling well enough to consider going back to school. During the interview, the physician noted that she had a pill-rolling tremor and masked facies. Upon examination, the patient also had cogwheel rigidity and a lack of arm swing when she walked.

After discussion with the patient and her mother, the decision was made to switch her from haloperidol to oral olanzapine 5 mg/day. The doctor called the patient a week later to discuss how she was doing on the new medication. The patient felt like some of her schizophrenia symptoms were returning, so he decided to increase the olanzapine dose to 10 mg/day. The doctor called the patient again a week later, and she stated her hallucinations and paranoia were improving as were the stiffness and rigidity she experienced on haloperidol, so the dose was maintained at 10 mg/day.

What symptom was the patient experiencing on haloperidol? What other treatments could have been considered besides switching agents?

Discuss the differences in the side effect profiles of haloperidol and olanzapine.

Table 38–4

First-Generation (Typical) Antipsychotics[a]

Class	Agent (Brand Name)	Dosage Range (mg/day)	Chlorpromazine Equivalents (mg)	Available Formulations
Butyrophenone	Haloperidol (Haldol)	5–30	2	T, LC, I
Dibenzoxazepine	Loxapine (Loxitane, Adasuve)	20–100	10	C, IP
Diphenylbutylpiperidine	Pimozide (Orap)[b]	1–10	1–2	T
Phenothiazines	Chlorpromazine (Thorazine)	300–800	100	T, I
	Fluphenazine (Prolixin)	2–40	2	T, L, LC, I
	Perphenazine (Trilafon)[c]	8–64	8–10	T
	Thioridazine (Mellaril)	300–800	100	T
	Trifluoperazine (Stelazine)	15–30	5	T
Thioxanthenes	Thiothixene (Navane)	5–60	4	C

[a] Low-potency antipsychotics include thioridazine, mesoridazine, and chlorpromazine. High-potency antipsychotics include haloperidol, fluphenazine, thiothixene, and pimozide.

[b] Poor CYP2D6 metabolizers, alternative dosing strategies; recommend 2D6 genotyping above certain doses.

[c] Poor 2D6 metabolizers may demonstrate higher plasma concentration.

C, capsule; I, injection; IP, inhalation powder; LC, liquid concentrate; L, liquid solution, elixir, or suspension; T, tablet.

response is generally associated with 60% D_2 receptor blockade, while 70% and 80% are associated with hyperprolactinemia and EPS, respectively. During the 1990s, SGAs began to replace FGAs as first-line therapy.

Doses for FGAs are frequently given as **chlorpromazine equivalents**, which are defined as the FGA equipotent dose with 100 mg of chlorpromazine. The target dose recommendation for acute psychosis is 400 to 600 chlorpromazine equivalents unless the patient's history indicates that dose may not be tolerated. Generally, maintenance therapy is 300 to 600 chlorpromazine equivalents daily. Dosing and available dosage forms are shown in Table 38–4. All FGAs are equally efficacious when studied in equipotent doses in groups of patients. Relative potency of FGA agents is related to side effect profile, with lower potency agents such as chlorpromazine demonstrating higher risk of anticholinergic and cardiovascular side effects and higher potency agents such as haloperidol displaying more potent EPS side effects. However, an individual patient may not respond equally to each antipsychotic. Selection of a particular antipsychotic is based on patient variables, such as the need to avoid certain side effects or drug–drug interactions or previous patient or family history of response. Long-acting formulations of FGA medications are shown in Table 38–5.

Side Effects of the First-Generation Antipsychotics

As previously mentioned, the low-potency FGA agents are less likely to cause EPS than the high-potency agents (see Table 38–4). Of note, high-potency and midpotency agents may cause less EPS than once believed and were similar to SGAs in the CATIE trial.[15]

The FGAs are commonly associated with early-onset EPS (including **akathisia** [motor or subjective restlessness], **dystonia** [muscle spasm], and pseudoparkinsonism [akinesia, tremor, and rigidity]) caused by dopamine antagonism in the nigrostriatal pathways. SGAs also may have these side effects. Akathisia, or the feeling of restlessness, occurs in 20% to 40% of FGA patients. Roughly half of the cases of akathisia present within 1 month of FGA initiation, though it may present within 5 to 10 days after the first dose or after an increase in dosage. Younger people and those taking high doses of high-potency antipsychotics are at greater risk for development of akathisia.

Acute dystonic reactions are abrupt in onset and are usually seen within 24 to 96 hours after a first dose or increase in dosage. Characteristic signs and symptoms include abnormal positioning or spasm of the muscles of the head, neck, limbs, or trunk. Dystonia may occur in 10% to 20% of patients. There is higher risk for dystonia in young male patients and those taking high-potency FGAs.

Pseudoparkinsonism may be present in 30% to 60% of people treated with FGAs. The onset of symptoms is usually within 1 to 2 weeks after dose initiation or dose increase. Clinical presentation may include cogwheel rigidity, pill-rolling hand movements, resting tremor, shuffling gait, stooped posture, and mask facies. Risk factors include older age, female gender, high doses, and possibly those with depressive symptoms. Anticholinergic medications are used for treatment of dystonic reactions and pseudoparkinsonism, while β-blocking agents are generally first line for akathisia.[28]

Tardive dyskinesia is a movement disorder characterized by abnormal choreiform (rapid, objectively purposeless, irregular, and spontaneous) and athetoid (slow and irregular) movements beginning late in relation to initiation of antipsychotic therapy. It usually develops over several months or after at least 3 months of cumulative exposure to antipsychotics. When antipsychotics are tapered or discontinued, there is typically a transient worsening of abnormal movements, and movements may be irreversible in some cases. Risk factors for TD include older age; longer duration of antipsychotic treatment; and presence of EPS, substance abuse, and mood disorders. SGAs have a lower risk of approximately 2% to 4% risk of TD than FGAs (5%–6%).[17] A variety of approaches have been used for treating TD including switching to clozapine, using high-dose vitamin E, and, most recently, the approval of new Food and Drug Administration (FDA)-approved medications for TD, valbenazine and deutetrabenazine, which inhibit vesicular monoamine transporter 2 (VMAT2).

Neuroleptic malignant syndrome (NMS), a life-threatening emergency characterized by severe muscular rigidity, autonomic instability, and altered consciousness, can occur uncommonly with all FGAs and may also occur with SGAs. Rapid dose escalation, use of high-potency FGAs at higher doses, and younger

Table 38–5

Antipsychotic Dosing of Long-Acting Preparations

Drug	Starting Dose	Maintenance Dose	Comments
Aripiprazole long-acting injection (Abilify Maintena)	400 mg monthly Give 14 consecutive days of concurrent oral aripiprazole (10–20 mg) or current oral antipsychotic after first injection	300–400 mg monthly	Establish tolerability with oral agent first Dosage adjustments for CYP2D6 poor metabolizers, and in persons who take strong CYP2D6 or 3A4 inhibitors; recommend to avoid use if strong 3A4 inducer Available as 300-, 400-mg kits
Aripiprazole lauroxil (Aristada)	441 if 10 mg/day oral 662 if 15 mg/day oral 882 if 20 mg/day or more oral Give 21 days of concurrent oral aripiprazole overlapping with first dose	Average 441–882 monthly or 882 every 6 weeks or 1064 every 2 months	Dose adjustments for CYP2D6 poor metabolizers, and persons who take strong CYP2D6 or 3A4 inhibitors; or CYP3A4 inducers > 2 weeks Available as 441-, 662-, 882, or 1064-mg prefilled syringes
Aripiprazole lauroxil (Aristada Initio)	675-mg injection and one 30-mg dose of aripiprazole as first dose	To be used as a single dose and not for repeated dosing; for initiating Aristada treatment	Avoid use in CYP2D6 poor metabolizers Not interchangeable with Aristada First Aristada injection may be administered on the same day as Aristada Initio or up to 10 days after Do not inject both concomitantly into the same deltoid muscle
Haloperidol decanoate	10–20 × oral haloperidol daily dose; in the elderly use 10–15 × oral haloperidol daily dose Generally, 100–450 mg/month Initial dose should not exceed 100 mg regardless of previous dose requirements (if > 100 mg, give 3–7 days apart) Oral supplementation may temporarily be necessary for first 2–3 injections unless loading dose given	10–15 × oral haloperidol daily dose, generally 50–300 mg/month	Deep IM injection generally with 21-gauge needle; maximum volume per injection site should not exceed 3 mL Available in 50 and 100 mg/mL (5-mL vials and 1-mL ampules)
Fluphenazine decanoate	Approximately 12.5-mg injection = 10-mg oral daily dose; usual starting dose 12.5–25 mg; generally, 12.5–mg/2–3 weeks Give ½ oral dose after first injection, discontinue oral after second injection	Based on starting dose and clinical response but usually 2–4 weeks; doses above 50 mg increase cautiously in 12.5-mg increments; do not exceed 100 mg Generally, 12.5–25 mg dosed at 2–4-week intervals (may be up to 6 weeks in some cases)	Can be administered IM or SC; 21-gauge needle, must be dry Should not exceed 100 mg; when dosing above 50 mg, should increase in increments of 12.5 mg Available in 25 mg/mL (5-mL vials)
Olanzapine (Zyprexa Relprevv)	To target oral 10-mg/day dose: Either 210 mg/2 weeks or 405 mg/4 weeks during first 8 weeks To target oral 15-mg/day dose: 300 mg/2 weeks for first 8 weeks To target 20-mg/day oral dose: 300 mg/2 weeks Establish tolerance with oral administration prior to initiation	To target oral 10-mg/day dose: after 8 weeks, give 150 mg/2 weeks or 300 mg/4 weeks To target oral 15-mg/day dose: after 8 weeks, 210 mg/2 weeks or 405 mg/4 weeks To target 20-mg/day oral dose: continue with 300 mg/2 weeks	Gluteal injection, 19-gauge needle Do not confuse with rapid-acting IM injection Must reconstitute with included diluent Measure amount to inject from vial (there will be remaining suspension in vial) Zyprexa Relprevv Patient Care Program: 3-hour observation period due to risk of postinjection delirium/sedation syndrome; patient must be accompanied to destination No refrigeration needed, use within 24 hours, or immediately once suspension is in syringe Available as 210, 300, 405 kits
Paliperidone monthly (Invega Sustenna)	Initiate with 234 mg on day 1 and 156 mg 1 week later, both in deltoid muscle Establish tolerance with oral administration prior to initiation	Recommended monthly maintenance dose is 117 mg (range, 39–234 mg)	First two doses must be given in the deltoid muscle; after that, monthly doses given in either the deltoid or gluteal muscle Adjust dose in mild renal impairment; avoid in moderate-to-severe impairment Available as 39-, 78-, 117-, 156-, and 234-mg prefilled syringes

(Continued)

Table 38–5

Antipsychotic Dosing of Long-Acting Preparations (*Continued*)

Drug	Starting Dose	Maintenance Dose	Comments
Paliperidone (every 3 months) (Invega Trinza)	If monthly 78 mg, 273 mg/3 months If monthly 117 mg, 410 mg/3 months If monthly 156 mg, 546 mg/3 months If monthly 234 mg, 819 mg/3 months Only initiate after at least 4 months of paliperidone monthly injections.	273–819 mg/3 months	Adjust dose in mild renal impairment; avoid in moderate to severe impairment Available as 273-, 410-, 546-, or 819-mg prefilled syringes
Risperidone long-acting injection (Risperdal Consta)	25 mg every 2 weeks Previous antipsychotics should be continued for 3 weeks after initial dose of risperidone long-acting injection	25–50 mg every 2 weeks	Recommended to establish tolerability with oral risperidone prior to initiation of long-acting injection Lower starting dose of 12.5 mg may be appropriate in some patients with renal/hepatic impairment Available in 12.5-, 25-, 37.5-, and 50-mg vial/kit; must use needle supplied with kit, administer IM
Risperidone subcutaneous long-acting injection (Perseris)	90 mg to 120 once monthly	90 to 120 mg every month	Establish tolerability with oral risperidone No oral supplementation recommended Administer monthly in abdomen by subcutaneous injection by a healthcare professional; Must reconstitute when ready to give dose; Available as 90 mg and 120 mg injection kits

IM, intramuscular; SC, subcutaneous.

patients have a higher risk of NMS. When NMS is diagnosed or suspected, antipsychotics should be discontinued and supportive, symptomatic treatment begun (eg, antipyretics, cooling blanket, intravenous fluids, oxygen, monitoring of liver enzymes, and complete blood cell count). Benzodiazepines and dantrolene are recommended treatments along with intensive care management as needed.[28]

Dermatologic side effects, photosensitivity, and cataracts may occur with the phenothiazine FGAs. Sedation is mediated by H_1 receptor antagonism; anticholinergic side effects (constipation, blurred vision, dry mouth, and urinary retention) are caused by M_1 receptor antagonism; and α_1 receptor blockade is associated with orthostatic hypotension and tachycardia (Table 38–6). QTc prolongation may occur with the lower-potency FGAs, and thioridazine has a black box warning for QTc prolongation.

Pharmacologic Treatment Guidelines and Algorithms

There have been a variety of treatment recommendations published for schizophrenia. The American Psychiatric Association (APA) Practice Guidelines for Schizophrenia[8] were updated in 2020. The World Federation of Societies of Biological Psychiatry Guidelines (WFSBP),[29] British Association of Psychopharmacology (BAP),[30] the Canadian Schizophrenia Guidelines,[31] and the National Institute for Health and Care Excellence (NICE) guidelines are also available.[10] While guidelines from the early 2000s generally recommend SGAs as first-line treatment, more recent guidelines generally suggest first-line treatment with either an FGA or SGA. Choice of the FGA/SGA is guided by side effect profiles and patient clinical characteristics. Treatment with a given antipsychotic at a recommended therapeutic dose should

Table 38–6

Side Effects of First-Generation Antipsychotics

	Relative Potency	Extrapyramidal Symptoms	Sedation	Anticholinergic Side Effects	Cardiovascular Side Effects	Seizure Effects/ QTc Prolongation
Chlorpromazine	100	++	++++	+++	++++	++
Thioridazine	100	++	++++	++++	++++	+++
Loxapine	10	+++	+++	++	+++	+
Perphenazine	8–10	+++	++	++	++	+
Trifluoperazine	2–5	+++	++	++	++	+
Thiothixene	4	+++	++	++	++	+
Fluphenazine	2	++++	++	++	++	+
Haloperidol	2	++++	+	+	+	+

+, very low; ++, low; +++, moderate; ++++, high.

be continued for 4 to 6 weeks to assess response. If response is not achieved, switching and cross titration to monotherapy with a different antipsychotic in conjunction with psychosocial support are recommended. Use of two antipsychotic medications concomitantly is discouraged in most circumstances due to increased side effect burden and paucity of data for increased efficacy.

Treatment Adherence

Antipsychotic nonadherence is estimated to occur in at least 40% to 50% of patients with schizophrenia. Patients who are nonadherent have about a fourfold greater risk of a relapse than those who are adherent.[32] Neurocognitive deficits, poor insight, and paranoid symptoms may hamper adherence, and identification of nonadherence by caretakers and providers can be challenging. Antipsychotic side effects such as EPS, weight gain, sexual dysfunction, substance use, and negative symptoms may all contribute to treatment nonadherence. For patients who have relapsed several times because of nonadherence have a history of dangerous behavior, or risk a significant loss of social or vocational gains when relapsed; treatment with long-acting injection (LAI) should be encouraged. However, more recent data suggest that both FGA and SGA LAIs are more effective at reducing rehospitalization risk compared to oral treatment,[33] and thus may be considered for all patients as a routine treatment option. The new APA guidelines[8] recommend LAI to patients who are interested in this delivery. Risperidone, paliperidone, olanzapine, and aripiprazole are available as LAIs. In general, oral tolerability of these agents should be ensured prior to initiating most of the LAIs. In recent years, many new SGA formulations have become available offering more flexibility with longer dosing intervals and easier loading strategies. Dosing and other information about these formulations are shown in Table 38–5. LAIs should be introduced early to patients as an option to improve efficacy and not just reserved for patients with lack of adherence to other treatments.

Special Populations

▶ *Dosing in Renal and Hepatic Impairment*

Table 38–7 shows dosing guidance on specific antipsychotic medications.

▶ *Children and Adolescents*

Around 10% to 30% of patients with schizophrenia have psychotic symptoms before their 18th birthday. The diagnosis of schizophrenia in children and adolescents is often challenging, and the differential diagnosis includes autistic spectrum disorders, attention-deficit/hyperactivity disorder, and language or communication disorders. The existence of prominent hallucinations or delusions helps make the diagnosis because they are not prominent in other disorders. Children and adolescents developing schizophrenia before age 18 years have premorbid abnormalities such as withdrawal, odd traits, and isolation. Treatment for psychotic children and adolescents ideally is intensive, comprehensive, and structured. Early intervention in psychosis services such as NAVIGATE should be employed in first-episode schizophrenia.[34] Pharmacologic treatment is indicated if psychotic symptoms cause significant impairments or interfere with other interventions. Children and adolescents are more vulnerable to EPS, particularly dystonias, than adults. Because of concerns about EPS and TD in children and adolescents, it is recommended that antipsychotic therapy be initiated with SGAs. Aripiprazole, risperidone, quetiapine, olanzapine, paliperidone, and lurasidone are approved by the FDA for the treatment of schizophrenia in adolescent patients. Initiation and target doses are lower for adolescents than adults.

Agents with significant sedative and anticholinergic side effects are not preferred because they can interfere with school performance. Compared with adults, children and adolescents tend to gain more weight when taking these agents.

▶ *Elderly*

Psychotic symptoms in late life (after 65 years of age) generally result from an ongoing chronic illness; however, a small percentage of patients develop psychotic symptoms *de novo*, defined as late-life schizophrenia. Other illnesses with psychotic symptoms are common in this population; approximately one-third of patients with Alzheimer disease, Parkinson disease, and vascular dementia experience psychotic symptoms.

Antipsychotics can be safe and effective for the treatment of schizophrenia in the elderly, if used at lower doses than those commonly used in younger adults. Older adults are particularly vulnerable to the side effects of the FGAs, and TD risk is over threefold risk in elderly patients.[17]

Orthostasis, estimated to occur in 5% to 30% of elderly patients, is a major contributing factor to falls that often lead to injuries and loss of independence. Low-potency antipsychotics and clozapine are more likely to cause significant orthostasis. Antipsychotics may cause or worsen anticholinergic effects, including constipation, dry mouth, urinary retention, and cognitive impairment. Greater antipsychotic-associated impairment in cognitive functioning may occur in the elderly compared to younger adults. In the elderly, this can lead to decreased independence, a very problematic issue. As a result of data showing a statistically significant increase in elderly dementia patients taking SGAs, a black box warning was added to the manufacturer's information for all antipsychotics. Patients and families should be informed of this risk before using these agents in patients with dementia. Dosing in the elderly is initiated lower, and titration is slower than in younger adults. Maximum doses are often half of adult doses (see Table 38–7).

▶ *Co-Occurring Substance Use Disorder*

Alcohol and illicit drug use is about threefold higher in schizophrenia than the general population.[5] In addition, nicotine use (most frequently, smoking tobacco) is highly prevalent in persons with schizophrenia, with rates at 58% to 90%. The most common drugs of abuse besides nicotine are cannabis, cocaine, and alcohol. Substance use often worsens the clinical course and complicates treatment. People with schizophrenia and substance use disorders are more likely to be nonadherent with treatment. They may have a poorer response rate to the FGAs, more severe psychosis, and higher rates of relapse and rehospitalization than people without co-occurring disorders. EPS may occur more frequently in substance-using patients, and alcohol use is a risk factor for developing TD. It is important to incorporate a dual treatment approach for substance use disorders and schizophrenia with nonpharmacologic and pharmacologic treatments.[35]

▶ *Treatment-Resistant Schizophrenia*

For 20% to 30% of people with schizophrenia, first-line antipsychotic treatment is ineffective, and another 30% of people have a partial treatment response.[29] A consensus guideline defines treatment-resistant schizophrenia (TRS) as (a) moderately severe

Table 38–7

Second-Generation Antipsychotic Dosing Recommendations for Special Populations

Medication	Pediatric	Geriatric	Renal Impairment	Hepatic	Pharmacogenomic Considerations
Aripiprazole	Oral: Ages 13–17 years (schizophrenia): Initiate 2 mg every day, increasing to 5 mg daily after 2 days and target of 10 mg after several days, 30 mg/day maximum	Long-acting injection: in general, dose selection should be cautious. Oral: No adjustment recommended	No adjustment required for oral or LAI	No adjustment required for oral or LAI	2D6 poor metabolizers: administer half of usual dose
Asenapine	No pediatric FDA indication for schizophrenia (bipolar I indication only)	No adjustment necessary based on age alone	No adjustments necessary	No adjustment necessary for mild-to-moderate impairment, but use contraindicated in severe impairment	
Brexpiprazole	No pediatric FDA indication	Experience is limited; low-dose initiation, up to 3 mg/day kinetics similar to adults with MDD in safety/tolerability trial	CrCl < 60 mL/min (1.0 mL/s): maximum 3 mg	Moderate to severe: Maximum 3 mg	2D6 poor metabolizers: Administer half of usual dose
Cariprazine	No pediatric FDA indication	Experience is limited; low-dose initiation	CrCl < 30 mL/min (0.50 mL/s): not recommended	Mild to moderate: No adjustment required; severe: not recommended	
Clozapine	No pediatric FDA indication	Experience is limited; low dose and slow titration	Adjustments may be necessary with significant impairment; no specific recommendations available	Adjustments may be necessary with significant impairment; no specific recommendations available	Dose reductions may be necessary in 2D6 poor metabolizers
Iloperidone	No pediatric FDA indication	Not sufficient information for recommendation	No adjustment information provided, but unlikely necessary	No adjustment needed for mild impairment; exercise caution with moderate impairment; not recommended for severe impairment	Dose reduced by one-half in 2D6 poor metabolizers
Lumateperone	No pediatric FDA indication	Not sufficient information for recommendation. Studies did not include any patients aged 65 or older	No recommendations listed	Not recommended for moderate-to-severe impairment	
Lurasidone	Ages 13–17 years (schizophrenia): Initial dose, 40 mg/day with target dose of 40–80 mg/day	Unknown if necessary to modify based on age alone	With moderate-to-severe renal impairment, recommended starting dose 20 mg daily; do not exceed 80 mg daily	With moderate impairment, initial dose 20 mg daily; maximum dose 80 mg daily With severe impairment, initial dose 20 mg daily, maximum dose 40 mg daily	
Olanzapine	Oral: Ages 13–17 years (schizophrenia): Initial dose, 2.5–5 mg orally every day with target dose of 10 mg/day; maximum dose, 20 mg/day Long-acting injection: Not approved in children	Oral: 5 mg/day, if escalation needed use caution Long-acting injection: Consider starting dose of 150 mg every 4 weeks for elderly or debilitated patients	Oral: In renal impairment, no adjustment usually necessary; however, consider a lower initial dose of 5 mg/day Long-acting injection: No information given	Oral: No dosage adjustment noted in prescribing information except in combination with fluoxetine Long-acting injection: No information given	

(Continued)

Table 38–7

Second-Generation Antipsychotic Dosing Recommendations for Special Populations (*Continued*)

Medication	Pediatric	Geriatric	Renal Impairment	Hepatic	Pharmacogenomic Considerations
Paliperidone	Oral: Ages 12–17 years (schizophrenia): Dose by body weight: < 51 kg, initiate 3 mg/day oral, increase at increments of > 5 days; maximum, 6 mg/day At least 51 kg, initiate at 3 mg/day, increase at increments of > 5 days, maximum of 12 mg/day	Long-acting injection: adjust dose based on renal function Oral: For patients with normal renal function, no adjustment is required, but if renal impairment guidance is available	Long-acting injection: CrCl 50–79 mL/min (0.83–1.32 mL/s); initiate with 156 mg IM day 1, 117 mg IM 1 week later, with maintenance at 78 mg IM monthly CrCl < 50 mL/min (0.83 mL/s): Use not recommended Oral: CrCl 50–79 mL/min (0.83–1.32 mL/s): 3 mg once daily initiation, maximum 6 mg/day CrCl between 10 and 49 mL/min (0.17–0.82 mL/s): 1.5 mg once daily initiation; maximum, 3 mg/day CrCl < 10 mL/min (0.17 mL/s): Use not recommended	Long-acting injection: No dosage adjustment needed for mild or moderate impairment; no guidance given for severe impairment Oral: No dose adjustment is required for mild or moderate impairment	
Quetiapine	Regular-release tablets: Indicated for schizophrenia (ages 13–17 years): Initiate 25 mg twice daily; recommended target dose 400–800 mg/day; maximum 800 mg/day Extended-release tablets: Initiate 50 mg/day; recommended target dose 400–800 mg	Regular-release tablets: Slower dose escalation and a lower target dose Extended-release tablets: Initiate at 50 mg/day and increase at 50-mg/day increments based on response or tolerance	No dosing recommendations for renal dysfunction	Regular-release tablets: Lower starting dose (25 mg) and slower titration may be needed Extended-release tablets: Should be initiated with 50 mg/day, increasing in 50-mg/day increments	
Risperidone	Oral: Pediatric ages 13 years and older (schizophrenia): Initiate at 0.5 mg orally daily, adjusting at intervals of at least 24 hours and in increments of 0.5–1 mg/day as tolerated Recommended target dose 3 mg/day	Long-acting IM: Initial dose, 25 mg IM every 2 weeks with a 3-week oral crossover; may consider 12.5 mg as starting dose Oral: Initiate at 0.5 mg twice daily; may increase by 0.5 mg twice daily, increases above 1.5 mg twice daily done at intervals of at least 1 week	Long-acting IM: Patients with renal impairment should receive titrated doses of oral risperidone before initiation of IM (more detail in prescribing information) Oral: Recommended initial dose in CrCl < 30 mL/min (0.50 mL/s), 0.5 mg twice daily; dose may be increased by 0.5 mg twice daily, but increases above 1.5 mg twice daily should be done at intervals of at least 1 week. Clearance of risperidone is decreased by 60% in patients with moderate-to-severe renal disease (CrCl < 60 mL/min [1.0 mL/s])	Long-acting IM: Titrate with oral risperidone (see renal dosing) Oral: Recommended initiation in Child-Pugh Class C (see renal dosing)	
Ziprasidone	No pediatric FDA indication	No official adjustment recommended; consider starting at lower end of the dosage range	Oral doses: No adjustment necessary for mild-to-moderate renal impairment IM doses: Use with caution because of cyclodextrin sodium excipient	No adjustment necessary for mild-to-moderate hepatic impairment; however, caution is warranted	

CrCl, creatinine clearance; FDA, Food and Drug Administration; IM, intramuscular; MDD, major depressive disorder.

illness as defined by rating instruments with a persistence of at least 5 years, (b) moderate or worse functional impairment, (c) treatment with at least two different antipsychotics given at adequate doses (a dose equivalent to at least 600 mg of chlorpromazine) for an adequate duration (6 weeks), (d) meeting minimum criteria of being adherent to current treatment, and (e) ideally having one prospective antipsychotic trial.[36]

Clozapine Clozapine is the only antipsychotic with proven superior efficacy and approved by the FDA for TRS.[16] It is efficacious after nonresponse to other SGAs, in partially responsive patients and patients who have had a poor response to other medication for years. According to published guidelines and recommendations, clozapine should be considered after two failed antipsychotic trials,[10,28,30] but may be considered sooner if the individual patient situation warrants.[8,29] Additionally, it is FDA approved for reducing the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder[37] and recommended for those with a substantial risk of aggression.[8]

It remains unknown which pharmacologic properties account for clozapine's superior efficacy. Clozapine interacts with a multitude of receptors but notably has a low affinity for and rapid dissociation from D_2 receptors, antagonism of D_1 receptors, and is a 5-HT_{2A} antagonist.

Clozapine's use is limited by the regulatory requirements resulting from the risk for severe neutropenia (ANC < 0.5×10^9/L [or 0.5×10^3/mm^3], was termed agranulocytosis previously). This is a rare but potentially life-threatening side effect occurring in less than 1% of people treated and is a "black box" warning for the medication. The required long-term hematologic monitoring (Table 38–8) can be a barrier for both patients and care providers. Other rare side effects include seizures, myocarditis, and cardiomyopathy (also "black box" warnings). Orthostatic hypotension, bradycardia, and syncope are also "black box" warning for clozapine. Common unpleasant side effects include sedation, dizziness, constipation, enuresis, weight gain, and hypersalivation.

Registration for clozapine must first occur prior to dispensing using a Clozapine REMS website. APA guidelines recognize the underuse of this medication and encourage its more widespread acceptance.[8]

The optimal plasma level of clozapine is a minimum trough level of 918 to 1071 nmol/L (300–350 ng/mL or mcg/L), usually corresponding to a daily dose of 200 to 400 mg, although dosage

Table 38–8

Monitoring of Absolute Neutrophil Count During Clozapine Treatment

	General Population	BEN Population
Initiation to 6 months	Initiate if ANC ≥ 1.5×10^9/L; weekly monitoring for 6 months as long as ANC remain ≥ 1.5×10^9/L	Initiate if ANC ≥ 1.0×10^9/L (obtain at least 2 baseline levels); weekly monitoring for 6 months if ANC remain ≥ 1.0×10^9/L
6–12 months	Every 2-week monitoring for 6 months as long as ANC levels remain ≥ 1.5×10^9/L	Every 2-week monitoring for 6 months as long as ANC remain ≥ 1.0×10^9/L
After 12 months of therapy	Every 4-week monitoring as long as ANC levels remain ≥ 1.5×10^9/L	Every 4-week monitoring as long as ANC levels remain ≥ 1.0×10^9/L
ANC 1.0–1.49 × 10^9/L	**Mild neutropenia (general population)** 1.0 to 1.49 × 10^9/L (confirm with repeat ANC within 24 hours) Recommendation to continue treatment Monitor ANC three times weekly until ANC ≥ 1.5×10^9/L, then return to patient's last normal range monitoring interval if appropriate	These ANC levels considered normal for BEN population, continue monitoring as generally indicated above
ANC 0.5–0.99 × 10^9/L	**Moderate neutropenia (general population)** ANC 0.5–0.99 × 10^9/L (confirm with repeat ANC within 24 hours) Recommend hematology consult; interrupt treatment if clozapine-induced neutropenia is suspected. Resume treatment once ANC is ≥ 1.0×10^9/L Monitor ANC daily until ANC ≥ 1.0×10^9/L, then three times weekly until ANC ≥ 1.5×10^9/L, then check weekly × 4 weeks, then return to patient's last normal range ANC interval, if appropriate	**BEN neutropenia** 0.5–0.99 × 10^9/L (confirm with repeat ANC within 24 hours) Recommend hematology consult Continue treatment Monitor ANC thrice weekly until ANC ≥ 1.0×10^9/L or up to patient's known baseline Once at ANC ≥ 1.0×10^9/L or patient's known baseline, check ANC weekly for 4 weeks, then return to patient's last normal BEN range ANC monitoring interval, if appropriate
ANC < 0.5×10^9/L	**Severe neutropenia (general population)** Daily ANC until ANC ≥ 1.0×10^9/L, then three times weekly until ANC ≥ 1.5×10^9/L Recommend hematology consultation Interrupt treatment for suspected clozapine-induced neutropenia; no rechallenge unless benefits > risks If patient is rechallenged, resume treatment as a new patient under "normal range" monitoring once ANC ≥ 1.5×10^9/L	**BEN severe neutropenia** Daily ANC until ≥ 0.5×10^9/L, then thrice weekly until ANC ≥ patient's baseline Recommend hematology consultation Interrupt treatment for suspected clozapine-induced neutropenia. Do not rechallenge unless benefit > risk. If patient is rechallenged, resume treatment as a patient under normal range monitoring once ANC ≥1.0×10^9/L or at patient's baseline
Whenever clozapine is discontinued	Weekly for at least 4 weeks from day of discontinuation	Weekly for at least 4 weeks from day of discontinuation

ANC, absolute neutrophil count (10^9/L is equivalent to 10^3/mm^3); BEN, benign ethnic neutropenia.

must be individualized. Males and smokers tend to require higher doses to achieve the targeted blood level due to more rapid metabolism.

▶ *Acutely Psychotic and Agitated Patients*

Psychiatric emergencies occur in emergency departments, psychiatric units, medical facilities, and outpatient settings. Although nonpharmacologic interventions such as relaxation techniques and decreasing sensory stimulation are most ideal for initial management, acutely psychotic and agitated patients also require pharmacologic interventions. Short-acting, intramuscular (IM) formulations are available for a number of FGAs (haloperidol most frequently) as well as the SGAs (ziprasidone and olanzapine). IM benzodiazepines are commonly used in addition to IM antipsychotics. IM lorazepam is generally suggested as it is the only benzodiazepine with rapid and complete IM absorption. Concomitant IM olanzapine and benzodiazepines may cause cardiorespiratory depression and should be avoided if possible. Loxapine oral inhalation is also available for acute agitation but is restricted to a REMS program and to enrolled healthcare facilities with onsite equipment and personnel to handle bronchospasm.

▶ *Pregnancy and Lactation*

Women with schizophrenia have higher rates of unwanted pregnancies and obstetric complications (eg, stillbirth, infant death, preterm delivery, low infant birth weight, and infants who are small for gestational age). Prolactin-related effects secondary to certain FGA and SGA treatments have led to infertility in the past. Irregular menstruation also complicates the ability to plan for pregnancies and potential false protection with sexual activity. When pregnancy occurs, the management of pregnancy and lactation in females with schizophrenia should include a multidisciplinary team and the patient's family should be involved if possible. The decision to continue antipsychotic must be weighed by the risks and benefits. The fetus is at risk for antipsychotic side effects, but also the risk of relapse with schizophrenia during pregnancy is associated with a higher risk of birth complications. Guidelines suggest that antipsychotics are increasingly being used in pregnancy. Older data suggested teratogenic effects; however, larger and more recent epidemiologic studies find the majority of antipsychotics to be associated with no greater risk. Patients should still be cautioned that while the risk is low, congenital malformations have occurred rarely. There is now more published safety data with SGAs than FGAs. The safety data for FGAs is primarily for haloperidol. Low-potency phenothiazines may increase the risk of congenital abnormalities when used in the first trimester. There is some evidence to suggest a higher risk of congenital malformations with risperidone; however, this risk difference is only slightly higher at 5% versus 3% in the general population comparative group. If pregnancy occurs during antipsychotic treatment, continuation of previous antipsychotic is preferred to decrease relapse risk. Data suggest that mothers who are pregnant have about a twofold risk of developing gestational diabetes; thus, monitoring and promoting healthy eating is very important. Babies born to mothers taking SGAs may also have increased birth weights compared to nonexposed mothers.[35,38] A labeling change for antipsychotic medications has been implemented by the FDA to address the potential risk for EPS and symptoms of withdrawal in newborns whose mothers were treated with antipsychotics in the third trimester. Withdrawal symptoms may include agitation, abnormal muscle tone (increased or decreased), tremor, sleepiness, and difficulty in breathing or feeding, which may last for hours to days after delivery. In some newborns, specific treatment for withdrawal is not needed, whereas in others, longer hospital stays may be required.

Although SGAs are excreted in breast milk, most case reports document a low frequency of deleterious effects on the infant. Breast-feeding while on clozapine should be avoided.[35,38]

Pharmacokinetics and Drug Interactions

Most antipsychotics are, at least to some extent, metabolized by hepatic cytochrome P450 (CYP450) metabolic enzymes to water-soluble compounds that are excreted by the kidneys (Table 38–9).[39] Unlike other antipsychotics, ziprasidone is mostly metabolized by aldehyde oxidase, a metabolic system independent of the CYP450 system. Paliperidone, the 9-OH metabolite of risperidone, is mostly excreted unchanged in the urine, although up to one-third may be metabolized. The transmembrane energy-dependent efflux transporter P-glycoprotein may limit the ability of drugs to penetrate the blood–brain barrier and therefore impact pharmacologic activity in the brain. Antipsychotics currently known to use this pathway include perphenazine, haloperidol, fluphenazine, quetiapine, risperidone, paliperidone, aripiprazole, and olanzapine.[40]

Patient Encounter, Part 4

The patient's olanzapine dose was maintained at 10 mg once daily for the next 3 months. She returned again for follow-up with her outpatient psychiatrist who noted the patient's symptoms were responding very well. The patient also stated she was very pleased with her treatment, and the pseudoparkinsonism symptoms were resolved. She again brought up the idea of returning to school. She really wants to go back to school but is worried about her friends seeing her take medications for a mental illness and feels uncomfortable about it. Her mother is afraid that if she goes back to school, she may not take the olanzapine. The physician suggests that the patient consider getting "a shot" of olanzapine once a month, then she would not need to take a pill every day. The patient's mother readily agrees that this is a reasonable solution. The patient is initially reluctant to get "a shot" but finally agrees, as she also does not want to get into power struggles with her mother about whether or not she is taking her medication.

The patient receives the loading dose of olanzapine and moves back to school. She sees a provider at the school's health clinic to receive her monthly injection. She remains stable on the long-acting intramuscular form of olanzapine.

How would a clinician discuss the advantages of taking a long-acting intramuscular medication?

What dose of olanzapine long-acting injection (Zyprexa Relprevv) is appropriate for someone taking oral olanzapine 10 mg once daily?

What side effects can occur and what monitoring is required with olanzapine injection?

Table 38–9

Metabolism and Drug Interactions With Antipsychotics

Antipsychotic	Major Metabolic Pathways	Other Metabolic Pathways	Increase Antipsychotic Concentrations	Decrease Antipsychotic Concentrations
Aripiprazole	CYP3A4	CYP2D6	Fluvoxamine, ketoconazole	Carbamazepine
Asenapine	Glucuronidation by UGT1A4 and CYP1A2	CYP3A4, CYP2D6	Fluvoxamine	
Brexpiprazole	CYP3A4, 2D6		Itraconazole, clarithromycin, ketoconazole, quinidine, paroxetine, fluoxetine	Rifampin, St. John's wort
Cariprazine	CYP3A4	CYP2D6	Itraconazole, ketoconazole	Rifampin, carbamazepine (use not recommended with strong CYP3A4 inducer)
Chlorpromazine	CYP2D6	CYP1A2, CYP3A4		
Clozapine	CYP1A2	CYP3A4, CYP2D6, CYP2C19, CYP2C9	Fluvoxamine, ciprofloxacin, paroxetine	Cigarette smoking
Fluphenazine	CYP2D6		Paroxetine	
Haloperidol	CYP2D6, CYP3A4	CYP1A2	Fluvoxamine, fluoxetine, ketoconazole	Carbamazepine
Iloperidone	CYP2D6, CYP3A4	CYP1A2, CYP2E1	Ketoconazole, fluoxetine, paroxetine	
Loxapine	CYP1A2, CYP2D6, CYP3A4			
Lumateperone	CYP3A4, UGT 1A1, 1A4, and 2B15	AKR 1C1, 1B10, and 1C4 CYP2C8, CYP1A2	Moderate or strong CYP3A4 inhibitors, UGT inhibitors (valproic acid)	CYP3A4 inducers (carbamazepine)
Lurasidone	CYP3A4		Ketoconazole, diltiazem	Rifampin
Olanzapine	CYP1A2, glucuronidation by UGT1A4	CYP2D6	Fluvoxamine, ciprofloxacin, paroxetine	Cigarette smoking
Paliperidone	CYP2D6, CYP3A4 (in vitro, but limited role in vivo)		Divalproex sodium, paroxetine	Carbamazepine (via increased renal elimination)
Perphenazine	CYP2D6		Fluvoxamine, fluoxetine, paroxetine	
Pimozide	CYP3A4	CYP1A2, CYP2D6	Strong CYP2D6 inhibitors, CYP3A4 inhibitors	CYP3A4 inducers
Quetiapine	CYP3A4	CYP2D6	Fluvoxamine, ketoconazole	Carbamazepine
Risperidone	CYP2D6	CYP3A4	Fluoxetine, paroxetine	Carbamazepine
Thioridazine	CYP2D6	CYP2C19	Fluvoxamine	Cigarette smoking
Thiothixene	CYP1A2		CYP1A2 inhibitors	CYP1A2 inducers
Trifluoperazine	CYP1A2		CYP1A2 inhibitors	CYP1A2 inducers
Ziprasidone	Aldehyde oxidase	CYP1A2, CYP3A4	Fluvoxamine, ketoconazole	Carbamazepine

AKR, aldoketoreductase; CYP450, cytochrome P450 isoenzyme; UGT, uridine 5′-diphospho-glucuronosyltransferase.

Additive side effects may occur with combined drug therapies, and a few clinically significant drug interactions are notable (see Table 38–9). Cigarette smoking decreases serum concentrations of clozapine and olanzapine by induction of CYP1A2. Although antipsychotics are highly protein bound, protein-binding interactions are generally not clinically significant. Absorption of most antipsychotics is not affected by food, with the exception of lumateperone, lurasidone, and ziprasidone. The mean maximum concentration of lurasidone increases threefold when administered with food, and ziprasidone's absorption is increased by 60% to 70% when given with meals. Ingesting a high-fat meal with lumateperone increases the mean area under the curve (AUC) by 9%. Caloric intake of 500 calories (2100 J) is recommended with ziprasidone and 350 calories (1500 J) with lurasidone.

Among SGAs, ziprasidone, iloperidone, and quetiapine have potential to prolong the QTc interval. Using them with other agents that prolong the QTc interval should be undertaken with caution. These other agents include, but are not limited to, quinidine, sotalol, chlorpromazine, droperidol, mesoridazine, pimozide, thioridazine, mefloquine, moxifloxacin, and pentamidine. Combining higher doses of ziprasidone, iloperidone, or quetiapine with ketoconazole or erythromycin should be undertaken cautiously.

Added pharmacodynamic effects are possible when combining antipsychotics with other drugs that can cause sedation, hypotension, anticholinergic symptoms, and weight gain or metabolic abnormalities.

Adjunct Treatments

The judicious use of pharmacologic therapies other than antipsychotics is often necessary for the treatment of motor side effects, anxiety, depression, mood elevation, and TRS that does not respond to clozapine. Anticholinergic medications (eg, benztropine, 1–2 mg twice daily; trihexyphenidyl, 1–3 mg thrice daily; and diphenhydramine, 25–50 mg twice daily) are used to treat EPS. They may be prescribed prophylactically with high-D_2-binding agents or in patients at risk for EPS or for treatment of EPS. β-Blockers (eg, propranolol 30–120 mg/day) are sometimes effective for patients who develop akathisia. In some situations, such as on an inpatient unit, the concomitant use of benzodiazepines (eg, lorazepam 1–3 mg/day) with the SGAs may be necessary for agitation.[28]

More recent guidelines suggest that regular assessment of depressive symptoms in schizophrenia is important and that waiting for the effect of antipsychotics to work instead of immediately adding an antidepressant is recommended. Evidence suggests that SGAs may be more effective than FGAs for depressive symptoms in people with schizophrenia; however, this evidence is limited.[35] Antidepressants may be useful for patients with schizophrenia who have depressive symptoms in the stable phase of schizophrenia; however, these agents may have the potential to worsen symptoms in the acute phase.[35] Because suicide risk may be increased, aggressive treatment may be necessary when depression is present. The selective serotonin reuptake inhibitors (SSRIs) are the preferred agents, but many (eg, fluoxetine, fluvoxamine, paroxetine, sertraline) may inhibit the CYP450 enzymes, thus potentially raising plasma concentrations of many antipsychotics. Mood stabilizers, such as lithium and the anticonvulsants, have been used adjunctively with the antipsychotics to treat the affective component of schizoaffective disorder.[35] One antipsychotic, olanzapine, is marketed in combination with fluoxetine for bipolar disorder. For patients with an inadequate response to clozapine, limited treatment options are available for these patients. A number of augmentation strategies have been tried, including FGAs, SGAs, mood stabilizers (eg, lithium, valproate, and topiramate), minocycline, antidepressants, transcranial magnetic stimulation (TMS), and electroconvulsive therapy (ECT). Though controlled trial results are mixed, some data support the adjunctive use of risperidone, lamotrigine, or aripiprazole in clozapine-treated patients.[29]

Patient Education

KEY CONCEPT Education of the patient and family regarding the benefits and risks of antipsychotic medications and the importance of treatment adherence must be ongoing and integrated into pharmacologic management. Medication management discussions offer an opportunity to provide illness and treatment education including the nature and course of schizophrenia and can serve as a time to hear the patient's life goals. Key considerations include:

- Involve families in the education and treatment plans because family psychoeducation may decrease relapse, improve symptomatology, and enhance psychosocial and family outcomes.[14]
- Be clear that there is no cure for schizophrenia and that medications can be effective in improving many symptoms.
- Explain common and rare but dangerous side effects.
- Stress the importance of medication and treatment adherence for improving long-term outcomes.
- Decision making on the best course of treatment should be a shared process. Shared decision making is a process where clinicians and patients work together to make treatment decisions based on clinical evidence. This process incorporates patient's preference and values as well as risks and expected outcomes.

Patient Encounter, Part 5

The patient remained on olanzapine long-acting injection for several years and graduated from college, but eventually her paranoia returned and she felt agitated on the drug. Over the next several years, she was switched to various other agents including ziprasidone, aripiprazole, and asenapine, to which she only had a partial response. At her most recent outpatient appointment, the doctor suggested that she might benefit from a trial of clozapine, but the patient was not sure if clozapine was right for her. In a separate phone call to her mother, the doctor reviewed the pros and cons of the clozapine trial. The patient and her mother discussed everything they discussed with the doctor and agreed to a trial of clozapine.

Why is the clinician considering a clozapine trial?

What are the rare serious side effects of clozapine versus the common manageable side effects?

The patient smokes cigarettes. How will cigarette smoking affect clozapine therapy?

OUTCOME EVALUATION

Developing a good working alliance with the patient is essential. In the absence of a solid therapeutic relationship, patients are frequently reluctant to share their beliefs, personal experiences, and life goals.

Symptom Monitoring

Many assessments are available to objectively rate positive and negative symptoms, level of function, and life satisfaction. The most commonly used scales in clinical trials to measure symptoms include:

- Positive and Negative Symptom Scale (PANSS)
- Brief Psychiatric Rating Scale (BPRS)
- Clinical Global Impression (CGI) Scale
- Calgary Depression Scale for Schizophrenia (CDSS)

Using these scales on a regular basis, particularly when switching medications or changing doses, is a more reliable means of monitoring symptoms. Symptom assessments cannot capture the full range of possible improvements, but they can be useful in deciding whether a medication is having substantial benefit.

Side Effect Monitoring

KEY CONCEPT Regularly monitor for side effects and overall health status.[8,27,31] Perform orthostatic blood pressure measurements and vital sign assessments before initiating antipsychotics and regularly throughout treatment. Ask about prolactin-related side effects such as impaired menstruation, libido, and sexual performance regularly. At baseline, check body weight and height (to calculate body mass index [BMI]), screen for diabetes risk factors, and measure fasting glucose and lipid profile. BMI should be assessed at every visit for 6 months, and least quarterly thereafter. Lipid profile and either fasting glucose or hemoglobin A_{1C} should be monitored at 4 months after initiating and at least annually thereafter. For patients at higher risk of developing diabetes and those who gain weight, check body weight more often. Every effort should be made to help with weight and metabolic side effects.[6,41-43] Metformin may be an option in addition to nonpharmacologic techniques for weight loss or attenuation of weight gain.[44]

Additionally, perform baseline electrocardiography for patients with preexisting cardiovascular disease or risk for arrhythmia. With clozapine therapy, there is a risk for the development of severe neutropenia, which is greatest in the first 6 months of treatment. Required monitoring of absolute neutrophil count (ANC) is described in Table 38–8. Separate monitoring guidelines now

Patient Care Process

Collect Information:

- Chief complaint and history of present illness.
- Family history, psychiatric history (age when first diagnosed, time of first hospitalization for mental illness), medical history. Obtain collateral information from family, past medical records, and other providers to help clarify the psychiatric history.
- Social history (housing arrangements, social and vocational goals, support systems, employment, substance use history).
- Physical examination.
- Key laboratory data and imaging studies.
- Mental status examination.
- Past and current medications (psychiatric and somatic, prescription, nonprescription, herbal or other dietary supplements).

Assess the Information:

- Review the patient's chief complaint, presenting symptoms, and history, including psychiatric history. Assess mental status examination for organization of thoughts and range of affect, presence of mood disturbance, likelihood of harm to self or others, and presence of hallucination, paranoia and/or delusions of control, evaluate judgment and insight.
- Assess medical records, including laboratory and imaging studies, to rule out medical causes of psychosis.
- Assess current treatments and outcomes of prior treatments for effectiveness and safety.
- Assess adherence to medications and willingness to take medications.

Develop a Care Plan:

- Identify medication-related problems.
- Determine the goals of therapy.
- Select or optimize the dose of an antipsychotic based on the side effect profile that is most appropriate and acceptable to the patient.
- Collaborate with other healthcare professionals or caregivers in the development of the plan.
- Consider how income, insurance coverage, and access to care might influence pharmacotherapy choice.

Implement the Care Plan:

- Initiate, modify, discontinue, or administer the appropriate medication therapy.
- Educate patient and caregiver (with patient consent) about the illness, medication treatments, possible side effects, and goals of treatment.
- Discuss medication adherence and healthy lifestyle goals, including substance and cigarette use.
- Enlist adjunctive treatments, including psychosocial therapies to optimize outcomes.
- Coordinate referrals or transition of care to other healthcare professionals, such as social workers, home care nurses, or other medical specialists.
- Recommend placement of individuals in ACT, group homes, transitional housing, rehabilitation, or long-term care.
- Schedule follow-up appointments.

Follow-up: Monitor and Evaluate:

- Monitor medication therapy for effectiveness, using psychiatric rating scales when necessary.
- Monitor medication therapy for adverse events of antipsychotics using the AIMS, Simpson–Angus Scale, and Extrapyramidal Symptom Rating Scale.
- Monitor appropriate laboratory measures to prevent or minimize adverse effects, including metabolic abnormalities.
- Assess for emergence of new target symptoms.
- Monitor for adherence to the medication regimen.
- Optimize dosing and consider clozapine if criteria are met for treatment resistance.

exist for general patients and those with benign ethnic neutropenia. Overall, encourage patients to have annual physical, gynecologic, and ophthalmologic examinations and regularly ask about physical health and side effects at each visit.

Commonly used rating scales to monitor for EPS include the Simpson–Angus Scale (SAS) and the Extrapyramidal Symptom Rating Scale (ESRS). Akathisia is commonly monitored by the Barnes Akathisia Scale (BAS). The emergence of dyskinesias could represent the emergence of TD. Monitor patients on SGAs for TD at least annually and patients taking FGAs at each visit. The most commonly used instrument to measure these symptoms is the Abnormal Involuntary Movement Scale (AIMS).

Abbreviations Introduced in This Chapter

5-HT	Serotonin
ACT	Assertive Community Treatment
AIMS	Abnormal Involuntary Movement Scale
ANC	Absolute neutrophil count
APA	American Psychiatric Association
BAS	Barnes Akathisia Scale
BPRS	Brief Psychiatric Rating Scale
CATIE	Clinical Antipsychotics Trials of Intervention Effectiveness
CBT	Cognitive behavioral therapy
CGI	Clinical Global Impression Scale
CR	Cognitive remediation
CYP450	Cytochrome P450 isoenzyme
D	Dopamine
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition
ECT	Electroconvulsive therapy
EPS	Extrapyramidal symptoms
ESRS	Extrapyramidal Symptom Rating Scale
FDA	Food and Drug Administration
FGA	First-generation antipsychotic
H	Histamine

IM	Intramuscular
LAI	Long-acting injection
M	Muscarinic
NMDA	*N*-methyl-D-aspartate
NMS	Neuroleptic malignant syndrome
PANSS	Positive and Negative Symptom Scale
PCP	Phencyclidine
PORT	Schizophrenia Patient Outcomes Research Team
QTc	Corrected QT interval
SAS	Simpson–Angus Scale
SGA	Second-generation antipsychotic
SSRI	Selective serotonin reuptake inhibitor
SST	Social skills training
TD	Tardive dyskinesia
TIMA	Texas Implementation of Medication Algorithms
TMS	Transcranial magnetic stimulation
TRS	Treatment-resistant schizophrenia
WBC	White blood cell

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39

Major Depressive Disorder

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the etiology and pathophysiology of major depressive disorder (MDD).
2. Identify the signs and symptoms of MDD.
3. Outline the treatment goals for a patient with MDD.
4. Recommend pharmacotherapy given a specific patient with MDD.
5. Develop a monitoring plan for a specific patient with MDD that includes the assessment of efficacy as well as adverse effects.
6. Predict, prevent, identify, and resolve potential drug-related problems.
7. Educate patients and caregivers on the proper use of antidepressant therapy.

INTRODUCTION

Major depression is a common, seriously disabling disorder nonresponsive to volitional efforts to feel better. Individuals with major depressive disorder (MDD) experience pervasive symptoms affecting mood, thinking, physical health, work, and relationships. Inadequately treated MDD increases the risk of suicide.[1]

Although antidepressants and agents used adjunctively in depression account for 16 of the top 200 prescription drugs dispensed in the United States, inadequate treatment remains a serious concern.[2,3]

Patient Encounter Part 1

A 35-year-old man presents to the psychiatry clinic with his brother. He complains of increased sleep and increased appetite although he still feels fatigued when he wakes up. He states that he has gained 12 lb (5.4 kg) in the last month. With prompting from his brother, he admits that he has lost interest in hunting, which is his favorite activity, especially now that it is deer hunting season. He has been going through a difficult divorce, and his wife has custody of his two children. He has been having difficulty waking up to go to work in the morning. He states that he has thoughts about driving his car across the interstate into oncoming traffic, but he would not do that because it is against his religion.

What symptoms of MDD does the patient have?

What medical or psychiatric issues could be contributing to the symptoms?

What additional information do you need to know before creating a treatment plan for this patient?

EPIDEMIOLOGY AND ETIOLOGY

At least 17.3 million adults over the age of 18 experience at least one episode of depression, and 8.1% of individuals over 20 years of age in the United States experienced depression in any given 2-week period.[4] Women are twice as likely to experience MDD.[4,5] According to the World Health Organization (WHO), depression is the leading cause of disability worldwide and a major contributor to the overall global burden of disease.[6]

PATHOPHYSIOLOGY

The cause of MDD is probably multifactorial. Multiple theories abound, and practitioners suggest that development of depression likely involves a complex interaction of genetic predisposition, psychological stressors, and underlying pathophysiology. There are no currently accepted unifying theories to adequately explain the pathophysiology of depression.[7]

Genetics

First-degree relatives of MDD patients are about two to four times more likely to develop MDD compared with controls.[5] Twin studies also suggest that MDD is due to genetic influences.[8] Major depression has been associated with four different genes including polymorphisms in the glucocorticoid receptor gene *NR3C1*, the monoamine oxidase A gene, the gene for glycogen synthase kinase-3β, and a group-2 metabotropic glutamate receptor gene (*GRM3*).[9]

Stress

There is an association between stress and depression, especially if a genetic predisposition exists. However, major life stressors do not always cause depression. Although acute stressors may precipitate depression, chronic stressors cause longer episodes and are more likely to lead to relapse and recurrence.[10]

Biogenic Amine and Receptor Hypotheses

KEY CONCEPT The primary hypothesis is the biogenic amine hypothesis which states that a deficit of norepinephrine (NE), dopamine (DA), or serotonin (5-HT) at the synapse is the cause of depression.[7] The fact that existing antidepressants increase synaptic monoamine concentrations supports this hypothesis (see Pharmacologic Therapy). One argument against this hypothesis is that patients with depression do not always have decreased monoamine levels. Additionally, monoamine levels are altered within hours of initiating antidepressant therapy, but response (usually defined as 50% reduction of symptoms) is delayed by 2 to 4 weeks or more.[7]

The receptor hypothesis suggests that depression is related to upregulation of monoamine neurotransmitter receptors in response to a depletion of monoamine neurotransmitters. In this hypothesis, chronic administration of antidepressants alters receptor sensitivity causing desensitization or downregulation of monoamine neurotransmitter receptors leading to therapeutic response.[7] Importantly, the time required for changes in receptor sensitivity correlates with antidepressant onset.[7] These hypotheses are oversimplifications of the pathophysiology of depression. MDD probably involves a complex dysregulation of monoamine systems that affect and are modulated by other neurobiological systems.

Other Neurobiological Hypotheses

At least three categories of peripheral hormones are associated with the pathophysiology of depression. They include (a) neurotrophic and other growth factors including brain-derived neurotrophic factor (BDNF); (b) the hypothalamic pituitary axis (HPA); and (c) proinflammatory cytokines including interleukin-1β, interleukin-6, and tumor necrosis factor-α.[11]

Proinflammatory cytokines are increased in individuals with MDD, and antidepressants suppress the synthesis of these cytokines.[11] HPA regulation is impaired in depression, and antidepressants can attenuate the neuroendocrine response.[11] Similarly, BDNF is decreased in patients with MDD, and antidepressants reverse this response.[11]

CLINICAL PRESENTATION AND DIAGNOSIS

The diagnosis of a major depressive episode (MDE) requires the presence of five symptoms for a minimum of 2 weeks that cause clinically significant distress or impairment.[5] The diagnosis of MDD is based on the presence of one or more MDEs during a person's lifetime (Table 39–1).[5]

Differential Diagnosis and Comorbidities

MDEs also occur in bipolar disorder. Individuals with bipolar disorder also experience hypomanic, manic, or mixed episodes (see Chapter 40) during the course of their illness, but individuals with MDD do not.[5]

Conditions that may coexist with MDD include anxiety, eating, personality, and substance use disorders.[5] Several chronic medical conditions including diabetes and coronary artery disease also have strong correlations with MDD.[12] Other medical disorders associated with depression are listed in Table 39–2. Identification and treatment of MDD in patients with chronic medical conditions is important. Inadequate recognition and undertreatment of depression may increase the mortality associated with these medical disorders.[12,13] Medications associated with depression are listed in Table 39–2.[14,15]

Other depressive disorders in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-5*) include persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, and disruptive mood dysregulation disorder.[5]

Table 39–1

Clinical Presentation of Depression: Diagnostic Criteria for Major Depressive Episode[5]

At least five of the following symptoms have been present during the same 2-week period and represent a change from previous functioning.

- Depressed mood[a]
- Markedly diminished interest or pleasure in usual activities[a]
- Increase or decrease in appetite or weight
- Increase or decrease in amount of sleep
- Increase or decrease in psychomotor activity (ie, agitation or retardation)
- Fatigue or loss of energy
- Feelings of worthlessness or guilt
- Diminished ability to think, concentrate, or make decisions
- Recurrent thoughts of death, suicidal ideation, or suicide attempt

The symptoms cause clinically significant distress or impairment in functioning.

The symptoms are not due to the direct physiologic effects of a substance or medical condition.

[a]One of these two symptoms must be present.

Data from American Psychiatric Association. Major Depressive Disorders. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatric Association; 2013:160–168.

COURSE AND PROGNOSIS

MDD may affect an individual at any age including children and elderly, although, the incidence peaks between 20 and 30 years of age in the United States.[5] Some individuals will experience only one

Table 39–2

Medical Conditions and Medications Associated with Depression[5,12-15]

Medical disorders	Medications
Hypothyroidism	CNS depressants (alcohol, benzodiazepines, opioids)
Cancer	Corticosteroids
Anemia	Contraceptives
Infections	Phenobarbital
Electrolyte disturbances	Brivaracetam
Folate deficiency	Levetiracetam
Neurologic disorders	Perampanel
Cardiovascular disease	Tiagabine
Respiratory disease	Topiramate
	Vigabatrin
	Gonadotropin-releasing hormone agonists
	Interferon α
	Interleukin 2
	Varenicline
	Mefloquine
	Isotretinoin
	Propranolol
	Clonidine
	Methyldopa
	Reserpine

CNS, central nervous system.

episode of depression, others will experience distinct episodes with few or no symptoms between, while others will rarely experience remission. The course of MDD varies markedly between patients.[5] **KEY CONCEPT** It is not uncommon for a patient to experience only a single MDE, but many patients with MDD experience multiple episodes. The longer an individual is in remission, the lower their risk of recurrence. Individuals with longer symptom duration, psychotic features, prominent anxiety, and severe symptoms predict lower recovery rates.[5] The risk of recurrence increases in individuals with persistent mild depressive symptoms, severe episodes, younger age, and in those with a history of previous episodes.[5,16] Individuals who have experienced one episode of depression have a 60% chance of recurrence, and those with a second episode of depression have a 70% chance of recurrence, while those with a third episode of depression have a 90% risk of recurrence and should continue antidepressant treatment indefinitely.[16] The presence of residual symptoms such as sleep or appetite disturbances after achieving remission increases the likelihood of relapse.[17]

MDD is a risk factor for suicide.[18] The WHO estimates that nearly 800,000 people die from suicide every year, and suicide is the second leading cause of death among 15- to 29-year-olds.[6]

TREATMENT

Desired Outcomes

The goal of therapy for patients with MDD is resolution of depressive symptoms, return to euthymia, and prevention of relapse and recurrence of symptoms.[18] **KEY CONCEPT** One extremely important goal is prevention of suicide and suicide attempts.

Nonpharmacologic Therapy

Evidence supports the efficacy of interpersonal and cognitive-behavioral therapy in the treatment of MDD. Psychotherapy alone is an initial treatment option for mild-to-moderate depression and may be useful when combined with pharmacotherapy for the treatment of severe depression.[18] This combination can be more effective than either treatment alone in severe or recurrent MDD.[18]

Electroconvulsive therapy (ECT) is a highly efficacious and safe treatment alternative for MDD. The response rate is about 80%, and it exceeds 50% for patients who have failed pharmacotherapy.[18] ECT may be beneficial for MDD that is complicated with psychotic features, severe suicidality, refusal to eat, pregnancy, or contraindication or nonresponse to pharmacotherapy.[18] Typically, 6 to 12 treatments are necessary with response occurring in 10 to 14 days.[18] Antidepressants are typically started or continued when initiating ECT, and when ECT is discontinued, antidepressants help maintain response.[18] In addition, some patients will receive maintenance ECT with/without antidepressants. Side effects after ECT include temporary confusion and retrograde and anterograde amnesia.[18]

Light therapy may be an effective treatment for mild-to-moderate depression associated with seasonal (eg, winter) exacerbations.[19] Light therapy involves using light intensity of 10,000 lux for 30 minutes daily for up to 6 weeks.[20,21] The mechanism of action of light therapy is thought to be readjustment of circadian rhythms.[20,21] Light therapy is well tolerated, and adverse effects can include eye strain, headache, nausea, and sedation.[20,21]

Vagus nerve stimulation (VNS) was approved by the Food and Drug Administration (FDA) in 2005 for treatment-resistant depression.[18] A pulse generator is surgically implanted around the vagal nerve that sends signals to the brain that may help relieve depressive symptoms.[22] Adverse effects of VNS include alterations in patients' voice, hoarseness, dyspnea, and neck pain.[18]

Transcranial magnetic stimulation is a noninvasive, well-tolerated procedure that is FDA approved for use after one failed trial of an antidepressant.[18]

Physical exercise is effective for mild-to-moderate depression.[20,21] The mechanism of action is thought to involve reduction of cortisol and increase in neurotransmitters including BDNF.[20,21] Both aerobic and nonaerobic exercises have been shown to be beneficial for reducing depression.[20,21] At least 30 minutes of supervised, moderate-intensity exercise, 3 days weekly, for at least 9 weeks has been proven effective.[20,21] Physical exercise is well tolerated with rare instances of adverse effects.[20,21]

Patient Encounter Part 2

PMH: History of diabetes, rheumatoid arthritis, hypertension, hypertriglyceridemia, gastric reflux

Past Psychiatric History: He was diagnosed with MDD when he was 16 and has had two previous psychiatric hospitalizations with the last being 6 months ago.

Past Psychiatric Medication Trials: Paroxetine (current), fluoxetine, sertraline, amitriptyline, alprazolam, and trazodone.

FH: Mother had diabetes mellitus and MDD, died at age 60; father had a history of alcoholism and died at age 58; brother has a history of alcohol use disorder.

SH: High school diploma. Works as an auto mechanic at Jiffy Lube franchise but is at risk of losing his job due to difficulty getting to work. Drinks a couple of beers at night and admits to drinking a 12 pack of beer on weekends. Currently going through a divorce. Has two children ages 8 and 10, but he does not have custody. Smokes 1.5 packs of cigarettes per day.

Current Meds:

- Paroxetine 50 mg by mouth once daily
- Metoprolol succinate 50 mg by mouth once daily
- Omeprazole 40 mg by mouth once daily
- Prednisone 20 mg by mouth once daily
- Metformin 1000 mg by mouth twice daily with meals
- Fish oil capsules by mouth once daily

ROS: Increased sleep; increased appetite; weight gain; fatigue

PE:

VS: Ht 5′11″ (180 cm), Wt 251 lb (114 kg), weight gain of 12 lb (5.4 kg) over past 4 weeks

MSE: Lack of interest/pleasure, increased sleep, increased appetite, fatigue, positive suicidal ideation with plan

Labs: Within normal limits. Urine drug screen—negative

Given this additional information, what is your assessment of the patient's condition?

Does the patient have risk factors for depression?

Identify treatment goals for the patient.

What nonpharmacologic and pharmacologic alternatives are available for this patient?

Table 39–3

Primary Pharmacologic Actions[a] of Antidepressants[7,11,30]

Action	MAOI	TCA	SSRI	Bup	SNRI	Esket	Brex	Vilaz	Traz	Nefaz	Mirtaz	Vorti
Monoamine oxidase inhibition	X											
Serotonin reuptake inhibition		X	X		X			X	X	X		X
Norepinephrine reuptake inhibition		X		X	X							
Dopamine reuptake inhibition				X								
α_2-Adrenergic receptor blockade											X	
GABA-A receptor modulator							X					
NMDA receptor blockade						X						
Serotonin$_{1A}$ receptor agonist												X
Serotonin$_{1A}$ receptor partial agonist								X				
Serotonin$_{1B}$ receptor partial agonist												X
Serotonin$_{2A}$ receptor blockade									X	X	X	
Serotonin$_{2C}$ receptor blockade									X	X	X	
Serotonin$_3$ receptor blockade											X	X
Serotonin$_7$ receptor blockade												X
α_1-Adrenergic receptor blockade		X							X	X		
Histamine-1 receptor blockade		X							X		X	
Muscarinic cholinergic receptor blockade		X										

[a]See text for discussion of secondary pharmacologic actions.

Brex, brexanolone; Bup, bupropion; Esket, esketamine; MAOI, monoamine oxidase inhibitor; Mirtaz, mirtazapine; Nefaz, nefazodone; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; Traz, trazodone; Vilaz, vilazodone; Vorti, vortioxetine.

Pharmacologic Therapy

Individual antidepressants, even those within the same class, have important pharmacologic differences (Tables 39–3 and 39–4).[7,23] Treatment guidelines categorize antidepressants by mechanism of action, chemical structure, or whether the medication is an "older antidepressant" that includes monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs).

► *Selective Serotonin Reuptake Inhibitors*

Selective serotonin reuptake inhibitors (SSRIs) inhibit postsynaptic reuptake of serotonin resulting in increased serotonin in the synaptic cleft.[7] Each SSRI has a unique pharmacologic profile.[7] For example, paroxetine has mild anticholinergic effects; citalopram has mild antihistaminic effects; and fluoxetine antagonizes the 5-HT$_{2C}$ receptor which may contribute to its antibulimic effects.[7]

Table 39–4

Efficacy and Adverse Effect Profile Based on Pharmacology[7,9]

Pharmacologic Action	Result
SRI	Antidepressant and antianxiety efficacy (via interaction of 5-HT at 5-HT$_{1A}$ receptors) Anxiety, insomnia, sexual dysfunction (via interaction of 5-HT at 5-HT$_{2A}$ receptors) Anxiety, anorexia (via interaction of 5-HT$_{2C}$ receptors) Nausea, GI problems (via interaction of 5-HT at 5-HT$_3$ receptors)
NRI	Antidepressant efficacy Tremor, tachycardia, sweating, jitteriness, increased blood pressure
Dopamine reuptake inhibition	Antidepressant efficacy, euphoria, psychomotor activation, aggravation of psychosis
α_2-Adrenergic receptor blockade	Increase in serotonergic and noradrenergic activity—see actions of SRI and NRI above
Serotonin$_{1A}$ receptor agonist	Antianxiety, antidepressant augmentation, decreased blood pressure
Serotonin$_{1A}$ partial agonism	Antianxiety, antidepressant augmentation, decreased blood pressure, decreased heart rate
Serotonin$_{2A}$ receptor blockade	Antianxiety efficacy Increased REM sleep; decreased sexual dysfunction
Serotonin$_{2C}$ receptor blockade	Antianxiety efficacy Increased appetite or weight gain
Serotonin$_3$ receptor blockade	Antiemetic, decreased GI problems
Serotonin$_7$ receptor blockade	Antidepressant, modulates glutamate
α_1-Adrenergic receptor blockade	Orthostatic hypotension, dizziness, reflex tachycardia
Histamine-1 receptor blockade	Sedation, weight gain
Muscarinic cholinergic receptor blockade	Dry mouth, blurred vision, constipation, urinary hesitancy, sinus tachycardia, memory problems

GI, gastrointestinal; 5-HT, serotonin; NRI, norepinephrine reuptake inhibition; REM, rapid eye movement; SRI, serotonin reuptake inhibition.

Serotonin Norepinephrine Reuptake Inhibitors

Venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran are 5-HT and NE reuptake inhibitors (SNRIs). Compared with venlafaxine and desvenlafaxine, which have primarily serotonin reuptake inhibitor (SRI) activity and dose-related affinity for norepinephrine reuptake inhibition (NRI), duloxetine has more balanced SRI and NRI activities.[7] Levomilnacipran has higher activity at NRI than SRI.[7]

Norepinephrine Dopamine Reuptake Inhibitor

Bupropion is a NE and DA reuptake inhibitor (NDRI).[7] Bupropion's effects on NRI and dopamine reuptake inhibition (DRI) are weak, but it is an efficacious antidepressant.[7] Bupropion is generally activating and may be especially useful at improving energy, alertness, as well as other symptoms of depression.[7]

Serotonin Antagonist and Reuptake Inhibitors

Nefazodone and trazodone are 5-HT antagonists (SARIs).[7] Their SRI activity is not as pronounced as that of the SSRIs, but they potently block 5-HT_{2A} receptors, which allow more 5-HT to interact at postsynaptic 5-HT_{1A} sites.[7] In addition, trazodone blocks histaminergic and α-adrenergic receptors, and nefazodone possesses weak NRI and α-adrenergic blocking properties.[7]

Other Newer Antidepressants

Finally, mirtazapine is a **noradrenergic** and specific serotonergic antidepressant (NaSSA).[7] It blocks presynaptic **α_2 autoreceptors** on noradrenergic neurons and **α_2 heteroreceptors** on serotonergic neurons, resulting in increases in NE and 5-HT synaptic concentrations.[7] Mirtazapine also blocks postsynaptic serotonergic receptors and histamine-1 receptors at lower doses inducing sleep and weight gain.[7] At higher doses, histaminic activity is offset by noradrenergic activity that reduces its effects on sleep and weight gain.[7,24]

Vilazodone is best characterized pharmacologically as a SRI and a partial agonist at 5-HT_{1A} receptors.[7] The 5-HT_{1A} effect is thought to reduce negative feedback on endogenous serotonin receptors which may improve the medication's antidepressant effect.[7]

Vortioxetine is an agonist/antagonist/partial agonist at various 5-HT receptors.[25] Vortioxetine has affinity for β-adrenergic receptors which may be associated with side effects, and histaminic and acetylcholine receptors which may have a positive effect on memory.[25]

Esketamine acts by nonselective and noncompetitive inhibition at the *N*-methyl-D-aspartate (NMDA) receptor to decrease the effects of glutamate which can be elevated by stress.[26] Brexanolone provides positive allosteric modulation of γ-aminobutyric acid (GABA) receptors which restores progesterone levels in the postpartum period.[27]

Monoamine Oxidase Inhibitors

MAOIs inhibit the enzyme responsible for the breakdown of 5-HT, NE, and DA.[7] There are two main forms of the MAO enzyme—MAO-A and MAO-B.[7] MAO-A and MAO-B are both located in the brain, and MAO-A is also present in the gut. MAO-A is responsible for the breakdown of 5-HT, DA, NE, and tyramine.[7] MAO-B is responsible for the breakdown of dopamine, phenylethylamine, and tyramine.[7] Dietary restrictions limiting the consumption of tyramine are necessary for orally available MAOIs due to inhibition of MAO-A in the gut.[7] Dietary restrictions are not required for the transdermal formulation of selegiline at the starting dose of 6 mg/24 hours.[7]

Tricyclic Antidepressants

The TCAs possess both SRI and NRI properties, but they also block other receptors, including α_1-adrenergic, histamine-1, and muscarinic cholinergic receptors, which contribute to side effects.[7]

Complementary and Alternative Treatments

The most recent Canadian Network for Mood and Anxiety Treatments (CANMAT) Guidelines and the American Psychiatric Association (APA) Task Force on Complementary and Alternative Medicine (CAM) offer recommendations on how CAM treatments should be used for treatment of depression.[20,21] From those recommendations, there is sufficient evidence to recommend several complementary treatments either as first- or second-line therapies. These include bright light therapy, exercise, St. John's wort, and omega-3 fatty acids as monotherapies for mild-to-moderate depression or adjunctive therapies for moderate-to-severe depression.

St. John's wort (*Hypericum perforatum*) is a herbal medication that has shown efficacy in mild-to-moderate depression and efficacy as an adjunctive therapy for moderate-to-severe depression.[20] It has mild MAO-inhibiting properties.[20] Many patients believe that herbal medications are devoid of adverse effects and drug interactions; however, St. John's wort can cause gastrointestinal (GI) irritation, headache, skin irritation, photosensitivity, and dry mouth.[20] It also triggers drug interactions through induction of CYP3A4 enzymes and P-glycoprotein.[18] St. John's wort should be used cautiously when combined with standard antidepressant medications due to risk of potential drug interactions and serotonin syndrome.[20]

S-adenosyl methionine (SAM-e), a naturally occurring compound in the body, tends to be lower in people with major depression.[20] The proposed mechanism of action involves its effects on the monoaminergic system. It is sold as a nutritional supplement and lacks the standardization of FDA-approved medications. The dose range is typically between 800 and 1600 mg/day, divided into three doses that are given with meals. The most common adverse effects with SAM-e include GI upset, insomnia, headache, anxiety, tachycardia, and fatigue.[20]

Low doses of omega-3 fatty acids (eicosapentaenoic [EPA], docosahexaenoic [DHA] acid, or both) have been used adjunctively for depression.[28] The usual dose is 3 to 9 g of EPA in addition to 1 to 2 g of DHA daily.[20] Omega-3 fatty acids are usually well tolerated. Adverse effects include nausea, diarrhea, and an aftertaste.[20,28]

Adverse Effects

The adverse effects of the antidepressants are often a function of their underlying pharmacologic profiles (see Table 39–4).

The adverse effect profile of the SSRIs includes sexual dysfunction, central nervous system (CNS) stimulation (eg, nervousness, insomnia), nausea, diarrhea, weight gain, anhedonia, and fatigue.[23] Nausea, anxiety, headache, and fatigue are often transient and improve with time.[7] **KEY CONCEPT** Sexual dysfunction, common and challenging to manage, may lead to nonadherence.[29] Various strategies to manage antidepressant-induced sexual dysfunction include waiting for symptoms to subside, reducing the dosage, permitting "drug holidays," prescribing adjunctive therapy, and switching antidepressants.[18,29] Some patients report an improvement in sexual functioning as a result of improvement in depressive symptoms.[30] Reducing the dose and drug holidays may weaken the antidepressant effects.[29] Clinicians often prescribe adjunctive therapy such as bupropion, cyproheptadine, and sildenafil or simply switch to antidepressants with less likelihood

Table 39–5

Relative Incidence of Adverse Effects of Newer Antidepressants[7,9,30]

Drug	Sedation	Activation	Weight Gain	Weight Loss	GI Upset	Sexual Dysfunction
Brexanolone	++++	+	+	+	+	+
Bupropion	+	++++	+	++	+++	+
Citalopram	+	+	+	+	++++	++++
Desvenlafaxine	++	+++	+	+	++++	++++
Duloxetine	+	+++	+	+	+++	++++
Escitalopram	+	++	+	+	++	++++
Esketamine	++++	+	+	+	+++	+
Fluoxetine	+	++++	+	+	++++	++++
Fluvoxamine	++	++	+	+	++++	++++
Levomilnacipran	+	+++	+	+	++	+
Mirtazapine	+++	+	++	+	+	+
Nefazodone	++	+	+	+	++	+
Paroxetine	++	++	+	+	++++	++++
Sertraline	+	+++	+	+	++++	++++
Venlafaxine	++	+++	+	+	++++	++++
Vilazodone	+	+	+	+	++++	++
Vortioxetine	+	+	+	+	++++	+

+, minimal; ++, low; +++, moderate; ++++, high; GI, gastrointestinal.

of causing these effects, such as bupropion, mirtazapine, nefazodone, or vortioxetine.[29]

Bupropion causes insomnia, nightmares, decreased appetite, anxiety, and tremors, but the most concerning adverse effect is seizures.[18,23] Because of the risk for seizures, patients with a CNS lesion, history of seizure disorder, head trauma, anorexia, or bulimia should not receive bupropion.[18,30] The total daily dose of bupropion should not exceed 450 mg/day, and any single dose of the immediate-release formulation should not exceed 150 mg.[30] The maximum dose of sustained release is 200 mg twice daily.[30] Insomnia and/or nightmares often respond to moving the last daily dose from bedtime to late afternoon.

The adverse effects of the SNRIs are similar to those of the SSRIs.[18] Nausea can be troublesome with venlafaxine and desvenlafaxine, which sometimes necessitates using lower starting doses and giving the medication with food.[18] A dose-related elevation in blood pressure can occur at higher doses, and blood pressure monitoring should be conducted for patients receiving venlafaxine or desvenlafaxine.[18] Duloxetine should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease due to the potential for hepatic injury.[30]

Trazodone causes sedation and is often used adjunctively with other antidepressants for sleep rather than as an antidepressant.[18] Priapism is a rare but serious adverse effect of trazodone.[18] There are no reported cases of priapism with nefazodone.[18] Unfortunately, nefazodone carries a black box warning for fatal hepatotoxicity.[18]

Mirtazapine can cause sedation and weight gain by blocking histamine-1 receptors.[7] Despite being serotonergic, it rarely causes serotonin-related adverse effects such as sexual dysfunction and nausea due to its blockade of postsynaptic 5-HT_2 and 5-HT_3 receptors, respectively, that may be associated with those effects.[7]

Esketamine can cause nausea, sedation, dizziness, derealization, taste distortions, anxiety, and blood pressure elevation.[30] Esketamine is available through a Risk Evaluation and Mitigation Strategy (REMS) program due to its sedative and dissociative effects.[31]

Brexanolone can cause sedation or sudden loss of consciousness during administration and is only available through a REMS program.[27] Other common adverse effects are hot flashes and dry mouth.[27]

The TCAs cause sedative, anticholinergic, and cardiovascular adverse effects.[7] The tertiary TCAs (eg, amitriptyline, imipramine) are more sedating and anticholinergic than the secondary TCAs (eg, desipramine, nortriptyline).[18] TCAs have a quinidine-like effect on the heart, which makes them toxic in overdose.[7] The lethal dose of a TCA can occur with as little as 15 mg/kg in a young adult, which is typically less than a 1-month supply.[23]

The incidence of adverse effects among the newer antidepressants is shown in Table 39–5.

Pharmacokinetic Parameters

Pharmacokinetic parameters related to the newer antidepressants are shown in Table 39–6. The elimination half-lives of paroxetine, nefazodone, and venlafaxine are relatively short compared with the other agents.[30] Conversely, fluoxetine has a very long half-life (ie, 4–6 days) with chronic dosing, and its active metabolite (norfluoxetine) has an even longer half-life.[18,30] Because of this, a 5-week washout of fluoxetine is required before starting an MAOI, whereas a 2-week washout is generally considered sufficient for other serotonergic agents.[18] Several antidepressants have active metabolites including amitriptyline (nortriptyline), imipramine (desipramine), and venlafaxine (desvenlafaxine), which have all been approved separately for the treatment of depression.[18]

Drug Interactions

Antidepressant drug interactions can be pharmacokinetic or pharmacodynamic resulting in a variety of drug-related problems. The usual pharmacodynamic drug interactions involve receptors blocked by some antidepressants (eg, histamine 1 [H_1], muscarinic, α-1).[7] TCAs can cause significant additive effects with other drugs that cause sedation, hypotension, or anticholinergic effects.[7,18] Similarly, trazodone can interact with other drugs that cause hypotensive and sedative effects.[18] By far, the most concerning pharmacodynamic interactions are hypertensive crisis and serotonin syndrome, which are both life-threatening.

Table 39–6

Pharmacokinetic Parameters of Newer Antidepressants,[15,30]

Drug	Protein Binding (%)	Elimination Half-Life (hours)	Active Metabolite	Cytochrome P450	
				Substrate	Inhibitor
Brexanolone	99	9	No	0	0
Bupropion	84	14–21	Yes	2B6	2D6 (+++)
Citalopram	80	35	Yes	3A4, 2C19	2D6 (+)
Desvenlafaxine	30	10–11.1	No	3A4 (minor)	2D6 (+)
Duloxetine	90	8–17	No	1A2, 2D6	2D6 (+++)
Escitalopram	56	27–32	No	3A4, 2C19	2D6 (+)
Esketamine	43–45	7–12	Yes	2B6, 2C9, 2C19, 3A4	0
Fluoxetine	95	4–6 days with chronic dosing; 4–16 days (active metabolite)	Yes	2D6	2C (++) 2D6 (++++) 3A4 (++)
Fluvoxamine	80	15.6	No	None	1A2 (++++), 2C (++), 2D6 (+), 3A4 (+++)
Levomilnacipran	22	12	No	3A4	0
Mirtazapine	85	26 (males)–37 (females)	Yes	1A2, 2D6, 3A4	0
Nefazodone	99	2–4	Yes	None	3A4 (++++)
Paroxetine	93–95	15–21	No	2D6	2D6 (++++)
Sertraline	98	26	Yes	2C19, 2D6	2C (++), 2D6 (+), 3A4 (+)
Venlafaxine	27–30	5	Yes	2D6	2D6 (+)
Vilazodone	96–99	25	No	3A4	0
Vortioxetine	98	66	No	2D6, 3A4/5, 2C9, 2C19, 2A6, 2C8, 2B6	0

++++, high; +++, moderate; ++, low; +, very low; 0, absent.

Hypertensive crisis is characterized by sharply elevated blood pressure, occipital headache, stiff or sore neck, nausea, vomiting, and sweating.[18] It may result during MAOI therapy if the patient takes a sympathomimetic drug, such as ephedrine, pseudoephedrine, phenylephrine, or stimulants such as amphetamines or methylphenidate or if the patient consumes foods rich in tyramine, such as tap beers, aged cheeses, fava beans, yeast extracts, liver, dry sausage, sauerkraut, or tofu.[18,32] There are lists of foods and drinks that are not permitted during therapy with MAOIs, and these should always be provided to patients.[32] Because many over-the-counter (OTC) products contain sympathomimetics, patients should always be told to consult with their healthcare provider before using OTC drugs with an MAOI.[18]

Serotonin syndrome is due to serotonin toxicity that may result from multiple serotonergic agents or overdose of a serotonergic agent(s). The Hunter Serotonin Toxicity criteria are described in Table 39–7.[33,34] Serotonin syndrome is complicated by (a) an unawareness by clinicians of the diagnosis and (b) the fact that many implicated drugs such as dextromethorphan, meperidine, tramadol, linezolid, and methylene blue are not primarily serotonergic in nature, and clinicians may not recognize their serotonergic properties.[35]

Many antidepressants inhibit cytochrome P450 isoenzymes, elevating plasma levels of substrates for those isoenzymes and potentially leading to adverse effects or toxicity (see Table 39–6).[30,36]

Table 39–7

Hunter Serotonin Toxicity Criteria[34]

History of serotonergic agent(s) and one of the following from 1-5 below

1. Spontaneous clonus OR
2. Inducible clonus with agitation or diaphoresis OR
3. Ocular clonus with agitation or diaphoresis OR
4. Tremor and hyperreflexia OR
5. Hypertonia, temperature >100.4°F (38°C), and ocular or inducible clonus

Dosing

Antidepressant dosing is summarized in Table 39–8.[18,30] The extended-release formulations of venlafaxine and bupropion allow for once-daily dosing.[23] There is a once-weekly formulation of fluoxetine that can be started 7 days after the last regular-release capsule or tablet.[30] Selegiline is available as a transdermal patch, and a dose of 6 mg/24 hours can be used without the dietary restrictions associated with MAOI use, although patients on the higher doses (9 and 12 mg/24 hours) should follow the usual MAOI dietary restrictions.[18] A number of antidepressants have liquid dosage forms and disintegrating tablets, which may be helpful for patients who have difficulty swallowing tablets or capsules. Esketamine is administered as a nasal spray by the patient in the presence of a clinician, and the patient must stay in the clinic to be monitored for 2 hours after the dose.[37] Blood pressure is monitored before and after the dose is given.[37] Brexanolone is given as an intravenous infusion over 60 hours, and a clinician must monitor the patient continuously for sedation and hypoxia.[38]

The starting dose is often a therapeutic dosage for most SSRIs, desvenlafaxine, duloxetine, and mirtazapine. Dose titration is necessary for venlafaxine, vilazodone, vortioxetine, bupropion, sertraline, levomilnacipran, nefazodone, and TCAs.[18] A common first step in the management of partial response to an antidepressant is to optimize the dose even if the initial starting dose is within the therapeutic range.[18] An advantage of TCAs is that

Table 39–8

Dosing of Antidepressants in Adults,[15,30]

Generic Name	Brand Name	Generic	Form	Initial Dose (mg/day)	Usual Dosing Range (mg/day)	Usual Dosage Schedule	Renal Dosing Adjustment	Hepatic Dosing Adjustment
MAOIs								
Phenelzine	Nardil	Yes	T	15	45–90	Three times daily	CI in severe renal disease	CI with history of liver disease
Selegiline	Emsam	No	TD	6	6–12	Once daily	No adjustment for mild or moderate symptoms renal impairment, not studied in ESRD	No adjustment for mild or moderate hepatic impairment; not studied in severe impairment
Tranylcypromine	Parnate	Yes	T	10	30–60	Twice daily	None	None
Isocarboxazid	Marplan	No	T	20	40–60	Twice daily	Avoid in severe renal impairment	Avoid with history of liver disease or abnormal LFTs
TCAs								
Amitriptyline	Elavil	Yes	T	25–50	100–300	Once or twice daily	None	Use with caution
Desipramine	Norpramin[a]	Yes	T	25–50	100–300	Once to four times daily	Use with caution	Use with caution
Doxepin	Sinequan[a]	Yes	C, Sol, T	25–50	100–300	Once to three times daily	Use with caution	Use a lower dose
Imipramine	Tofranil[a]	Yes	C, T	25–50	100–300	Once daily or divided doses	Use with caution	Use a lower dose
Nortriptyline	Pamelor	Yes	C, Sol	25	50–150	Once or twice daily	Use with caution	Use a lower dose
SSRIs								
Citalopram	Celexa	Yes	Sol, T	20	20–40[b]	Once daily	No adjustment for CrCl > 20 mL/min (0.33 mL/s); for CrCl < 20 mL/min (0.33 mL/s), use with caution	20 mg/day maximum
Escitalopram	Lexapro	Yes	Sol, T	10	10–20	Once daily	No adjustment for CrCl > 20 mL/min (0.33 mL/s); for CrCl < 20 mL/min (0.33 mL/s), use with caution	10 mg/day
Fluoxetine	Prozac	Yes	Sol, Syr, C, T	10–20	20–80	Once daily	None	Use lower or less frequent dosing
	Prozac weekly	Yes	C	20	80	Once weekly	None	Use lower or less frequent dosing
Fluvoxamine	Luvox[a]	Yes	T	50	50–300	Twice daily	None	Reduce dose
	Luvox CR	Yes	C	100	100–300	Once daily	None	Reduce dose
Paroxetine	Paxil	Yes	Sus, T	10–20	20–50	Once daily	In CrCl < 30 mL/min (0.5 mL/s), initial dose 10 mg/day; increase weekly to a dose of 40 mg/day or less	Severe impairment, initial dose 10 mg daily; increase weekly to dose of 40 mg/day
	Paxil CR	Yes	T	12.5–25	25–62.5	Once daily	In CrCl < 30 mL/min (0.5 mL/s), initial dose 12.5 mg daily; may increase weekly to a dose of 50 mg/day or less	Severe impairment, initial dose 12.5 mg daily, increase weekly to dose of 50 mg/day or less
Sertraline	Zoloft	Yes	Sol, T	25–50	50–200	Once daily	None	Use a lower dose

(Continued)

Table 39–8

Dosing of Antidepressants in Adults,[15,30] (*Continued*)

Generic Name	Brand Name	Generic	Form	Initial Dose (mg/day)	Usual Dosing Range (mg/day)	Usual Dosage Schedule	Renal Dosing Adjustment	Hepatic Dosing Adjustment
NDRI								
Bupropion	Wellbutrin	Yes	T	150	300–450[c] (max single dose is 150 mg)	Twice to three times daily (separated by 6 hours)	Consider lower dose	75 mg/day
	Wellbutrin SR	Yes	T	150	300–400[c] (max single dose is 200 mg)	Twice daily (separated by 8 hours)	Consider lower dose	100 mg/day or 150 mg every other day
	Wellbutrin XL	Yes	T	150	300–450[c]	Once daily	Consider lower dose	150 mg every other day
SNRIs								
Desvenlafaxine	Pristiq	Yes	XR T	50	50–100	Once daily	CrCl 30–50 mL/min (0.5–0.83 mL/s), 50 mg maximum daily dose; CrCl < 30 mL/min (0.5 mL/s), 50 mg every other day	100 mg/day maximum
Duloxetine	Cymbalta	Yes	DR C	40–60	60–120	Once to twice daily	Use lower dose; not recommended for CrCl < 30 mL/min (0.5 mL/s)	Not recommended for chronic liver disease or cirrhosis
Venlafaxine	Effexor[a]	Yes	T	37.5–75	75–375[c]	Once, twice, or three times daily	Reduce dose 25%–50%	Reduce dose by 50% or more
	Effexor XR	Yes	C, T	37.5–75	75–225[c]	Once daily	Reduce dose 25%–50%	Reduce dose by 50%
Levomilnacipran	Fetzima	No	XR C	20	40–120[c]	Once daily	CrCl < 60 mL/min (1.0 mL/s), 80 mg/day maximum; CrCl < 30 mL/min (0.5 mL/s), 40 mg/day maximum	None
SARIs								
Nefazodone	Serzone[a]	Yes	T	100–200	300–600	Twice daily	Use with caution	Do not use; discontinue if ALT/AST is > 3X normal
Trazodone	Desyrel[a]	Yes	T	50	150–300 (max 600)	Three times daily	Use with caution	Use with caution
NaSSA								
Mirtazapine	Remeron	Yes	ODT, T	15	15–45	Once daily	CrCl < 40 mL/min (0.67 mL/s), 30% decreased clearance CrCl < 10 mL/min (0.17 mL/s), 50% decreased clearance; use with caution	Clearance decreased by 30%; monitor closely
SRI/5-HT_{1A}								
Vilazodone	Viibryd	No	T	10	20–40[c]	Once daily with food	None	Use with caution
Vortioxetine	Trintellix	No	T	10	20[c]	Once daily	None	None

(*Continued*)

Table 39–8

Dosing of Antidepressants in Adults,[15,30] (*Continued*)

Generic Name	Brand Name	Generic	Form	Initial Dose (mg/day)	Usual Dosing Range (mg/day)	Usual Dosage Schedule	Renal Dosing Adjustment	Hepatic Dosing Adjustment
Miscellaneous								
Esketamine	Spravato	No	NS	56	56–84	Twice weekly (1–4) Once weekly (5–8) Then individualize	None	Avoid in severe hepatic impairment
Brexanolone	Zulresso	No	IV	30 mcg/kg/hour (0–4 hours) 60 mcg/kg/hour (4–24 hours)	90 mcg/kg/hour (24–52 hours) 60 mcg/kg/hour (52–56 hours) 30 mcg/kg/hour (56–60 hours)	One time dose	Avoid with ESRD, eGFR,15mL/min/1.73 m^2	None

[a]Brand no longer available in the United States.

[b]Maximum dose is 40 mg/day.

[c]Upper limit of this range is the maximum dose.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; C, capsule; CI, contraindicated; CrCl, creatinine clearance; DR, delayed release; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IV, intravenous; LFT, liver function test; MAOI, monoamine oxidase inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; NDRI, norepinephrine and dopamine reuptake inhibitor; NS, nasal spray; ODT, orally disintegrating tablet; SARI, serotonin antagonist and reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; Sol, solution; SRI/5-HT$_{1A}$, partial agonist-serotonin reuptake inhibitor/serotonin$_{1A}$ partial agonist; SSRI, selective serotonin reuptake inhibitor; Sus, suspension; Syr, syrup; T, tablet; TCA, tricyclic antidepressant; TD, transdermal; XR, extended release.

plasma levels may help guide dosing, especially with nortriptyline which has a well-defined therapeutic plasma level (50–150 mcg/mL [190–570 nmol/L]).[39]

Efficacy of Pharmacotherapy

KEY CONCEPT Each antidepressant has a response rate of approximately 50% to 75%, and no antidepressant medication or class has been reliably shown to be more efficacious than another.[18] There is some evidence that dual-action antidepressants, such as TCAs and SNRIs, may be more effective in patients with severe depression than the single action drugs such as the SSRIs, but the more general assertion that multiple mechanisms of action confer efficacy advantages is controversial.[18]

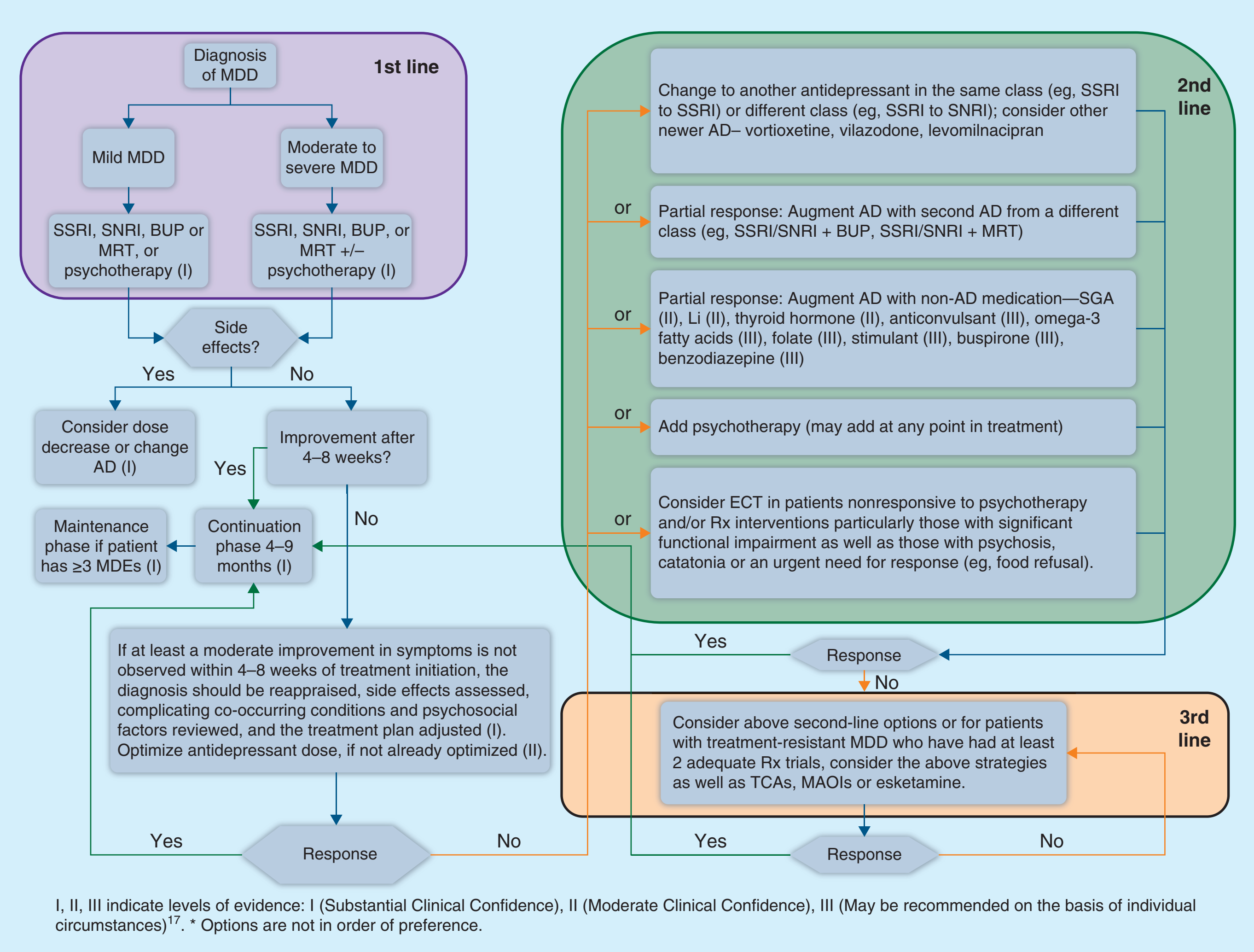
Selection of Medication

Figure 39–1 depicts an algorithm based on the APA Practice Guideline for the Treatment of Patients with Major Depressive Disorder and the Veterans Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline for the Management of Major Depressive Disorder.[18,40] As depicted in the algorithm, the guidelines recommend the use of SSRI, SNRI, bupropion, or mirtazapine as a first-line treatment for patients with mild-to-severe depression.[18,40] Patients with mild depression may be managed with psychotherapy alone.[18,40]

Various factors must be taken into account when selecting antidepressant therapy for a particular patient. The most reliable predictor of response is the patient's history of response (eg, efficacy, side effects, and overall satisfaction) to antidepressants.[18] To a lesser extent, the history of a first-degree relative's response to antidepressants may be used to predict a patient's response.[18] Adverse effect profiles should be considered, because adherence is influenced by tolerability.[23] The patient is the best source of information regarding acceptability of adverse effects. Patients should be educated about how to manage side effects (eg, using sugarless chewing gum, hard candy, or ice chips for dry mouth). The clinician must anticipate and be vigilant for potential drug–drug and drug–disease interactions. For instance, a patient with a seizure disorder would be an inappropriate candidate for bupropion therapy. The presence of comorbid psychiatric conditions can suggest the best antidepressant to choose. For example, an SSRI can treat both MDD and panic disorder, obviating the need for two separate medications. Likewise, a patient with MDD and a chronic pain condition may be treated with an SNRI with efficacy for both conditions. The potential for accidental or intentional overdose must be considered. Patients with risk of accidental or intentional overdose should not be prescribed TCAs. Additionally, affordability of the medication influences drug selection.

Time Course of Response

Antidepressants do not produce an immediate clinical response. Improvement in physical symptoms, such as sleep, appetite, and energy, can occur within the first or second week of treatment. **KEY CONCEPT** Although a meta-analysis suggests earlier effects of antidepressant treatment, it is widely accepted that approximately 2 to 4 weeks of treatment is required before improvement


1st line
Diagnosis of MDD
Mild MDD
Moderate to severe MDD
SSRI, SNRI, BUP or MRT, or psychotherapy (I)
SSRI, SNRI, BUP, or MRT +/– psychotherapy (I)
Side effects?
Yes
No
Consider dose decrease or change AD (I)
Improvement after 4–8 weeks?
Yes
No
Maintenance phase if patient has ≥3 MDEs (I)
Continuation phase 4–9 months (I)
If at least a moderate improvement in symptoms is not observed within 4–8 weeks of treatment initiation, the diagnosis should be reappraised, side effects assessed, complicating co-occurring conditions and psychosocial factors reviewed, and the treatment plan adjusted (I). Optimize antidepressant dose, if not already optimized (II).
Yes
Response
No
2nd line
Change to another antidepressant in the same class (eg, SSRI to SSRI) or different class (eg, SSRI to SNRI); consider other newer AD– vortioxetine, vilazodone, levomilnacipran
or
Partial response: Augment AD with second AD from a different class (eg, SSRI/SNRI + BUP, SSRI/SNRI + MRT)
or
Partial response: Augment AD with non-AD medication—SGA (II), Li (II), thyroid hormone (II), anticonvulsant (III), omega-3 fatty acids (III), folate (III), stimulant (III), buspirone (III), benzodiazepine (III)
or
Add psychotherapy (may add at any point in treatment)
or
Consider ECT in patients nonresponsive to psychotherapy and/or Rx interventions particularly those with significant functional impairment as well as those with psychosis, catatonia or an urgent need for response (eg, food refusal).
Yes
Response
No
3rd line
Consider above second-line options or for patients with treatment-resistant MDD who have had at least 2 adequate Rx trials, consider the above strategies as well as TCAs, MAOIs or esketamine.
Yes
Response
No

I, II, III indicate levels of evidence: I (Substantial Clinical Confidence), II (Moderate Clinical Confidence), III (May be recommended on the basis of individual circumstances)[17]. * Options are not in order of preference.

FIGURE 39–1. Algorithm based on the American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder and VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder.[18,40] (AD, antidepressant; BUP, bupropion; ECT, electroconvulsive therapy; Li, lithium; MAOI, monoamine oxidase inhibitor; MDD, major depressive disorder; MDE, major depressive episode; MRT, mirtazapine; Rx, prescription; SGA, second-generation antipsychotic; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant).

is seen in emotional symptoms such as sadness and anhedonia. Six to eight weeks may be required to see full antidepressant effects.[18,41]

Managing Partial or No Response

Approximately one-third of patients with MDD do not respond satisfactorily to their first antidepressant medication.[42] In such cases, the clinician must evaluate the adequacy of antidepressant therapy, including dosage, duration, patient adherence, verification of the patient's diagnosis, and reconsideration of clinical factors that could be impeding successful therapy, such as concurrent medical conditions (eg, thyroid disorder), comorbid psychiatric conditions or substance use disorders (eg, alcohol abuse), and psychosocial issues (eg, marital stress).[18]

A series of reports from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial revealed that remission is associated with a better overall prognosis than symptom improvement alone.[3] STAR*D also established that in patients with a greater level of nonresponse to treatment, clinicians are less likely to push the patient to achieve remission, and those patients with the greatest levels of nonresponse had the highest rates of relapse.[3] STAR*D established that for patients experiencing a partial response, extending the medication trial and/or using higher doses within the recommended dosage range may be helpful.[3] Another option used in the STAR*D trials is augmentation therapy, that is adding a nonantidepressant such as lithium, buspirone, or triiodothyronine.[3]

Second-generation antipsychotics, aripiprazole, brexpiprazole, and the extended-release formulation of quetiapine are approved by the FDA for adjunctive treatment of MDD along with an antidepressant.[43,44] Efficacy has been suggested for dopaminergic drugs (eg, pramipexole), psychostimulants (eg, methylphenidate), anticonvulsants (eg, lamotrigine), and modafinil although the evidence is less for these agents.[18,43] A third option is combination therapy, whereby another antidepressant, typically from a different pharmacologic class, is added to the first antidepressant.[43] Examples include combining bupropion or mirtazapine with SSRIs or SNRIs.[7] Switching to a different

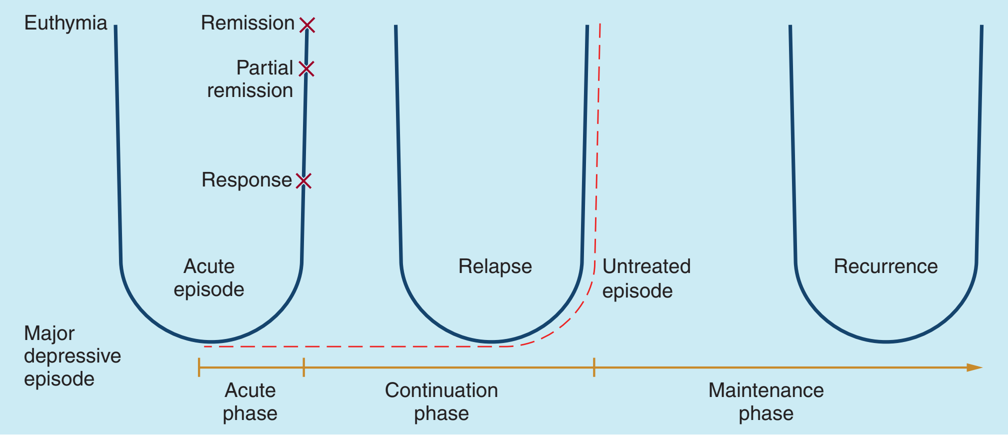


FIGURE 39–2. The course of depression and phases of treatment.[7,18]

antidepressant is a common strategy for patients who have had no response to initial antidepressant therapy, but also is acceptable in cases of partial response.[18] Relative to augmentation or combination therapy, advantages of switching include improved adherence, decreased costs, and less concern over drug–drug interactions. Disadvantages include loss of time, exacerbation of illness, and loss of any improvement seen with the initial drug. When switching from one antidepressant to another, clinicians may choose to stay within the same class (eg, sertraline to fluoxetine) or go outside of the class (eg, paroxetine to venlafaxine). The olanzapine-fluoxetine combination, Symbyax, and esketamine (Spravato) nasal spray, are approved for treatment-resistant depression.[37,43]

Nonpharmacologic interventions in cases of treatment nonresponse include adding or changing to psychotherapy or initiating ECT.[18,40]

Duration of Therapy

Treatment of MDD encompasses three phases: acute, continuation, and maintenance (Figure 39–2).[18] The acute phase of treatment typically lasts 6 to 12 weeks.[18] **KEY CONCEPT** Because the typical MDE lasts 6 months or longer, if antidepressant therapy is interrupted after the acute phase, the patient may relapse into a depressive episode.[16,18] When treating the first depressive episode, antidepressants must be given for an additional 4 to 9 months in the continuation phase to prevent relapse.[18]

Maintenance treatment takes place after the normal course of an MDE to prevent recurrence, which is the development of future episodes.[18] This phase can last for years, or for a lifetime.[18] Although patients who have an MDE should receive acute and continuation treatment, not all of them require maintenance treatment, because not all patients experience multiple MDEs.[18] In some patients with multiple episodes, many years may separate the episodes.[18] Therefore, the clinician must consider various factors in determining whether an individual requires maintenance treatment. A major factor is the number of prior episodes experienced by the patient. The more prior episodes experienced, the higher the risk for future episodes.[18] After three MDEs, maintenance treatment is recommended due to the risk of recurrence.[15,18] Other factors to consider are the severity of previous episodes, previous suicide attempts, presence of psychotic features, and patient preference.[18] The antidepressant dose required in the acute phase of treatment should be sustained during the continuation and maintenance phases.[18]

Discontinuing Therapy

When discontinuing therapy, it is best to gradually taper the antidepressant for two reasons. First, almost all antidepressants can produce withdrawal syndromes if discontinued abruptly or tapered too rapidly, especially antidepressants with shorter half-lives (eg, venlafaxine, paroxetine).[18,45] Antidepressant withdrawal can cause flu-like symptoms including nausea, headache, light-headedness, chills and body aches, and other symptoms such as insomnia and paresthesias.[18,45] In general, the antidepressant dose should be tapered by no more than 25% per week to minimize the risk of withdrawal symptoms. Tapering and discontinuation can be completed over weeks to months depending on the pharmacokinetics of the antidepressant.[45] Second, depression may return upon taper or discontinuation of the antidepressant.[45] So, if the medication is gradually tapered, then early signs of depression can be countered with a return to the original dosage.[45] Depending on the patient's illness and the clinical circumstances, tapering of the antidepressant can be extended for weeks or even months because of the concern over relapse or recurrence. Liquid formulations may be utilized to achieve small doses for individuals having difficulty with discontinuation.[45]

Special Considerations

▶ *Pregnant or Breast-feeding Patients*

Depression is common in pregnancy, especially for women with a history of depression.[18] Untreated depression carries risks for both the fetus and the mother. Likewise antidepressants have reported risks.[18] As such, both maternal and fetal well-being must be considered when weighing risks and benefits of antidepressant therapy during pregnancy.[18] Overall risk of teratogenicity with antidepressants after the first trimester appears to be low.[18] Paroxetine has been associated with an increased risk of cardiac malformations and should not be considered a first-line treatment in pregnancy.[18] Fluoxetine has a long half-life and is more likely to be present at high levels in newborns after in utero exposure.[18] Antidepressant use late in pregnancy has been reported to occasionally cause perinatal sequelae, such as poor neonatal adaptation, feeding problems, and jitteriness.[18] Use of a single medication over multiple medications is favored in managing depression during pregnancy.[18] ECT may also be considered as a treatment option for pregnant patients.[18] Brexanolone is an antidepressant marketed specifically for postpartum depression.[38] It is given to women who develop postpartum depression between the third trimester and up to 4 weeks after delivery.[38] Studies show an

Patient Encounter Part 3

On the basis of information presented, create a care plan. Your plan should include (a) a statement of the drug-related needs and/or problems, (b) a patient-specific detailed therapeutic plan, and (c) monitoring parameters to assess efficacy and safety.

improvement in symptoms versus placebo for up to 4 weeks after a 60-hour infusion.[38]

There is some drug exposure to the infant from nursing mothers who are taking antidepressants.[18] Although there have been rare anecdotal reports of respiratory depression and seizure-like episodes in infants exposed to antidepressants through breast milk, it is generally accepted that the benefits of breastfeeding outweigh the risks.[18,46] However, the decision needs to be made on an individual basis. Esketamine should be avoided in breast-feeding due to possible neurotoxicity in infants.[37] One to two percent of brexanolone passes into breast milk.[38]

▶ *Geriatric Patients*

Depression in older adults is underrecognized and undertreated.[18,47,48] There is some evidence that depression in older adulthood presents with more somatic complaints (eg, pain and GI problems) possibly contributing to underdiagnosis.[48] Age-related pharmacokinetic and pharmacodynamic changes cause older patients to be more sensitive to antidepressant medications. Thus, lower starting doses of antidepressants and slow upward titrations as tolerated are generally recommended for geriatric patients. However, many older patients require the same dose as younger adult patients.[47] The SSRIs are chosen frequently for geriatric depression because of their overall favorable adverse effect profiles and low toxicity; however, the maximum dose of citalopram in patients over 60 years is 20 mg due to a risk of QT prolongation.[30,47] Most TCAs are avoided due to anticholinergic, cardiovascular, and sedative properties.[47] Desipramine and nortriptyline are more tolerable in terms of these adverse effects and may be used in geriatric depression.[18] Other antidepressants, such as SNRIs, bupropion, vortioxetine, and mirtazapine, are alternatives for the treatment of geriatric patients.[47] Esketamine has a favorable safety profile, but no studies have found efficacy of esketamine versus placebo in patients over 64 years.[37]

▶ *Pediatric Patients*

Antidepressants appear to be useful for children and adolescents with depression, particularly those who have severe or psychotic depression, fail psychotherapy, or experience chronic or recurrent depression.[49] Fluoxetine and escitalopram are the only antidepressants FDA approved for depression in children younger than 18 years.[30] The SSRIs generally are considered the initial antidepressants of choice, but comorbid conditions may favor alternative agents.[49] "Behavioral activation" can occur with SSRIs, including symptoms such as impulsivity, silliness, daring conduct, and agitation.[49] Esketamine and brexanolone have not been studied in pediatric patients.[37,38]

▶ *Suicidal Patients*

All antidepressants have a black box warning regarding an increase in suicidal thinking and behavior in children and young adults.[50] A large analysis of clinical trials showed the risk of such events was 4% for antidepressants versus 2% for placebo, although no completed suicides occurred in the trials.[50] Following the addition of the black box warning in 2003, prescriptions for antidepressants decreased among primary care providers by 58%.[51] The Centers for Disease Control and Prevention (CDC) estimated that suicide rates increased 8% in 2003 to 2004; however, a definite link between the black box warning and increased suicide rates has not been conclusively determined.[51] Because antidepressants carry a black box warning regarding suicide among children and young adults, medication guides must be distributed with each prescription or refill of antidepressants.[50] **KEY CONCEPT** Patients 24 years and younger should be observed closely for suicidality, worsened depression, agitation, irritability, and unusual changes in behavior, especially during the initial few months of therapy and at times of dosage changes. Furthermore, families and caregivers should be advised to monitor patients for such symptoms.[50] Whereas the TCAs and MAOIs have significant toxicity risk on overdose, most newer antidepressants are safer in overdose.[18]

Patient Counseling

Major counseling points are outlined in Table 39–9. **KEY CONCEPT** Lack of patient understanding concerning optimal antidepressant therapy frequently leads to partial or nonadherence with therapy; thus, the primary purpose of antidepressant counseling is to enhance adherence and improve outcomes.[52] Patients should be educated that while they may see some improvement in some symptoms like sleep and appetite as early as the first week, generally at least 4 to 8 weeks is required for optimal mood changes to occur. Patients should also recognize common side effects including how long those side effects might last, and if there are any simple remedies for treatment (eg, using ice chips or sugarless gum for dry mouth).

OUTCOME EVALUATION

Symptom Assessment

The patient interview should assess response of target symptoms. Rating scales are useful in this regard and may improve treatment outcomes. The Hamilton Depression Scale (HAM-D) and the Montgomery-Åsberg Depression Rating Scale (MADRS) are clinician-rated scales often used in depression research studies to assess treatment efficacy.[18] The Patient Health Questionnaire (PHQ-9) is a nine-item depression scale that is patient-rated (Table 39–10).[18,53] A score of four or less would be considered normal mood and greater than 20 as severe depression.[18,53]

Monitoring Adverse Effects

Adverse effects associated with the treatments for depression can often be predicted based on knowledge of pharmacologic profiles (Table 39–3) as well as familiarity with the most common adverse effects (Table 39–4). Evaluation for suicidal ideation should be a part of every patient visit. Patients can be taught to manage side effects such as sedation, constipation, and dry mouth. Potential side effects such as weight gain and sexual dysfunction should be discussed with the patient and monitored at each visit. SNRIs may increase blood pressure, and patients should have their blood pressure monitored regularly during treatment.[18] Patients with cardiovascular risk factors or over the age of 40 should have an electrocardiogram (ECG) completed prior to initiating a TCA.[18] Patients

Table 39–9

Patient Counseling[14, 18]

Counseling Point	Clinical Rationale
Mechanism of action—The medication works by affecting certain chemicals in the brain	Patient may feel that depression is a character weakness or personality flaw instead of a biological disorder
Lack of addiction potential—Although the medication affects certain chemicals in the brain, it is not addicting	Patient may worry that because the antidepressant is psychoactive, it must be addicting
Need for routine use—The medication will only work if it is taken as prescribed every day	Patient may try taking the medication on an as-needed basis
Delayed onset of action—It may take several weeks to see significant improvement in symptoms	Patient may prematurely discontinue therapy before the onset of beneficial effects
Prolonged duration of therapy—The medication should be taken for at least 6–12 months; do not discontinue it without consulting with the prescriber	Patient may prematurely discontinue therapy after symptoms have remitted, which could lead to relapse or recurrence
Adverse effects—Mention common and expected adverse effects as well as what to do if they occur	Patient may be more likely to discontinue therapy and distrust the prescriber if adverse effects occur without forewarning
Avoidance of alcohol and CNS depressants—Use of alcohol or other CNS depressants could cause worsened depression and additive adverse effects with the medicine	Patient may be unaware of the possible consequences of drinking alcohol or taking other drugs with antidepressants
Risk of suicidality—Be alert to symptoms of worsening depression and suicidality	Patient may become suicidal or have suicidal thinking while taking the antidepressant

CNS, central nervous system.

taking TCAs such as amitriptyline, imipramine, nortriptyline, or desipramine should have antidepressant serum levels checked if overdose, side effects, or nonadherence is an issue.[18] Patients should be monitored for serotonin syndrome if they are taking two or more serotonergic medications.[18,34]

Pharmacogenomic testing is currently available for evaluating enzymes that metabolize antidepressants, especially cytochrome P450 2D6 and 2C19. These pharmacogenomic tests can measure whether an individual is a fast or slow metabolizer. Patients might be more susceptible to decreased medication efficacy in the case of fast or rapid metabolizers, or they might experience more adverse effects in the case of slow or poor metabolizers. There is controversy in the medical community over the usefulness of pharmacogenomic testing. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has evidence-based guidelines that can be used to help guide clinicians regarding medication adjustments.[54] At the current time, more research needs to be completed in order to determine the best use of pharmacogenomics monitoring for antidepressant use.[55]

Table 39–10

Patient Health Questionnaire-9[53]

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at All	Several Days	More Than Half the Days	Nearly Every Day
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3
Trouble falling or staying asleep, or sleeping too much	0	1	2	3
Feeling tired or having little energy	0	1	2	3
Poor appetite or overeating	0	1	2	3
Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
Trouble concentrating on things, such as reading the newspaper or watching TV	0	1	2	3
Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Total Score = ________

Depression Severity, PHQ-9 Total Score: 1–4 minimal, 5–9 mild, 10–14 moderate, 15–19 moderately severe, 20–27 severe

If you checked any problems, how difficult have these problems made it for you to do your work, take care of things at home or get along with other people?

	Not Difficult at All	Somewhat Difficult	Very Difficult	Extremely Difficult

Patient Care Process

Collect Information:

- Perform a medication history for antidepressant and other psychotropic drug use as well as nonprescription medications and dietary supplements. Identify allergies to medications and other substances.
- Review the psychiatric history, medical history, physical assessment, laboratory findings, family history, and social history.
- Speak with the patient and review medical records to identify lifestyle habits, preferences, beliefs, health goals, and socioeconomic factors that may affect medication access and other aspects of care.

Assess the Information:

- Determine whether the patient is taking any substances that could induce or worsen the depressive episode.
- Based on the psychiatric and medical history, determine whether the patient has any factors that would suggest the selection of certain antidepressants or adjunctive agents.
- Identify comorbidities associated with MDD.
- Evaluate relevant laboratory tests (eg, complete blood count [CBC], thyroid-stimulating hormone [TSH], urine drug screen).
- Assess the efficacy, safety, and patient adherence with current pharmacotherapy.
- Identify any significant adverse drug effects or interactions.
- Determine whether the patient may benefit from nonpharmacologic therapy (ie, psychotherapy, lifestyle modifications).

Develop a Care Plan:

- Based on discussions with the patient, determine whether a change in antidepressant therapy is warranted or if the addition of another antidepressant or nonantidepressant adjunctive agent is more appropriate.
- Select lifestyle modifications nonpharmacologic and pharmacologic therapy that are likely to be effective and safe for the patient.
- Choose medications and doses that are optimal for the patient.

Implement the Care Plan:

- Educate the patient about changes in drug therapy, medication administration, potential new adverse effects, and how to manage and report any adverse effects that may occur.
- Review the patient's practices for self-monitoring symptoms of depression as well as his support system.
- Address any patient concerns about depression and its management.
- Discuss importance of medication adherence and lifestyle modifications to manage symptoms of depression.
- Determine whether recommended agents are included on the institution's formulary (for inpatient setting) and whether the patient has insurance coverage for the medication as an outpatient.

Follow-up: Monitor and Evaluate:

- Follow-up every 2 to 4 weeks after changes in pharmacotherapy until the patient reaches remission, then every 3 to 6 months.
- Review medication adherence as well as rating scale assessment of patient's symptoms of depression and adverse effects.

Abbreviations Introduced in This Chapter

5-HT	Serotonin
APA	American Psychiatric Association
BDNF	Brain-derived neurotrophic factor
CAM	Complementary and alternative medicines
CANMAT	Canadian Network for Mood and Anxiety Treatments
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
CNS	Central nervous system
CPIC	Clinical Pharmacogenetics Implementation Consortium
DA	Dopamine
DHA	Docosahexaenoic acid
DRI	Dopamine reuptake Inhibitor
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition
EPA	Eicosapentaenoic acid
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
FDA	Food and Drug Administration
GABA	γ-Aminobutyric acid
GI	Gastrointestinal
GRM3	Glutamate metabotropic receptor 3
HAM-D	Hamilton Depression Rating Scale
HPA	Hypothalamic pituitary axis
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitor
MAO-A	Monoamine oxidase A
MAO-B	Monoamine oxidase B
MDD	Major depressive disorder
MDE	Major depressive episode
NaSSA	Noradrenergic and specific serotonergic antidepressant
NDRI	Norepinephrine and dopamine reuptake inhibitor
NE	Norepinephrine
NMDA	*N*-methyl-D-aspartate
NRI	Norepinephrine reuptake inhibitor
NR3C1	Nuclear receptor subfamily 3 group C member 1
OTC	Over-the-counter
PHQ-9	Patient Health Questionnaire-9
REMS	Risk Evaluation and Mitigation Strategy
SAM-e	S-adenosyl methionine
SARI	Serotonin antagonist and reuptake inhibitor
SNRI	Serotonin and norepinephrine reuptake inhibitor
SRI	Serotonin reuptake inhibition
SSRI	Selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
TSH	Thyroid-stimulating hormone

TCA	Tricyclic antidepressant
VA/DoD	Veterans Administration Department of Defense
VNS	Vagus nerve stimulation
WHO	World Health Organization

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Bipolar Disorder

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the pathophysiologic mechanisms underlying bipolar disorder.
2. Recognize the symptoms of a manic episode in patients with bipolar disorder.
3. Identify common psychiatric comorbidities of bipolar disorder.
4. Recognize the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-5*), criteria for bipolar disorder as well as the subtypes of bipolar I disorder, bipolar II disorder, and cyclothymic disorder.
5. List the desired therapeutic outcomes for patients with bipolar disorder.
6. Identify the optimal use of medications as first-line therapy in bipolar disorder, including appropriate dosing.
7. Recommend drug therapy for acute treatment of mania and depressive episodes.
8. Recommend baseline and routine monitoring for assessment of adverse effects of medications used in the treatment of bipolar disorder.
9. Identify general treatment differences for agents used to treat bipolar disorder in the pediatric population.
10. Explain why medication education is important for patients with bipolar disorder.

INTRODUCTION

Bipolar disorder is characterized by one or more episodes of mania or hypomania, in addition to one or more major depressive episodes.[1] It is chronic, with recurrent episodes and remissions. Mood episodes can be manic, hypomanic, or depressed, and each separated by periods of long stability or cycle rapidly. They occur with or without psychosis. Disability and other consequences (eg, increased risk of suicide) can be devastating to patients and families. Correct and early diagnosis and treatment are essential to prevent complications and maximize response to treatment.

EPIDEMIOLOGY

The lifetime prevalence of bipolar I disorder and bipolar II disorder in the United States is estimated at approximately 1% and 1.1%, respectively. When including the entire spectrum of bipolar disorders, the prevalence is 2.4% worldwide.[2] Bipolar I disorder affects men and women equally. Bipolar II, rapid cycling, and mixed mood features are more common in women.

The mean age of onset is 20 years, although onset may occur in early childhood to the mid-40s.[1] If onset occurs after age 60, medical causes, such as thyroid dysfunction, electrolyte imbalances, or dementia should be ruled out as they can cause symptoms that mimic mania, hypomania, or depression. An early onset of bipolar disorder is associated with greater comorbidities, more mood episodes, a greater proportion of days depressed, and greater lifetime risk of suicide attempts compared with later onset. Substance use and anxiety disorders are more common in patients with early onset. Patients with bipolar disorder have higher rates of suicidal thoughts, attempts, and completed suicides than the general population.

ETIOLOGY

The precise etiology is unknown. Results of family studies suggest a genetic basis. Heritability of bipolar disorder is estimated to be between 5% and 10% with first-degree relatives and up to 70% in monozygotic twin studies. A variety of factors may enhance gene expression such as trauma, environmental factors, anatomical abnormalities, and exposure to chemicals or drugs.[3,4]

PATHOPHYSIOLOGY

Neurochemical

The pathophysiology of bipolar disorder remains incompletely understood. Imaging techniques such as positron emission tomography (PET) scans and functional magnetic resonance imaging (fMRI) are used to elucidate the cause. Historically, research focused on neurotransmitters such as norepinephrine (NE), dopamine (DA), and serotonin. One hypothesis is that bipolar disorder is caused by an imbalance of cholinergic and catecholaminergic activity. Serotonin is suggested to modulate catecholamines. Dysregulation of this relationship could cause mood disturbance. A variety of neurotransmitters are involved that interact with multiple neurochemical and neuroanatomic pathways.[3] The pathophysiology is also hypothesized based on the mechanisms of lithium and other drugs. Lithium, a gold standard medication in the treatment of bipolar disorder, has effect on neuronal growth that is reversible by inositol, supporting a hypothesis that bipolar disorder may be related to inositol

Patient Encounter Part 1

Chief Complaint: "I was arrested for disorderly conduct and public indecency. The judge recommended to my family that I get psychiatric help."

History of Present Illness: Patient is a 23-year-old graduate student accompanied by her parents following an incident at a football tailgating party. Per her parents, the patient attended a pre-football game tailgating party where large quantities of alcohol were consumed, and the patient apparently began to disrobe while dancing. The patient refused to put her clothes back on and became belligerent and aggressive toward police officers. She was subsequently arrested and jailed briefly overnight. The patient has had no prior medical or psychiatric history.

Labs and Diagnostics: Comprehensive metabolic profile, complete blood count, thyroid function, B_{12} and folate, electrocardiogram, and chest X-ray were unremarkable.

Mental Status Examination: Well-nourished, well-developed, Caucasian female appearing her stated age. She is attired in a revealing halter top and cut-off shorts with stiletto heels. She is wearing heavy makeup to include blue lipstick and nail polish as well as silver glitter eye shadow. She has difficulty maintaining appropriate social distance during the interview and is flirtatious and seductive at times. Speech is loud, pressured, and difficult to interrupt. She is distractible, looking around the room, and frequently changing topics in midsentence. Patient's mood is expansive and described as "fabulous."

Patient states she has lost 10 lb (4.5 kg) recently. She also admits to partying more than usual with friends, and her grades have been slipping. She expresses plans to go to Los Angeles and become a famous actress. Patient's parents report that recently she has been calling and asking them for money when her bank notified her of insufficient funds, and her credit cards were cancelled. The patient stated she needed an expensive new wardrobe to impress the directors and producers in Los Angeles.

What diagnoses are suggested by this patient's presentation?

What additional information is needed to clarify the diagnosis?

disturbance.[5] Brain-derived neurotrophic factor (BDNF) may play a role in bipolar disorder. Serum BDNF is low in mania and improves with treatment.[6]

CLINICAL PRESENTATION AND DIAGNOSIS

Diagnosis of Bipolar Disorder

KEY CONCEPT Patients presenting with depressive or elevated mood features and a history of abnormal or unusual mood swings should be assessed for bipolar disorder. According to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-5*), the diagnostic manual for psychiatric disorders, bipolar disorder is a mood disorder defined by distinct episodes of mania and/or hypomania in addition to major depressive episodes that are not caused by a medical condition, substance use, or other psychiatric disorder. Bipolar disorders are categorized into five subtypes: bipolar I disorder, bipolar II disorder, and other specified and unspecified bipolar and related disorders (ie, cyclothymic disorder). Bipolar I disorder is characterized by one or more manic episodes, whereas bipolar II disorder is characterized by at least one hypomanic episode. Both disorders also include alternating periods of euthymia and/or major depressive episodes. [1]

Initial episodes of bipolar disorder are mostly depressive with studies showing patients with bipolar I spend about 32% of weeks with depressive symptoms compared with 9% of weeks with manic or hypomanic symptoms.[7,8] Patients with bipolar II disorder spend 50% of weeks symptomatic for depression and only 1% with hypomania.[9] Bipolar disorder is often misdiagnosed as major depressive disorder (MDD) or underdiagnosed. It is helpful to use a screening tool such as the Mood Disorder Questionnaire.[10] *DSM-5* criteria for the diagnosis of major depressive, manic, and hypomanic episodes are summarized in Table 40–1.

▶ *Bipolar I Disorder*

The diagnosis of bipolar I disorder requires at least one episode of mania lasting for at least 1 week (or any duration if hospitalization due to symptoms is required). Mania is characterized by a persistently elevated, expansive, or irritable mood with related symptoms of increased goal-directed activity or energy including grandiosity, decreased need for sleep, excessive talkativeness, racing thoughts, flight of ideas (FOI), distractibility, and a propensity to be involved in high-risk activities.[1] It is essential to rule out past episodes of hypomania or mania to avoid misdiagnosing bipolar disorder as MDD. If bipolar depression is mistaken for MDD and the patient is treated with antidepressants, it can precipitate a manic episode or induce rapid cycling.

▶ *Bipolar II Disorder*

The distinguishing feature of bipolar II disorder is a current or past hypomanic episode and a current or past major depressive episode. Hypomanic symptoms last for at least 4 days, but fewer than 7 and include the same symptoms as mania without causing severe impairment or requiring hospitalization. Psychotic features are not present,[1] while irritability and anger are common. There cannot have been a prior full-manic episode.[1]

▶ *Cyclothymic Disorder*

Cyclothymic disorder is a chronic mood disturbance lasting at least 2 years (1 year in children and adolescents) and is characterized by mood swings that include periods of hypomanic symptoms that do not meet the criteria for a hypomanic episode and depressive symptoms that do not meet the criteria for a major depressive episode.

Suicide

Patients with bipolar disorder have high risk of suicide. Factors that increase risk are early age at onset, high number and severity of depressive episodes, comorbid alcohol use disorder, comorbid personality disorder, history of antidepressant-induced mania, history of previous suicide attempt, and family history of suicidal behavior. About one-third of individuals with bipolar disorder report a previous suicide attempt.[11] The risk of suicide in people with bipolar disorder is at least 15 times higher than the general population.[1] Patients should be assessed for potential for violence and harm to themselves or others. Friends or family can be asked to remove from the home guns, caustic chemicals, medications, and objects that patients might use to harm themselves or others.

Table 40–1

Evaluation and Diagnosis of Mood Episodes

Diagnosis Episode	Impairment of Functioning or Need for Hospitalization[a]	*DSM-5* Criteria[b]
Major depressive	Yes	At least 2-week period of either depressed mood or loss of interest or pleasure in normal activities, associated with at least five of the following symptoms: • Depressed, sad mood (adults); can be irritable mood in children • Decreased interest and pleasure in normal activities • Decreased or increased appetite, weight loss or weight gain • Insomnia or hypersomnia • Psychomotor retardation or agitation • Decreased energy or fatigue • Feelings of excessive guilt or worthlessness • Impaired concentration or indecisiveness • Recurrent thoughts of death, suicidal thoughts or attempts
Manic	Yes	At least 1-week period of abnormally and persistently elevated mood (expansive or irritable) and energy, associated with at least three of the following symptoms (four if the mood is only irritable): • Inflated self-esteem (grandiosity) • Decreased need for sleep • Increased talking (pressure of speech) • Racing thoughts (flight of ideas) • Distractibility (poor attention) • Increased goal-directed activity (socially, at work, or sexually) or psychomotor agitation • Excessive involvement in activities that are pleasurable but have a high risk for serious consequences (buying sprees, sexual indiscretions, poor judgment in business ventures)
Hypomanic	No	At least 4 days of abnormally and persistently elevated mood (expansive or irritable) and energy, associated with at least three of the following symptoms (four if the mood is only irritable): • Inflated self-esteem (grandiosity) • Decreased need for sleep • Increased talking (pressure of speech) • Racing thoughts (flight of ideas) • Distractibility (poor attention) • Increased goal-directed activity (socially, at work, or sexually) or psychomotor agitation • Excessive involvement in activities that are pleasurable but have a high risk for serious consequences (buying sprees, sexual indiscretions, poor judgment in business ventures)

[a] Impairment in social or occupational functioning; may include need for hospitalization because of potential self-harm, harm to others, or psychotic symptoms.

[b] The disorder is not caused by a medical condition (eg, hypothyroidism) or substance-induced disorder (eg, antidepressant treatment, medications, drugs of abuse). Numerous specifiers are available to further characterize episodes (eg, with mixed features, with anxious distress, with rapid cycling, with melancholic features).

DSM, Diagnostic and Statistical Manual of Mental Disorders.

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Differential Diagnosis

Schizophrenia, schizoaffective disorder, and bipolar disorder can share certain symptoms, including psychosis.[1] A thorough history with collateral from friends and family, if possible, needs to be obtained to differentiate between the illnesses. Personality disorders and bipolar disorder may be comorbid, and patients with personality disorders may have mood symptoms. The two diagnoses are distinguished by the episodic course of bipolar disorder in contrast to the stability and persistence of the behavioral patterns of personality disorders.

Comorbid Psychiatric and Medical Conditions

Lifetime prevalence rates of psychiatric comorbidity with bipolar disorder are as high as 75%.[2] Comorbidities place the patient at risk for a poorer outcome, higher rates of suicidality, increased episodes of depression, and higher costs of treatment. Common psychiatric comorbidities include personality disorders, alcohol and substance use disorders, anxiety disorders, obsessive-compulsive disorder, eating disorders, and attention-deficit/hyperactivity disorder. Medical comorbidities include migraine, multiple sclerosis, type 2 diabetes mellitus, and obesity.

TREATMENT

Desired Outcomes

KEY CONCEPT Goals of treatment are to reduce symptoms, induce remission, prevent relapse, improve patient functioning, and minimize adverse effects of drug therapy.

General Approach to Treatment

Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) treatment guidelines are commonly used for treating bipolar

Patient Encounter Part 2: Medical History, Physical Examination, and Laboratory Examination

Past Medical History: No known medical problems, however, patient admits to being treated for chlamydia and gonorrhea several months ago.

Past Psychiatric History: Noncontributory.

Family History:

Parents: Alive and well with no known medical or psychiatric illnesses.

Paternal aunt: Depression.

Grandfather: Completed suicide in his 40s.

Brother: Anxiety.

Patient denies prior suicide attempts or psychiatric hospitalizations.

Social History: Single, never married, has no children, and denies prior pregnancies. She admits to multiple sexual partners beginning during her senior year in high school and during college. She has had several brief relationships while in college, none lasting more than a few weeks.

Substance Use History: The patient denies use of hallucinogens, opioids, amphetamines, benzodiazepines, or intravenous drugs. She admits to smoking two to three joints of marijuana several times per week. She drinks alcohol occasionally, consuming four to five mixed drinks with either gin or vodka. She does not drink coffee but consumes three to four energy drinks such as Red Bull each day. She denies use of vitamins, herbal supplements, or nicotine products.

Medications: Oral contraceptives.

Review of Systems: Decreased need for sleep over the past week, obtaining 2 to 3 hours per night. Decreased appetite with recent 10-lb (4.5-kg) weight loss. Increased energy, pressured speech, distractibility with difficulty concentrating on schoolwork, hypersexuality, and grandiosity. Last menstrual period 3 weeks ago.

Physical Examination:

Vital Signs: BP 140/94 mm Hg, P 100 beats/min, RR 20 breaths/min, T 98.5°F (36.7°C).

HEENT: Everything within normal limits.

CV: Heart with increased rate and regular rhythm; no murmurs, gallops, or rubs.

Abdomen: Soft, nontender, no organomegaly or masses. Positive bowel sound in all four quadrants.

Extremities: Without clubbing, cyanosis or edema. Peripheral pulses full and equal bilaterally.

CN: Cranial nerves II to XII intact.

Labs: Urine drug screen positive for tetrahydrocannabinol (THC). HIV negative. Basic metabolic profile reveals Na$^+$ 138 mEq/L (mmol/L); K$^+$ 3.8 mEq/L (mmol/L); Cl$^-$ 100 mEq/L (mmol/L); CO$_2$ 25 mEq/L (mmol/L); BUN 20 mg/dL (7.1 mmol/L); creatinine 1.3 mg/dL (115 μmol/L); glucose 80 mg/dL (4.4 mmol/L). Urinalysis clear, dark yellow, negative for glucose, ketones, or protein.

The team decides to start lithium for this patient. What additional laboratory values would you recommend prior to starting pharmacotherapy with lithium?

disorder. A general treatment algorithm for manic and depressive episodes of bipolar disorder, including evidence provided from the CANMAT, ISBD guidelines as well as clinical research, can be found in Table 40–2.

The mainstay of drug therapy has been mood-stabilizing drugs, but research indicates antipsychotic drugs, both first-generation (FGAs) and second-generation (SGAs), may be more effective for acute mania.[12] Antipsychotic drugs may be used as monotherapy or adjunctively with mood-stabilizing drugs. A person receiving treatment for a first mood episode in bipolar disorder must have a complete assessment and careful diagnosis to rule out nonpsychiatric causes. A variety of conditions can cause similar symptoms (Table 40–3). Because early and accurate diagnosis is essential to maximizing response to treatment, pharmacologic and nonpharmacologic therapy should begin as soon as possible. Although it is a goal of treatment, not all patients achieve remission, and treatment is often lifelong. Comorbid conditions should also be addressed.

Patient Encounter Part 3: Creating a Care Plan

Based on all information presented, create a care plan for this patient's bipolar disorder. Your plan should include (a) a statement of the drug-related needs or problems, (b) the goals of therapy, (c) a patient-specific therapeutic plan, and (d) a plan for follow-up to assess therapeutic response and adverse effects.

Nonpharmacologic Therapy

KEY CONCEPT Interpersonal, family, or group psychotherapy with a qualified therapist or clinician adjunctive to medication assists individuals with bipolar disorder to improve functional outcomes. They may also help treat or prevent mood episodes, establish a daily routine and sleep schedule, and improve interpersonal relationships.[13]

Cognitive-behavioral therapy (CBT) is a type of psychotherapy that stresses the importance of recognizing patterns of cognition and how thoughts influence subsequent feelings and behaviors. Other people, situations, and events external to the individual are not seen as the sources of thoughts and behaviors. With CBT, patients are taught self-management skills to change negative thoughts even if external circumstances do not change.

Electroconvulsive therapy (ECT) is the application of electrical impulses to the brain for the treatment of severe or treatment refractory depression, psychotic depression, and treatment refractory mania. It also may be used in pregnant women who cannot take carbamazepine, lithium, or divalproex.

Education for patients, families, and groups about chronicity of bipolar disorder and self-management through sleep hygiene, nutrition, exercise, stress reduction, and abstinence from alcohol or drugs is critical to success. The development of a crisis intervention plan is essential.

Pharmacologic Therapy

KEY CONCEPT The primary treatment modality for manic episodes is mood-stabilizing agents or antipsychotic drugs, often in combination with each other.[14,12]

Table 40–2

Guidelines for the Acute Treatment of Mood Episodes in Patients With Bipolar I Disorder

Acute Manic or Mixed Episode	Acute Depressive Episode
General Guidelines	**General Guidelines**
Assess for secondary causes of mania or mixed states (eg. alcohol or drug use) Discontinue antidepressants Taper off stimulants and caffeine if possible Treat substance abuse Encourage good nutrition (with regular protein and essential fatty acid intake), exercise, adequate sleep, stress reduction, and psychosocial therapy	Assess for secondary causes of depression (eg. alcohol or drug use) Taper off antipsychotics, benzodiazepines, or sedative-hypnotic agents if possible Treat substance abuse Encourage good nutrition (with regular protein and essential fatty acid intake), exercise, adequate sleep, stress reduction, and psychosocial therapy

Hypomania	Mania	Mild-to-Moderate Depressive Episode	Severe Depressive Episode
First, optimize current mood stabilizer if noncompliance is suspected OR initiate mood-stabilizing medication: lithium[a], valproate[a], carbamazepine[a], or SGAs Consider adding a benzodiazepine (lorazepam or clonazepem) for short-term adjunctive treatment of agitation or insomnia if needed Alternative medication treatment options: oxcarbazepine **Second**, if response is inadequate, consider a two-drug combination: Lithium[a] **plus** an anticonvulsant or an SGA Aanticonvulsant **plus** an anticonvulsant or SGA	**First**, optimize previously prescribed mood stabilizer or medication regimen if noncompliance suspected OR initiate new mood-stabilizing two- or three-drug combinations (lithium[a], valproate[a], or SGA) **plus** a benzodiazepine (lorazepam or clonazepam) and/or antipsychotic for short-term adjunctive treatment of agitation or insomnia; lorazepam is recommended for catatonia Do not combine antipsychotics Alternative medication treatment options: carbamazepine[a]; if patient does not respond or tolerate, consider oxcarbazepine **Second**, if response is inadequate, consider a three-drug combination: Lithium[a] **plus** an anticonvulsant **plus** an antipsychotic Aanticonvulsant **plus** an anticonvulsant **plus** an antipsychotic **Third**, if response is inadequate, consider ECT for mania with psychosis or catatonia,[b] or add clozapine for treatment-refractory illness	**First**, initiate and/or optimize mood-stabilizing medication: lithium[a], quetiapine, lurasidone Alternative anticonvulsants: lamotrigine[c], valproate[a]; antipsychotics: fluoxetine/olanzapine combination	**First**, optimize current mood stabilizer if noncompliance is suspected OR initiate a new mood-stabilizing medication: lithium[a] or quetiapine or lurasidone Alternative fluoxetine/olanzapine combination If psychosis is present, initiate an antipsychotic in combination with above Do not combine antipsychotics Alternative anticonvulsants: lamotrigine[c], valproate[a] **Second**, if response is inadequate, consider carbamazepine[a] or antidepressant[d] **Third**, if response is inadequate, consider a three-drug combination: Lithium **plus** lamotrigine[c] **plus** an antidepressant[d] Lithium **plus** quetiapine **plus** antidepressant[d] **Fourth**, if response is inadequate, consider ECT for treatment-refractory illness and depression with psychosis or catatonia[b]

[a] Use standard therapeutic serum concentration ranges if clinically indicated; if partial response or breakthrough episode, adjust dose to achieve higher serum concentrations without causing intolerable adverse effects; valproate is preferred over lithium for mixed episodes and rapid cycling; lithium and/or lamotrigine is preferred over valproate for bipolar depression.

[b] ECT is used for severe mania or depression during pregnancy and for mixed episodes; prior to treatment, anticonvulsants, lithium, and benzodiazepines should be tapered off to maximize therapy and minimize adverse effects.

[c] Lamotrigine is not approved for the acute treatment of depression, and the dose must be started low and slowly titrated up to decrease adverse effects if used for maintenance therapy of bipolar I disorder. Lamotrigine may be initiated during acute treatment with plans to transition to this medication for long-term maintenance. A drug interaction and a severe dermatologic rash can occur when lamotrigine is combined with valproate (ie, lamotrigine doses must be halved from standard dosing titration).

[d] Controversy exists concerning the use of antidepressants, and they are often considered third line in treating acute bipolar depression, except in patients with no recent history of severe acute mania or potentially in bipolar II patients.

ECT, electroconvulsive therapy; SGA, second-generation antipsychotic.

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Mood-stabilizing drugs like lithium and divalproex are generally first-line treatments for acute mania. Many of the SGAs also have approvals for acute mania and are often used in combination with mood stabilizers especially if psychosis is present or faster response is needed. Carbamazepine can be considered as second-line therapy. Oxcarbazepine can be considered as third-line treatment in combination with divalproex or lithium. Benzodiazepines are used adjunctively for agitation and insomnia in acute manic episodes. Often the medications used for acute episodes are continued for maintenance therapy.

KEY CONCEPT The primary treatment for depressive episodes in bipolar disorder is mood-stabilizing agents or certain antipsychotics.

For treatment of bipolar depressive episodes, quetiapine, lithium, lamotrigine, or lurasidone monotherapy are recommended as first-line treatment options. Combinations of two mood-stabilizing drugs or a mood-stabilizing drug and either an

Table 40–3

Secondary Causes of Mania

Medical conditions that induce mania

- CNS disorders (brain tumors, strokes, head injuries, subdural hematoma, multiple sclerosis, systemic lupus erythematosus, temporal lobe seizures, Huntington's disease)
- Infections (encephalitis, neurosyphilis, sepsis, human immunodeficiency virus)
- Electrolyte or metabolic abnormalities (calcium or sodium fluctuations, hyperglycemia or hypoglycemia)
- Endocrine or hormonal dysregulation (Addison's disease, Cushing disease, hyperthyroidism or hypothyroidism, menstruation-related or pregnancy-related or perimenopausal mood disorders)

Medications or drugs that induce mania

- Alcohol intoxication
- Drug withdrawl states (alcohol, α_2-adrenergic agonists, antidepressants, barbiturates, benzodiazepines, opiates)
- Antidepressants (MAOIs, TCAs, 5-HT and/or NE and/or DA reuptake inhibitors, 5-HT antagonists)
- DA-augmenting agents (CNS stimulants: amphetamines, cocaine, sympathomimetics; DA agonists, releasers, and reuptake inhibitors)
- Hallucinogens (LSD, PCP)
- Marijuana intoxication precipitates psychosis, paranoid thoughts, anxiety, and restlessness
- NE-augmenting agents (α_2-adrenergic antagonists, β-agonists, NE reuptake inhibitors)
- Steroids (anabolic, adrenocorticotropic hormone, corticosteroids)
- Thyroid preparations
- Xanthines (caffeine, theophylline)
- Nonprescription weight loss agents and decongestants (ephedra, pseudoephedrine)
- Herbal products St. John's wort

Somatic therapies that induce mania

- Bright light therapy
- Deep brain stimulation
- Sleep deprivation

CNS, central nervous system; DA, dopamine; 5-HT, serotonin; LSD, lysergic acid diethylamide; MAOI, monoamine oxidase inhibitor; NE, norepinephrine; PCP, phencyclidine; TCA, tricyclic antidepressant.

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antipsychotic or antidepressant drug are common, especially in acute mood episodes. Antidepressants may be used but along with a mood stabilizer to reduce risk of a mood switch to mania and after the patient has failed to respond adequately to mood-stabilizing therapy. Evidence of efficacy of antidepressant drugs in bipolar depression is considered controversial.[14,15] Among antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (TCAs) are more likely than other antidepressants to cause a pharmacologic mood switch to mania or a mood episode with mixed mood features and are not recommended by current guidelines.[14]

KEY CONCEPT The primary treatment for relapse prevention is mood-stabilizing agents, often combined with antipsychotic drugs.

Lamotrigine, lithium, aripiprazole (oral and long-acting injectable [LAI] formulations), risperidone LAI, and quetiapine are approved for maintenance therapy. Table 40–4 includes a summary of current drug therapy for bipolar disorder. An algorithm for treatment of bipolar mania is shown in Table 40–2.

▶ *Mood-Stabilizing Drugs*

The optimal mood-stabilizing drug is effective in treatment of acute mania, hypomania, acute bipolar depression, and in prevention of mania relapse and bipolar depression relapse. All currently approved mood-stabilizing drugs have demonstrated efficacy over placebo for one or more of these types of episodes, but there are differences among them especially for specific patient populations. The choice of treatment is dictated by patient characteristics, patient history, and side effect profile. Few studies systematically compare mood stabilizers with each other. Efficacy of individual agents in placebo-controlled trials is similar.

Lithium Lithium, the first approved mood-stabilizing drug, remains a first-line agent and sets the standard for efficacy against which other drugs are measured. It is antimanic, prevents relapse, and has modest efficacy for acute bipolar depression.[14] In most studies, the efficacy of lithium is equivalent to that of anticonvulsant mood stabilizers and SGAs. It is most effective for patients with few previous episodes, symptom-free interepisode remission, and a family history of bipolar disorder with good response to lithium.[14,16] However, patients with rapid cycling are less responsive to lithium than to other mood-stabilizing drugs such as divalproex.[14,17] It may also be less effective in mood episodes with mixed mood features (symptoms of mania and depression occurring simultaneously). Evidence shows lithium reduced the risk of suicide when compared to placebo.[18]

The mechanism of action of lithium is not well understood and is multimodal. Possibilities include altered ion transport, effects on neurotransmitter signaling, blocking adenyl cyclase, effects on inositol, neuroprotection or increased BDNF, and inhibition of second messenger systems.[19]

Lithium is usually initiated at a dosage of 600 to 900 mg/day. Although it is commonly given in a divided dosage, once-daily dosing is recommended, especially with sustained-release formulations. Once-daily dosing can improve adherence and reduce the risk of developing renal insufficiency. Lithium has a narrow therapeutic index, meaning the toxic dosage is not much greater than the therapeutic dosage. Lithium requires regular serum concentration monitoring as a guide to titration and to minimize adverse effects. At least weekly monitoring is recommended until the level is therapeutic; then the frequency can be decreased. Well-maintained patients who tolerate lithium without difficulty can be monitored by serum concentration as infrequently as twice yearly. The dosage is titrated to achieve a serum lithium concentration of 0.6 to 1.2 mEq/L (mmol/L). Higher serum concentrations are required to treat an acute episode than to prevent relapse. Serum lithium above 0.8 mEq/L (mmol/L) may be more effective at preventing relapse than lower serum concentrations. The suggested therapeutic serum concentration range is based on a 12-hour postdose sample collection at steady state. At least 2 weeks at a suggested therapeutic serum concentration is required for an adequate trial. If unable to achieve remission with lithium monotherapy, it is common to combine with other mood stabilizers or antipsychotics to achieve complete remission.

The most common adverse effects are gastrointestinal (GI) upset, tremor, and polyuria, which are dose-related.[20] Nausea, dyspepsia, and diarrhea are minimized by coadministration with food, use of the sustained-release formulation, and giving smaller doses more frequently to reduce the amount of drug in the GI tract. Fine hand tremor at therapeutic serum levels is common in patients. Low-dose β-blockers, such as propranolol 20 to 60 mg/day, may be used to reduce tremor.

Lithium impairs the kidney's ability to concentrate urine because of its inhibitory effect on vasopressin. This causes an increase in thirst, urine volume, and frequency of urination.

Table 40–4

Product Formulation, Dose, and Clinical Use of Agents Used in Treatment of Bipolar Disorder

Drug "Brand Name"	Initial Dosing	Usual Dosing; Special Population Dosing	Comments
Lithium salts			
Lithium carbonate "Eskalith[a,b]" "Eskalith CR" Lithium citrate "Cibalith-S[a,b]"	300 mg twice daily	900-2,400 mg/day in two to four divided doses, preferably with meals Renal impairment: lower doses required with frequent serum monitoring There is wide variation in the dosage needed to achieve therapeutic response and trough serum lithium concentration (ie, 0.6-1.2 mEq/L [mmol/L] for maintenance therapy and 0.8-1.2 mEq/L [mmol/L] for acute mood episodes taken 12 hours after the last dose)	Use alone or in combination with other medications (eg, valproate, carbamazepine, antipsychotics) for the acute treatment of mania and for maintenance treatment
Anticonvulsants			
Divalproex sodium "Depakote[a]" "Depakote ER" Valporic acid[a] "Depakene" Valproate sodium "Depacon"	250-500 mg twice daily A loading dose of divalproex (20-30 mg/kg/day) can be given	750-3,000 mg/day (20-60 mg/kg/day) given once daily or in divided doses Titrate to clinical response Dose adjustment needed with hepatic impairment	Use alone or in combination with other medications (eg, lithium, carbamazepine, antipsychotics) for the acute treatment of mania and for maintenance treatment Use caution when combining with lamotrigine of potential drug interaction
Lamotrigine "Lamictal[b]"	25 mg daily	50-400 mg/day in divided doses. Dosage should be slowly increased (eg, 25 mg/day for 2 weeks, then 50 mg/day for weeks 3 and 4, and then 50-mg/day increments at weekly intervals up to 200 mg/day) Dose adjustment needed with hepatic impairment	Use alone or in combination with other medications (eg, lithium, carbamazepine) for long-term maintenance treatment for bipolar I disorder
Carbamazepine "Equetro[a]" "Tegretol" "Epitol" "Tegretol-XR" "Carbatrol"	200 mg twice daily	200-1,800 mg/day in two to four divided doses Titrate to clinical response Dose adjustment needed with hepatic impairment	Use alone or in combination with other medications (eg, lithium, valproate, antipsychotics) for the acute and long-term maintenance treatment of mania or mixed episodes for bipolar I disorder. APA guidelines recommend reserving it for patients unable to tolerate or who have inadequate response to lithium or valproate Extended-release tablets should be swallowed whole and not be broken or chewed "Carbatrol" capsules can be opened and contents sprinkled over food
Oxcarbazepine "Trileptal"	300 mg twice daily	300-1,200 mg/day in two divided doses Titrate based on clinical response Dose adjustment required with severe renal impairment	Use after patients have failed treatment with carbamazepine or have intolerable side effects May have fewer adverse effects and be better tolerated than carbamazepine
Atypical antipsychotics			
Aripiprazole "Abilify[a,b]" "Abilify Maintena[b]"	10-15 mg daily	10-30 mg/day once daily	
Asenapine "Saphris[a]"	5-10 mg twice daily sublingually	5-10 mg twice daily sublingually	
Cariprazine "Vraylar[a]"	1.5 mg daily	3-6 mg daily	
Lurasidone "Latuda[c]"	20 mg daily	20-120 mg daily with food	
Olanzapine "Zyprexa[a,b]" "Zyprexa Zydis"	2.5-5 mg twice daily	5-20 mg/day once daily or in divided doses	
Olanzapine and fluoxetine "Symbyax[c]"	6 mg olanzapine and 25 mg fluoxetine daily	6-12 mg olanzapine and 25-50 mg fluoxetine daily	
Quetiapine "Seroquel[a,b]"	50 mg twice daily	50-800 mg/day in divided doses or once daily when stabilized	

(*Continued*)

Table 40–4

Product Formulation, Dose, and Clinical Use of Agents Used in Treatment of Bipolar Disorder (*Continued*)

Drug "Brand Name"	Initial Dosing	Usual Dosing; Special Population Dosing	Comments
Risperidone "Risperdal[a]" "Risperdal M-Tab" "Risperdal Consta[b]"	0.5-1 mg twice daily	0.5-6 mg/day once daily or in divided doses	
Ziprasidone "Geodon[a]"	40-60 mg twice daily	40-160 mg/day in divided doses	
Benzodiazepines			
Various	Dosage should be slowly adjusted up and down according to response and adverse effects	Use in combination with other medications (eg, antipsychotics, lithium, valproate) for the acute treatment of mania or mixed episodes Use as a short-term adjunctive sedative–hypnotic agent	

[a]FDA-approved for acute mania.

[b]FDA-approved for maintenance.

[c]FDA-approved for acute bipolar depression.

FDA-approved agents may be used as monotherapy in various phases of the illness as noted in table footnotes.[a,b,c]

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Polyuria and polydipsia occur in up to 60% of patients.[19] A severe form of polyuria, when urine volume exceeds 3 L/day, is termed lithium-induced nephrogenic diabetes insipidus. It can be treated with hydrochlorothiazide or amiloride. If the former is used, the lithium dosage should be reduced to account for the drug–drug interaction that increases serum lithium and causes toxicity. Long-term lithium has been associated with structural kidney changes, such as glomerular sclerosis or tubular atrophy. Once-daily dosing of lithium is less likely to cause renal adverse effects than divided-daily dosing.[19]

Hypothyroidism can develop in up to 10% of patients taking lithium, and 23% have subclinical disease. Women are at greater risk of this adverse effect.[19] Lithium-induced hypothyroidism is not usually an indication to discontinue the drug. Patients can be supplemented with thyroid hormone replacement therapy.

Other common adverse effects include poor concentration, acneiform rash, alopecia, worsening of psoriasis, weight gain, metallic taste, impaired glucose regulation, and benign leukocytosis. Lithium causes a flattening of the T wave of the electrocardiogram (ECG), considered benign and not clinically significant. Less commonly, it can cause or worsen arrhythmias.[20]

Lithium and other mood-stabilizing drugs require baseline and routine laboratory monitoring to help determine medical appropriateness for initiation of therapy and monitoring of adverse effects. Guidelines for such monitoring are outlined in Table 40–5.

Acute lithium toxicity, which usually occurs at serum concentrations over 2 mEq/L (mmol/L), can be severe and life threatening, necessitating emergency treatment. Milder toxicity can occur at concentration between 1.5 and 2 mEq/L (mmol/L).[20] Symptoms of toxicity include vomiting and diarrhea; deterioration in motor coordination, including coarse tremor, ataxia, and dysarthria; and impaired cognition. In its most severe form, seizures, cardiac arrhythmias, coma, and kidney damage are reported. Treatment includes discontinuation of lithium, IV fluids to correct fluid and electrolyte imbalance, and osmotic diuresis or hemodialysis. In case of overdose, gastric lavage is indicated if the person presents within 1 hour of ingestion and is not somnolent. Clinical symptoms continue after the serum concentration is lowered because clearance from the central nervous system (CNS) is slower than from serum. Factors predisposing people to lithium toxicity include dehydration, acute illness, exercise (sweating), or drug interactions that increase serum lithium.[20]

Drug interactions involving lithium are common. Because lithium is not metabolized or protein bound, it is not associated with metabolic drug interactions that occur with other mood-stabilizing drugs. Common and significant drug interactions involve thiazide diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin receptor blockers (ARBs), and angiotensin-converting enzyme (ACE) inhibitor drugs. If a diuretic must be used with lithium, and a thiazide is not required, loop or potassium-sparing diuretics such as furosemide or spironolactone are less likely to increase lithium retention. ACE inhibitors and ARBs can abruptly increase serum lithium with the potential for acute toxicity, including fatal toxicity, even after months of no change in serum lithium. This combination is strongly discouraged.[20] Any drug or condition that can cause hyponatremia may increase lithium toxicity.

Divalproex Sodium and Valproic Acid Divalproex sodium is composed of sodium valproate and valproic acid. The delayed- and extended-release formulations are converted in the intestine into valproic acid (VPA), which is systemically absorbed. It is FDA approved for treatment of the manic phase of bipolar disorder. It is equal in efficacy to lithium and some antipsychotics for bipolar mania. It has utility in bipolar disorder with rapid cycling, mood episodes with mixed mood features, and substance use comorbidity. Although not FDA approved for relapse prevention, studies support its use, and it is widely prescribed for maintenance therapy. Divalproex can be used as monotherapy or in combination with lithium or an antipsychotic.[14]

Its mechanism for bipolar disorder is not well understood. It is known to affect ion transport and enhance activity of γ-aminobutyric acid (GABA).[19]

Divalproex is commonly initiated at 500 to 1000 mg/day, but studies indicate a therapeutic serum VPA concentration can be reached more quickly through a loading dose approach of 20 to 30 mg/kg/day. Using this approach, patients may respond with

Table 40–5

Guidelines for Baseline and Routine Laboratory Tests and Monitoring for Agents Used in the Treatment of Bipolar Disorder

	Baseline: Physical Examination and General Chemistry[a]	Hematologic Tests[b]		Metabolic Tests[c]		Liver Function Tests[d]		Renal Function Tests[e]		Thyroid Function Tests[f]		Serum Electrolytes[g]		Dermatologic[h]		Pharma-cogenomic Testing
	Baseline	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline
SGAs[i]	X			X	X											
Carbamazepine[j]	X	X	X			X	X	X				X	X	X	X	X
Lamotrigine[k]	X													X	X	
Lithium[l]	X	X	X	X	X			X	X	X	X	X	X	X	X	
Oxcarbazepine[m]	X											X	X			X
Valproate[n]	X	X	X	X	X	X	X							X	X	

[a] Screen for drug abuse and serum pregnancy.

[b] Complete blood cell count (CBC) with differential and platelets.

[c] Fasting glucose, serum lipids, and weight.

[d] Lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, and alkaline phosphatase.

[e] Serum creatinine, blood urea nitrogen, urinalysis, urine osmolality, and specific gravity.

[f] Triiodothyronine, total thyroxine, thyroxine uptake, and thyroid-stimulating hormone.

[g] Serum sodium.

[h] Rashes, hair thinning, and alopecia.

[i] Second-generation antipsychotics: Monitor for increased appetite with weight gain (primarily in patients with initial low or normal body mass index); monitor closely if rapid or significant weight gain occurs during early therapy; cases of hyperlipidemia and diabetes reported.

[j] Carbamazepine: Manufacturer recommends CBC and platelets (and possibly reticulocyte counts and serum iron) at baseline, and that subsequent monitoring be individualized by the clinician (eg, CBC, platelet counts, and liver function tests every 2 weeks during the first 2 months of treatment, and then every 3 months if normal). Monitor more closely if patient exhibits hematologic or hepatic abnormalities or if the patient is receiving a myelotoxic drug; discontinue if platelets are$<100,000/\text{mm}^3$ (100×10^9/L), if white blood cell (WBC) count is$<3,000/\text{mm}^3$ (3×10^9/L), or if there is evidence of bone marrow suppression or liver dysfunction. Serum electrolyte levels should be monitored in the elderly or those at risk for hyponatremia. Carbamazepine interferes with some pregnancy tests.

[k] Lamotrigine: If renal or hepatic impairment, monitor closely and adjust dosage according to manufacturer's guidelines. Serious dermatologic reactions have occurred within 2 to 8 weeks of initiating treatment and are more likely to occur in patients receiving concomitant valproate, with rapid dosage escalation, or using doses exceeding the recommended titration schedule.

[l] Lithium: Obtain baseline electrocardiogram for patients older than 40 years or if preexisting cardiac disease (benign, reversible T-wave depression can occur). Renal function tests should be obtained every 2 to 3 months during the first 6 months, and then every 6 to 12 months; if impaired renal function, monitor 24-hour urine volume and creatinine every 3 months; if urine volume >3 L/day, monitor urinalysis, osmolality, and specific gravity every 3 months. Thyroid function tests should be obtained once or twice during the first 6 months, and then every 6 to 12 months; monitor for signs and symptoms of hypothyroidism; if supplemental thyroid therapy is required, monitor thyroid function tests and adjust thyroid dose every 1 to 2 months until thyroid function indices are within normal range, and then monitor every 3 to 6 months.

[m] Oxcarbazepine: Hyponatremia (serum sodium concentrations<125 mEq/L [mmol/L]) has been reported and occurs more frequently during the first 3 months of therapy; serum sodium concentrations should be monitored in patients receiving drugs that lower serum sodium concentrations (eg, diuretics or drugs that cause inappropriate antidiuretic hormone secretion) or in patients with symptoms of hyponatremia (eg, confusion, headache, lethargy, malaise). Hypersensitivity reactions have occurred in approximately 25% to 30% of patients with a history of carbamazepine hypersensitivity and require immediate discontinuation.

[n] Valproate: Weight gain reported in patients with low or normal body mass index. Monitor platelets and liver function during first 3 to 6 months if evidence of increased bruising or bleeding. Monitor closely if patients exhibit hematologic or hepatic abnormalities or in patients receiving drugs that affect coagulation, such as aspirin or warfarin; discontinue if platelets are$<100,000/\text{mm}^3$/L (100×10^9/L) or if prolonged bleeding time. Pancreatitis, hyperammonemic encephalopathy, polycystic ovary syndrome, increased testosterone, and menstrual irregularities have been reported; not recommended during first trimester of pregnancy due to risk of neural tube defects.

SGAs, second-generation antipsychotics.

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a significant reduction in symptoms of acute mania within the first few days of treatment but with increased risk of GI adverse effects. The dosage is titrated according to response, tolerability, and serum concentration. The most often referenced VPA serum concentration is 50 to 125 mcg/mL (mg/L; 347–866 μmol/L); however, this range was initially established for seizure control, and the correlation with these levels and response in the treatment of bipolar disorder is not well established. It is not unusual for patients to require higher concentrations in the therapeutic range for optimal efficacy. Some patients require high dosages in order to reach a desired serum concentration. The suggested serum concentration range is based on trough values at steady state. Serum concentration monitoring is recommended at least every 2 weeks until stabilized, then less frequently. The systemic bioavailability of extended-release divalproex is about 15% less than that of the delayed-release formulation. Patients who have difficulty swallowing large tablets can use the sprinkle formulation, which is delayed release. The immediate-release formulation, either capsules or syrup, is given three or four times per day.[21]

The most common adverse effects are GI-related (loss of appetite, nausea, dyspepsia, diarrhea), tremor, and drowsiness. GI distress can be reduced by coadministration with food, switching to the delayed- or extended-release formulations, or reducing the dose. As with lithium, a low-dose β-blocker may alleviate tremor.

Other adverse effects include alopecia or a change in hair color or texture. Hair loss can be minimized by supplementation with a vitamin containing selenium and zinc. Weight gain also commonly occurs. Polycystic ovarian syndrome associated with increased androgen production is reported. Thrombocytopenia is more common with high serum levels, and the platelet count should be monitored periodically. It is a dose-related, reversible adverse effect and usually asymptomatic, but the drug is usually stopped if the platelet count is less than $100 \times 10^3/\text{mm}^3$ ($100 \times 10^9/\text{L}$). Rarer are hepatic toxicity and pancreatitis, which are not always dose related. There is a black box warning for both as fatalities have occurred. Severe GI symptoms of hepatic or pancreatic toxicity include vomiting, abdominal pain, and loss of appetite. When these occur, the patient should be evaluated for possible hepatitis or pancreatitis. Hyperammonemia has been reported. If patients develop unexplained lethargy and vomiting or changes in mental status, an ammonia level should be measured. Divalproex has a wide therapeutic index. Acute toxicity for high dosages or over dosage is not life threatening.

Drug interactions involving divalproex are common. It is a weak inhibitor of some drug metabolizing liver enzymes and can affect metabolism of other drugs. The interaction between divalproex and lamotrigine is significant. The risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), a dangerous, life-threatening rash, increases with this combination due to divalproex inhibiting the metabolism of lamotrigine causing rapid increases in lamotrigine serum concentrations. Conversely, the metabolism of divalproex can be increased by enzyme-inducing drugs such as carbamazepine and phenytoin. Divalproex is highly protein bound and may displace other protein-bound medications (ie, phenytoin, warfarin, etc). Carbapenem antibiotics can significantly reduce serum valproic acid levels, requiring close therapeutic monitoring.[21]

Carbamazepine Although all formulations are used as a mood stabilizer, only the extended-release formulation is FDA approved for treatment of bipolar disorder. Carbamazepine has efficacy for mood stabilization; however, it is less desirable as a first-line agent because of adverse effects and drug interactions. Carbamazepine may be considered in patients who have a history of head trauma, comorbid anxiety, and substance use disorder. Carbamazepine can be used as monotherapy or in combination with lithium or divalproex.[14]

The mechanism of action of carbamazepine for bipolar disorder is not well understood. It blocks ion channels and inhibits sustained repetitive neuronal excitation, but whether this explains its efficacy as a mood stabilizer is not known.[22]

Carbamazepine is initiated at 400 to 600 mg/day. The immediate-release formulation can be given in two to four divided doses and the sustained-release formulation can be given in two divided doses. An additional extended-release formulation contains a matrix of 25% immediate-release, 40% extended-release, and 35% enteric-release beads.[22] The suggested therapeutic serum concentration is 4 to 12 mcg/mL (mg/L; 17–51 μmol/L); however, this range was initially established for seizure control, and the correlation with these levels and response in the treatment of bipolar disorder is not well established. The dosage can be increased by 200 to 400 mg/day as often as every 2 to 4 days. Serum concentration monitoring is suggested at least every 2 weeks until concentrations stabilize, due to autoinduction.[22]

The most common adverse effects are GI upset, drowsiness, dizziness, ataxia, lethargy, and confusion. At mildly toxic levels, it causes diplopia and dysarthria. These can be minimized through dosage adjustments, use of sustained-release formulations, and giving more of the drug late in the day. Carbamazepine has an antidiuretic effect similar to the syndrome of inappropriate antidiuretic hormone secretion and can cause hyponatremia. Mild elevations in liver enzymes can occur; hepatotoxicity is less common. Mild, dose-related leukopenia is not unusual and not an indication for discontinuation. Black box warnings exist for aplastic anemia and agranulocytosis, which are rare but life threatening.[22] Additionally, TEN and SJS have been reported. Higher risk of these serious dermatologic reactions is associated with the HLA-B*1502 allele found almost exclusively in Asian ancestry. Per the black box warning, patients with ancestry from the at-risk population should have genetic testing done prior to initiation of carbamazepine.[22,23] See Chapter 32 for a full discussion. Suggested baseline and routine laboratory monitoring are reviewed in Table 40–5.

Carbamazepine induces hepatic metabolism of many drugs, including other anticonvulsants, antipsychotics, some antidepressants, oral contraceptives, and antiretroviral agents. Carbamazepine is an autoinducer (ie, it induces its own metabolism). The dosage may require an increase up to a month after initiation because of this effect. Conversely, the metabolism of carbamazepine can be slowed by enzyme-inhibiting drugs such as some antidepressants; macrolide antibiotics, including erythromycin and clarithromycin; azole antifungal drugs, including ketoconazole and itraconazole; and grapefruit juice.

Lamotrigine Lamotrigine is effective for maintenance treatment of bipolar disorder. It is more effective for depression relapse prevention than for mania relapse prevention. Its primary limitation as an acute treatment is the time required for titration to an effective dosage. In addition to maintenance monotherapy, lamotrigine is sometimes used in combination with other mood stabilizers.[24]

The mechanism of action of lamotrigine appears to involve blockage of ion channels and effects on glutamate transmission, although the precise mechanism in bipolar disorder is not clear.[24]

Lamotrigine is initiated at 25 mg/day for 2 weeks, then increased in a dose-doubling manner every 2 weeks to a target of 200 to 400 mg/day if no drug interactions are present. However, differing dose titrations are required with certain other drugs like divalproex or phenytoin. For example, lamotrigine would be initiated at a 50% higher dose with phenytoin and the titration with divalproex would be slowed by 50% to 25 mg every other day for 2 weeks, then 25 mg daily. If lamotrigine therapy is interrupted for more than five half-lives, it should be restarted at the initial dosage and retitrated. Serum concentration monitoring is not recommended.[24]

The adverse effect of greatest significance is a maculopapular rash, occurring in up to 10% of patients.[24] Although usually benign and temporary, some rashes can progress to life-threatening SJS and TEN. The risk of rash is greater with a rapid dosage titration, when given concurrently with divalproex or other metabolic enzyme inhibitors, and in pediatric patients.[24] The risk is minimal in adults when the dosage titration schedule is completed according to the package insert. Other side effects include dizziness, drowsiness, headache, blurred vision, and nausea. In contrast to other mood-stabilizing drugs such as lithium and divalproex, lamotrigine does not significantly influence body weight.

The mechanisms of drug–drug interactions involving lamotrigine are unclear. The primary route of metabolism for lamotrigine is conjugative glucuronidation. It is not significantly metabolized by CYP P450 enzymes. It does not affect drug-metabolizing hepatic enzymes. When the combination of divalproex and lamotrigine is used, 50% dose decreases of lamotrigine are necessary due to the drug–drug interaction. Conversely, carbamazepine and estrogen-containing oral contraceptives increase the rate of lamotrigine metabolism. Upward adjustment in lamotrigine dosage is usually needed.[24]

Oxcarbazepine Oxcarbazepine is an analogue of carbamazepine, developed as an anticonvulsant. An advantage over carbamazepine is that routine monitoring of hematology profiles and serum concentrations is not indicated because it is less likely to cause hematologic abnormalities.[25] Additionally, drug interactions are less significant, although it is a mild inducer of certain metabolic pathways. Vigilance for drug interactions is needed, especially with oral contraceptives. Oxcarbazepine appears in the most recent treatment algorithms for bipolar disorder,[14] but clinical trial data are limited.[26]

Common adverse effects include drowsiness, dizziness, GI upset, and hyponatremia, the latter two of which may be more likely than with carbamazepine.[25]

Others Benzodiazepine agents such as clonazepam and lorazepam are used as adjunctive therapy, especially during acute mania, to reduce anxiety and improve sleep.[14,27] As complementary or alternative medicines gain wider usage, omega-3 fatty acids have been studied in mood disorders but are not recommended in treatment guidelines.

▶ *Antipsychotic Drugs*

Antipsychotics, such as aripiprazole, asenapine, cariprazine, haloperidol, olanzapine, quetiapine, risperidone, and ziprasidone, are effective and frequently used in the treatment of acute mania both as monotherapy and in combination with mood stabilizers. Studies demonstrate combination therapy with SGAs, and lithium or divalproex is more effective, with 20% more patients responding compared to monotherapy with lithium or divalproex. In addition, adjunctive therapy with antipsychotics is preferred if a rapid response is needed. Antipsychotics also play a role in the treatment of bipolar depression. Quetiapine, lurasidone, cariprazine, and the combination of olanzapine and fluoxetine are approved for treatment of acute bipolar depression.[14,28]

The mechanisms of action, usual dosages, pharmacokinetics, adverse effects, and drug interactions involving antipsychotic drugs are discussed in detail in Chapter 38. Dosages in bipolar disorder are similar to those used in schizophrenia; however, higher dosages are often required to treat an acute manic episode while lower doses are used in the treatment of bipolar depressive episodes. The recommended dosage of aripiprazole for bipolar disorder is 20 to 30 mg/day, somewhat higher than the average dosage used in schizophrenia.[29] The recommended dosage for quetiapine in treatment of acute bipolar depression is 300 mg/day, whereas 600 mg/day is recommended in acute mania.[30]

The SGAs are less likely than FGAs to cause movement abnormalities but are more likely to cause metabolic side effects, such as weight gain, glucose dysregulation, and dyslipidemia.[31] Among SGAs approved for treatment of bipolar disorder, olanzapine is most likely to cause metabolic side effects.

▶ *Antidepressants*

Treatment of depressive episodes in patients with bipolar disorder presents a challenge because of the risk of a drug-induced mood switch to mania. The FDA requires the product label of all antidepressants to contain language about the potential risk of inducing a mood switch to mania. Most research shows no advantage for adjunctive antidepressant use compared with mood-stabilizer therapy alone.[14,15] When usual treatment fails, antidepressants may be used.[14,15]

When antidepressants are used, they should be combined with a mood stabilizer to reduce risk of mood switch.[14] The MAOIs, TCAs, and SNRIs are thought to carry greater risks of causing a mood switch to mania. A comparison of venlafaxine, sertraline, and bupropion as adjunctive therapy to a mood stabilizer showed venlafaxine with highest risk of a mood switch to mania or hypomania and bupropion with the least.[32]

Special Populations

Assessment and management by appropriate psychiatric specialists are important for special populations, such as pediatric, geriatric, and pregnant patients.

▶ *Pediatrics*

Evidence regarding treatment of bipolar disorder in children and adolescents is more limited than in adults. Lithium is FDA approved for treatment of bipolar disorder in children and adolescents as young as age 12. Aripiprazole, olanzapine/fluoxetine combination, quetiapine, and risperidone are FDA approved in children and adolescents as young as age 10.[14,33]

Initial dosages in the pediatric population are lower than in adults. Metabolic elimination rates of many drugs are increased in children, so they may require higher dosages on a weight-adjusted basis. Dosages are titrated carefully according to response and tolerability.

Children and adolescents are especially likely to experience weight gain from SGAs.[34] Cognitive toxicity, manifested as confusion, memory or concentration impairment, or impaired learning, is difficult to detect and is a consideration in the pediatric population so that intellectual and educational development is not hindered.

For comorbid bipolar disorder and attention-deficit/hyperactivity disorder when stimulant therapy is indicated, treatment of mania is recommended before starting the stimulant to avoid exacerbation of mood symptoms.

▶ *Geriatrics*

Treatment of older adults with bipolar disorder requires care because of increased risks associated with medical conditions and drug–drug interactions.[35] General medical conditions, including endocrine, metabolic, or infectious diseases, can mimic mood disorders. Patients should be evaluated for such medical illnesses that cause or worsen mood symptoms. As physiologic systems change with aging, elimination of drugs is slowed. Examples are slowed renal elimination of lithium and slowed hepatic metabolism of VPA. Also, changes in membrane permeability increase risk of CNS side effects. As a result, older patients may respond at lower serum levels of drugs and may experience toxicity when serum levels are within the normal therapeutic range for younger adults. Increased frequency of patient monitoring is required, including serum drug concentration monitoring.

Vigilance for drug–drug interactions in the geriatric population is required because more medications tend to be prescribed to older adults. Pharmacokinetic interactions include metabolic enzyme induction or inhibition and protein binding displacement interactions (eg, divalproex and warfarin). Pharmacodynamic interactions include additive sedation and cognitive toxicity, which increase risk of falls and other impairments.

▶ *Pregnancy and Postpartum*

Treatment of bipolar disorder during pregnancy is complex, and the relative risk of teratogenicity of medications must be balanced with the risk of harm to patient and fetus from untreated bipolar disorder. Clinicians should discuss pregnancy planning with every patient with bipolar disorder who is of childbearing potential. A pregnancy test should be obtained before initiating therapy. For a patient with severe illness or a history of multiple mood episodes, rapid cycling, or suicide attempts, discontinuing treatment, even for a planned pregnancy, is unwise. For a patient with a remote history of a single mood episode with subsequent long-term stability and contemplating pregnancy, the answer is less clear. Patients should be provided clear and reliable information about risks versus benefits of stopping or continuing therapy so they can make an informed decision. Patients who decide to discontinue medication before pregnancy should taper medication slowly.[14,36]

Lithium administration during the first trimester is associated with **Ebstein anomaly**, a downward displacement of the tricuspid valve. Although cardiac defects are more likely to occur in children of patients who took lithium during pregnancy, the absolute risk appears to be small.[37] Lithium can also cause hypotonicity and cyanosis in the neonate, termed the "floppy baby" syndrome.[36]

Pharmacokinetic handling of lithium changes as pregnancy progresses. Renal lithium clearance increases, which requires a dosage increase to maintain a therapeutic serum concentration. It is advisable to decrease or discontinue lithium at term or onset of labor to avoid toxicity postpartum when there is a large reduction in fluid volume.[38]

Lithium is readily transferred via breast milk. Breastfeeding is not advised for patients taking lithium unless the benefits to the mother outweigh the risks to the infant.[20]

The risk of facial abnormalities is increased with VPA and carbamazepine. Neural tube defects such as spina bifida occur in up to 3.8% of infants exposed to VPA.[36]. The risk of neural tube defects is related to exposure during the third and fourth weeks of gestation. As such, women with unplanned pregnancies may not know they are pregnant until after the risk of exposure has occurred. Children born to mothers exposed to VPA during pregnancy have substantially lower IQ than children exposed to other antiseizure medications. Women of childbearing potential should not receive VPA therapy unless all other therapies have failed and utilize effective contraception.[38]

Carbamazepine can cause fetal vitamin K deficiency. Vitamin K is important for facial growth and for clotting factors, and neonatal bleeding is increased in infants of mothers who are treated with carbamazepine during pregnancy.[39,40]

Fewer data are available on other anticonvulsant mood-stabilizing drugs. Lamotrigine may be associated with an increased risk of oral clefts but, overall, is relatively safer in pregnancy than other anticonvulsants.[39,40]

The FGAs have been available for many years, and more data are available on their use in pregnancy compared with SGAs, but guidelines for bipolar disorder do not support FGAs as an initial choice.[14]

Use of antidepressant drugs during pregnancy is discussed in Chapter 39.

OUTCOME EVALUATION

Assessment of Therapeutic Effects

Effective interviewing skills and a therapeutic relationship with the patient are essential to assessing medication therapy. It is important to understand the patient's symptom profile and specific needs of individual patients. In addition, therapeutic level monitoring is indicated for optimal efficacy of some mood-stabilizing drugs. These are some of the primary therapeutic monitoring parameters. In addition to the clinical interview, some clinicians use symptom rating scales such as the Young Mania Rating Scale (YMRS) for mania and the Hamilton Depression Rating Scale (HAM-D) for depression (discussed in Chapter 39). The YMRS is composed of 11 items based on a patient's perception over the preceding 48 hours. Adjunctive information is obtained from clinical observations. The scale takes about 15 to 30 minutes to administer.[41] The frequency of follow-up visits depends on response, tolerability, and adherence.

Assessment of Adverse Effects

Adverse effects frequently contribute to medication nonadherence. Monitor patients regularly for adverse effects and health status, especially since mood stabilizers and antipsychotics commonly cause metabolic side effects such as weight gain. Periodically monitor laboratory tests for renal and thyroid function for patients taking lithium and hematology and liver function for patients taking

Patient Encounter Part 4: Outcome Evaluation

After an initial psychiatric assessment, including evaluation of potential suicidality, support systems, and need for inpatient versus outpatient treatment, the patient was hospitalized briefly and then referred for follow-up in the community. Patient's school performance and grades are improving, although she remains on academic probation. While hospitalized, she was stabilized on lithium carbonate 900 mg by mouth daily and quetiapine 400 mg by mouth every night. Recent lithium level was 1 mEq/L (mmol/L). She now returns to the clinic for routine follow-up. Patient initially reported a mild bilateral hand tremor secondary to lithium, but this has resolved with the addition of propranolol 20 mg by mouth daily. She denies other medication side effects but asks how long she must continue the medication since she is feeling "completely like my old self."

How would you assess therapeutic and adverse effects of treatment for this patient?

How would you educate the patient regarding the need for continued maintenance treatment?

Patient Care Process

Collect information:

- Assess the patient's symptoms.
- Review the family history, including the history of response to treatment by family members.
- Obtain an initial medical evaluation to rule out other causes of mood episodes.
- Evaluate physiologic parameters that may influence pharmacokinetics.
- Obtain a thorough medication use history, including present and past prescription and nonprescription drugs, the patient's self-assessment of response and side effects, alcohol, tobacco, caffeine, illicit substances, herbal products, dietary supplements, allergies, and adherence.

Assess the Information:

- Assess potential drug–disease, drug–drug, and drug–food interactions.

Develop a Care Plan:

- Develop a plan for monitoring therapeutic outcomes, focusing on the individual symptom profile and level of function of the patient. Include a plan for dosage adjustments or alternate therapy if the patient fails to respond adequately. Include serum drug concentration monitoring for efficacy if a therapeutic level is established (eg, lithium therapeutic level 0.6–1.2 mEq/L [mmol/L]).
- Develop a monitoring plan for drug side effects. Include measures to prevent side effects as well as management if they occur. Include appropriate laboratory measures.
- Determine the role of nonpharmacologic therapy and how it is to be integrated with drug therapy.

Implement the Care Plan:

- Educate the patient on the nature of bipolar disorder, its treatment, and what to expect regarding response and side effects and stress the need for adherence to treatment even when feeling well.
- Encourage a healthy lifestyle, including eliminating or stopping substance abuse, smoking cessation, and encouraging proper nutrition and exercise.

Follow-up: Monitor and Evaluate:

- Monitor the patient daily if hospitalized or every 1 to 4 weeks depending on presentation and symptom severity if outpatient to assess efficacy and safety until stabilized. Utilize the clinical interview, physical examination, and laboratory tests.
- Once stabilized, follow-up at decreased frequency, every 1 to 6 months with decreasing follow-up the longer someone is stabilized. Use the same parameters and check for new drugs or drug–drug interactions as necessary.

carbamazepine or divalproex. More specific discussion of side effect monitoring of patients taking SGAs is provided in Chapter 38.

Patient Education

KEY CONCEPT Educate the patient regarding benefits and risks of drug therapy, and the importance of adherence must be integrated into treatment plans. Discuss the nature and chronic course of bipolar disorder and risks of repeated relapses. Help patients understand treatment is not a cure but that many patients enjoy symptom-free or nearly symptom-free function. Educate patients and their family about the purpose of medication, common adverse effects, management of adverse effects, and when to seek medical attention.

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Abbreviations Introduced in This Chapter

5-HT	5-Hydroxytryptamine
ACE	Angiotensin-converting enzyme
ARB	Angiotensin receptor blocker
BDNF	Brain-derived neurotrophic factor
CBC	Complete blood count
CBT	Cognitive-behavioral therapy
CNS	Central nervous system
DA	Dopamine
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
FDA	Food and Drug Administration
FGA	First-generation antipsychotic
fMRI	Functional magnetic resonance imaging
FOI	Flight of ideas
GABA	γ-Aminobutyric acid
GI	Gastrointestinal
HAM-D	Hamilton Depression Rating Scale
β-HCG	Beta-human chorionic gonadotropin
HIV	Human immunodeficiency virus
LMP	Last menstrual period
MDD	Major depressive disorder
MRI	Magnetic resonance imaging
NE	Norepinephrine
PET	Positron emission tomography
SGA	Second-generation antipsychotic
THC	Tetrahydrocannabinol
VPA	Valproic acid
YMRS	Young Mania Rating Scale

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41

Anxiety and Trauma-Related Disorders

Bridget Bradley

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the pathophysiologic mechanisms underlying anxiety disorders.
2. Recognize common presenting symptoms of generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), and posttraumatic stress disorder (PTSD).
3. List treatment goals for patients with GAD, PD, SAD, and PTSD.
4. Identify appropriate lifestyle modifications and over-the-counter medication use in these patients.
5. Compare the efficacy and tolerability profiles of psychotherapy and pharmacotherapy interventions for anxiety disorders.
6. Design a patient-specific pharmacotherapy treatment plan for patients with GAD, PD, SAD, and PTSD.
7. Develop a monitoring plan for patients with anxiety disorders.
8. Formulate appropriate educational information to be provided to a patient receiving pharmacotherapy for anxiety disorders.

INTRODUCTION

Anxiety disorders are among the most frequent mental disorders encountered by clinicians.[1,2] All anxiety disorders are highly comorbid and share features of fear and anxiety that differ from developmentally typical fear or anxiety by being excessive, persistent, and resulting in behavioral disturbances.[1] Anxiety disorders are associated with significant patient and family burden, functional impairment, and increased risk of developing comorbid major depressive disorder (MDD).[1-4]

Initial detection and diagnosis generally falls to primary care clinicians, to whom most patients present in the context of other complaints.[4] Anxiety disorders are often missed or attributed incorrectly to other medical illnesses, and most patients are treated inadequately.[4] Untreated anxiety disorders are associated with increased healthcare utilization, morbidity and mortality, and a poorer quality of life.[1-4]

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

▶ *Prevalence*

Data from the National Comorbidity Survey, Replication not revised (NCS-R) estimate the lifetime prevalence of anxiety disorders in adults (18-64), collectively is 33.7%.[3] This estimate includes PTSD and OCD, although the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-5*) recategorized it to a trauma and stressor-related disorders and obsessive-compulsive and related disorders, respectively.[1] The estimated lifetime prevalence for each anxiety disorder is specific phobia 13.8%, social anxiety disorder 13%, generalized anxiety disorder 6.2%, panic disorder 5.2%, and posttraumatic stress disorder 8%.[3]

Anxiety disorders are more prevalent among women than men (2:1).[2] Prevalence rates across the anxiety spectrum increase from the younger age group (18–29 years) to older age groups (30–44 and 45–59 years); however, rates are substantially lower for those older than age 59 years.[5]

▶ *Course of Illness*

PTSD, PD, and GAD have median ages of onset of 23, 24, and 31 years, respectively, whereas SAD develops earlier, 13 years.[6] It is likely that anxiety disorders are underdiagnosed and that symptoms are present for years prior to diagnosis.

Anxiety disorders are chronic, and symptoms tend to wax and wane, with fewer than one-third of patients experiencing spontaneous symptom remission.[7] As such, the risk for relapse and recurrence of symptoms is high. In a 12-year follow-up study of anxiety disorders, recurrence rates ranged from 39% for SAD, 56% for PD without agoraphobia, and 45% for GAD.[8] The rate of remission for PTSD is estimated to be lower; one study found only a 20% remission rate over a 15-year follow-up.[9]

Remission, if achieved with treatment, is most likely to occur within the first 2 years of an index episode.[7] Similarly, the highest rates of relapse are within the same time frame. This suggests that many patients need ongoing maintenance treatment. Rates of remission and relapse do not appear to vary by sex.[7] Patients with anxiety disorders spend a significant portion of time “being ill” during a particular episode, ranging from 41% to 80% of the time.[8] Appropriate treatment improves overall quality of life and psychosocial functioning.[10]

▶ *Comorbidity*

More than 90% of individuals with an anxiety disorder have a lifetime history of one or more other psychiatric disorder(s).[10] Depression is the most common comorbidity, followed by alcohol and substance use disorders, as well as other co-occurring anxiety disorders.[10]

Etiology

Both genetic and psychosocial factors appear to play a role in the initiation and expression of anxiety disorders.[11] Moderate genetic risk has been identified for all anxiety disorders. Family and twin epidemiologic studies support familial aggregation of anxiety disorders (odds ratio [OR] 4–6) with heritability of 30% to 50%.[11] Twin studies further suggest that anxiety disorders share genetic risk factors that may help to explain the pattern of comorbidity. Candidate gene studies as well as genome-wide association sequence (GWAS) studies seeking to identify genes contributing to risk have been inconclusive to date.[11]

Genetic factors may create a vulnerable phenotype for anxiety disorders, but environmental factors (eg, stressful life events, illness, parental relationships, trauma) contribute to the development and persistence of the disorder.[11] Others factors that may increase risk of anxiety disorder diagnosis include positive family history of anxiety disorders, female sex, loneliness, low education, adverse parenting, and chronic somatic illness (cardiovascular disease, diabetes, asthma, obesity).[12] A 2018 analysis of the National Epidemiological Survey on Alcohol and Related Conditions found that adverse life events (death of family or friend, illness/injury of family or friend, victim of a crime, financial crisis, job loss, and ending of relationship) have a role in the onset of panic, generalized, and social anxiety disorders.[13] PTSD requires an exposure to a traumatic event(s), either intentional or unintentional. Approximately 80% of the US population will experience at least one traumatic event and 13% of women and 6% of men will develop PTSD.[14] Symptoms can occur soon after or years after the trauma.[1]

PATHOPHYSIOLOGY

The thalamus, amygdala, nucleus accumbens, hippocampus, hypothalamus, and prefrontal cortex are key components of the neurocircuitry of fear response[15] and may play a central role in most anxiety disorders (Figure 41–1). Sensory data from environmental threats are first processed by the thalamus. Information is simultaneously passed on to cortical centers for finer processing and to the amygdala for rapid assessment of highly charged emotional information. The amygdala provides emotional valence or importance of the information and enables quick action or response to an ambiguous but vital threat. The cortex performs a more detailed analysis and sends updates to the amygdala for comparison and any needed course corrections.

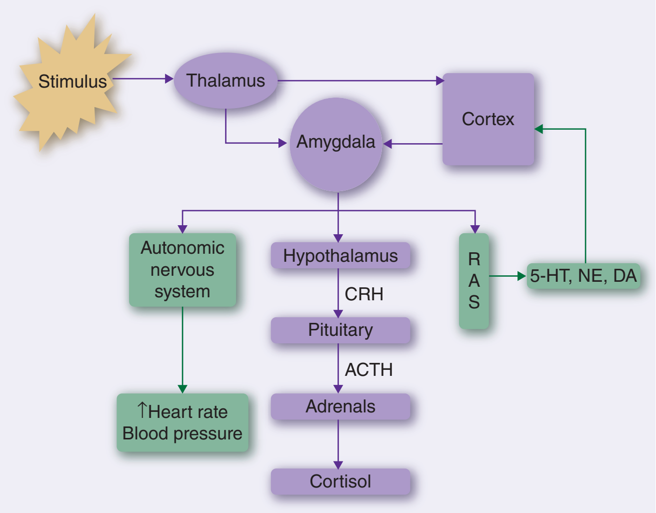

FIGURE 41–1. Neurocircuitry and key neurotransmitters involved in mediating anxiety disorders. (ACTH, adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone; DA, dopamine; 5-HT, serotonin; NE, norepinephrine; RAS, reticular activating system.)

Anxiety disorders develop when the fear-response system leads to maladaptive behavior or distress. Anxiety occurs independent of stimuli (eg, PD), is associated with benign stimuli (eg, phobias), or continues beyond the stimulus duration (eg, GAD). Direct and indirect connections to the reticular activating system (RAS), a region spanning the medulla, pons, and midbrain, help to regulate arousal, vigilance, and fear. These connections are modulated by serotonin (5-HT) and norepinephrine (NE), which have their primary origins in the RAS.[16] The amygdala sends projections to the hypothalamus, thus influencing the autonomic nervous system to affect heart rate, blood pressure, and stress-associated changes. It also influences the hypothalamic–pituitary–adrenal (HPA) axis, leading to a cascade of stress hormones.[16] Elevation of stress hormones, such as cortisol, for prolonged periods can damage the brain and other organs.[16]

Noradrenergic System

Norepinephrine-producing cells reside primarily in a region of the brain called the locus ceruleus (LC). Increased activity in this region is associated with an increase in arousal, anxiety, and panic. Drugs such as yohimbine that increase activity in the LC can be anxiogenic; drugs that decrease activity in the LC appear to improve anxiety. Furthermore, dysregulation of this region is implicated by elevated levels of NE or its metabolites in subjects with GAD, PD, and specific phobias.[17]

Serotonergic System

The raphe nuclei and the resident cell bodies of 5-HT-producing neurons have a complicated role related to anxiety symptoms. Activity of 5-HT cells in the raphe nuclei over time inhibits firing of noradrenergic cells in the LC. Other influences include their ability to regulate cells in the prefrontal cortex and amygdala. Perhaps the strongest evidence for the involvement of the serotonergic system is the success of serotonin reuptake inhibitors in treatment of anxiety disorders.[15]

γ-Aminobutyric Acid

γ-Aminobutyric acid (GABA) plays a complex role as an inhibitory neurotransmitter with nonspecific effects. GABA-ergic drugs reduce anxiety, but the lack of a specific target for their effect leads to multiple undesirable effects. Current research is focused on defining receptor subtypes that may allow for greater specificity in targeting anxiety symptoms.[15]

Hypothalamic–Pituitary–Adrenal Axis

The HPA axis provides a critical mechanism for regulation of the stress response and its effects on the brain and other organ systems. Several important hormones, including corticotropin-releasing hormone and cortisol, are involved in this pathway. These hormones regulate the effects of anxiety on the body and provide positive feedback to the brain.[14] A cycle of anxiety and sensitization by such feedback could, if unchecked, result in escalation of symptoms. Neuropeptides may provide one mechanism to balance positive and negative feedback, helping to minimize such escalation.

Patient Encounter 1, Part 1

A 34-year-old man presents to his primary care team with complaints of nausea, diarrhea, abdominal pain, and fatigue. He recently had a full workup for his gastrointestinal complaints which came back negative. He continues to be worried that something more is wrong medically. He is also worried that he is not performing well at his job. He becomes very upset thinking he will lose his job and then will be homeless, and his wife will leave him. He is an accountant and has been employed with the same firm for the last 10 years but is concerned that he is having trouble concentrating at work. He has recently increased his caffeine as his sleep has been poor. He has one to two beers every evening and denies use of tobacco or other illicit drug use. His medical history is positive for hypertension.

What manifestations described above are suggestive of an anxiety disorder?

What additional information do you need to establish a diagnosis and develop a treatment plan?

What other diagnoses should be considered in your differential diagnosis?

Neuropeptides

Several neuropeptides (eg, neuropeptide Y [NPY], corticotropin-releasing factor, and cholecystokinin) have been investigated for their role in anxiety disorders.[18]

CLINICAL PRESENATION AND DIAGNOSIS

Anxiety disorders share common etiology and risk factors yet have distinct clinical presentation, diagnostic criteria, and treatment recommendations and thus will be discussed separately. Treatment guidelines recommend screening for the presence of anxiety symptoms using general questions such as "During the past 2 weeks, how much have you been bothered by the following: (1) feeling nervous, anxious, frightened, worried, or on edge, (2) feeling panic or being frightened, (3) avoiding situations that make you anxious."[1,19] Positive responses should result in further assessment. Suicide risk assessment is recommended for all anxiety disorders as the risk of suicide attempts is increased irrespective of the presence of a comorbid mood disorder.[19,20]

TREATMENT: GENERALIZED ANXIETY DISORDER

Desired Outcomes

The goals of therapy for GAD are to acutely reduce the severity and duration of anxiety symptoms and restore overall functioning. The long-term goal is to achieve and maintain remission.

General Approach to Treatment

KEY CONCEPT Patients with GAD may be managed with psychotherapy, pharmacotherapy, or both. Treatment should be individualized based on symptom severity, comorbid illnesses, medical status, age, access to care, cost, and patient preference. Patients with severe symptoms resulting in functional impairment should receive an antianxiety medication.

Clinical Presentation and Diagnosis of GAD

General

Onset is typically in early adulthood. The intensity and duration of anxiety is out of proportion to the likelihood or impact of the anticipated event. Laboratory evaluation usually is reserved for later onset, atypical presentation, or poor response to treatment.

Symptoms[1]

- Essential feature is excessive anxiety or worry involving multiple events or activities occurring more days than not for at least 6 months
- Difficulty controlling worry
- Anxiety and worry associated with at least three of the following (unless assessing children):
  - Restlessness
  - Easily fatigued
  - Poor concentration or mind going blank
  - Irritability
  - Muscle tension
  - Insomnia or unsatisfying sleep
- The anxiety or worry causes significant distress or functional impairment and is *not* attributable to another substance, medical, or psychiatric condition

Differential Diagnosis

Rule out underlying medical or psychiatric disorders and medications that may cause anxiety (Tables 41–1 and 41–2)

Laboratory Evaluation

- Urine drug screen
- Basic metabolic panel and HbA1c
- Thyroid-stimulating hormone
- Electrocardiogram

Table 41–1

Medical Conditions That Can Cause Anxiety[1,12]

Psychiatric Disorders
Mood disorders, hypochondriasis, personality disorders, alcohol or substance use, alcohol or substance withdrawal, other anxiety disorders

Neurologic Disorders
CVA, seizure disorders, dementia, stroke, migraine, encephalitis, vestibular dysfunction

Cardiovascular Disorders
Angina, arrhythmias, congestive heart failure, mitral valve prolapse, myocardial infarction

Endocrine and Metabolic Disorders
Hypothyroidism or hyperthyroidism, hypoglycemia, Cushing disease, Addison disease, pheochromocytoma, hyperadrenocorticism, hyponatremia, hyperkalemia, vitamin B_{12} deficiency

Respiratory Disorders
Asthma, COPD, pulmonary embolism, pneumonia, hyperventilation

Other
Carcinoid syndrome, anemias, SLE

COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; SLE, systemic lupus erythematosus.

Table 41–2

Medications Associated with Anxiety Symptoms[1,6,29]

Category	Examples
Anticonvulsants	Carbamazepine, ethosuximide
Antidepressants	Bupropion, SSRIs, SNRIs, TCAs
Antihypertensives	Felodipine
Antimicrobials	Cephalosporins, ofloxacin, isoniazid
Antiparkinson drugs	Levodopa
Bronchodilators	Albuterol, isoproterenol, theophylline
Corticosteroids	Prednisone, methylprednisolone
Decongestants	Pseudoephedrine, phenylephrine
Herbals	Ma huang, St. John's wort, ginseng, guarana, belladonna
NSAIDs	Ibuprofen, indomethacin
Stimulants	Amphetamines, caffeine, cocaine, methylphenidate, nicotine
Thyroid hormones	Levothyroxine
Toxicity	Anticholinergics, antihistamines, digoxin
Withdrawal of CNS depressants (abrupt)	Alcohol, barbiturates, benzodiazepines

CNS, central nervous system; NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Nonpharmacologic Therapy

Nonpharmacologic therapy includes psychoeducation, exercise, stress management (eg, applied relaxation), and psychotherapy (eg, cognitive-behavioral therapy, mindfulness-based). Psychoeducation should provide information on GAD and its management. Patients should be instructed to avoid stimulating agents, for example, caffeine, decongestants, diet pills, and excessive alcohol use. Regular exercise is also recommended, and higher-intensity exercise may have more benefit than lower-intensity exercise.[21] Cognitive-behavioral therapy (CBT) is the most effective psychological therapy for GAD patients. It helps patients to recognize and alter patterns of distorted thinking and dysfunctional behavior. Treatment gains with CBT may be maintained for 1 year[6] and up to 3 years.[19] CBT may be delivered in individual or group settings.[19,21] Internet-based CBT (iCBT) that is supported by a therapist was found to be effective and may offer an alternative to face-to-face therapy for patients with access barriers.[22] The effect sizes of trials with CBT are comparable to those of pharmacologic therapies, although benefit may be seen earlier with therapy.[6,12] CBT is effective for children with anxiety disorders and combined with medication may be superior to either treatment alone.[23]

Patient Encounter 1, Part 2

After reviewing the negative GI workup and the patient's presenting symptoms, he is diagnosed with GAD.

PMH: Hypertension

FH: Mother treated for GAD; father, hypertension

SH: One to two beers every evening; lives with spouse and two children

Meds: Amlodipine 10 mg PO daily for hypertension

What are first-line treatment options for this patient?

What factors should be considered in selecting the patient's treatment?

What is the role of benzodiazepines for this patient?

How should the patient be monitored when receiving an antidepressant?

Pharmacologic Therapy

Antidepressants, benzodiazepines, pregabalin, buspirone, hydroxyzine, and the second-generation antipsychotics (SGAs) have controlled clinical trial data supporting their use in GAD. **KEY CONCEPT** Antidepressants are the drugs of choice for chronic GAD because of tolerable side effect profiles, no risk for dependency, and efficacy in common comorbid conditions, including major depression, panic disorder, obsessive-compulsive disorder (OCD), and SAD. Benzodiazepines remain the most effective and commonly used treatment for short-term management of anxiety when immediate relief of symptoms is desired. They may be used for intermittent or adjunctive treatment during GAD exacerbation or for sleep disturbance during the initiation of antidepressant treatment.[6,12] Buspirone and pregabalin are alternative agents for patients with GAD without depression. Hydroxyzine is usually adjunctive and is less desirable for long-term treatment because of side effects such as sedation and anticholinergic effects.

Patients with GAD should be treated to symptom remission. Continuation of antidepressant therapy after acute response significantly decreases the risk of relapse (OR 0.2 [0.15–0.26]).[24] Guidelines vary on how long to continue treatment after remission, and the duration varies from at least 6 months and up to 12 months.[6,12,21,25] An algorithm for the pharmacologic management of GAD is shown in Figure 41–2.

▶ *Antidepressants*

Antidepressants (Table 41–3) reduce the psychic symptoms (eg, worry and apprehension) of anxiety with a modest effect on autonomic or somatic symptoms (eg, tremor, rapid heart rate, and/or sweating). All antidepressants provide a similar degree of anxiety reduction. The onset of antianxiety effect is 2 to 4 weeks. Selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) are preferred over tricyclic antidepressants (TCAs) because of improved safety and tolerability. Selection of a specific antidepressant generally is based on history of prior response, side effect and drug interaction profile (see Chapter 39), cost, or formulary availability.

Antidepressants modulate synaptic 5-HT, NE, and/or dopamine (DA) reuptake and receptor-activated neuronal signal transduction. These intracellular changes modify the expression of genes and proteins important in stress response (eg, glucocorticoid receptors, brain-derived neurotrophic factor, corticotropin-releasing hormone).[26] Activation of these "stress-adapting" pathways may improve both somatic and psychic symptoms of anxiety.[26]

Selective Serotonin Reuptake Inhibitors The SSRIs paroxetine, escitalopram, and sertraline have been shown to be significantly more effective than placebo in reducing anxiety symptoms in adults with GAD. Response rates range from 56% to 68% during acute treatment, with remission achieved in approximately one-third of patients.[6,12,25,27] Common side effects include somnolence, headache, nausea, dry mouth (paroxetine), diarrhea (sertraline), sweating (sertraline), decreased libido, ejaculation disorder, anorgasmia, and asthenia.

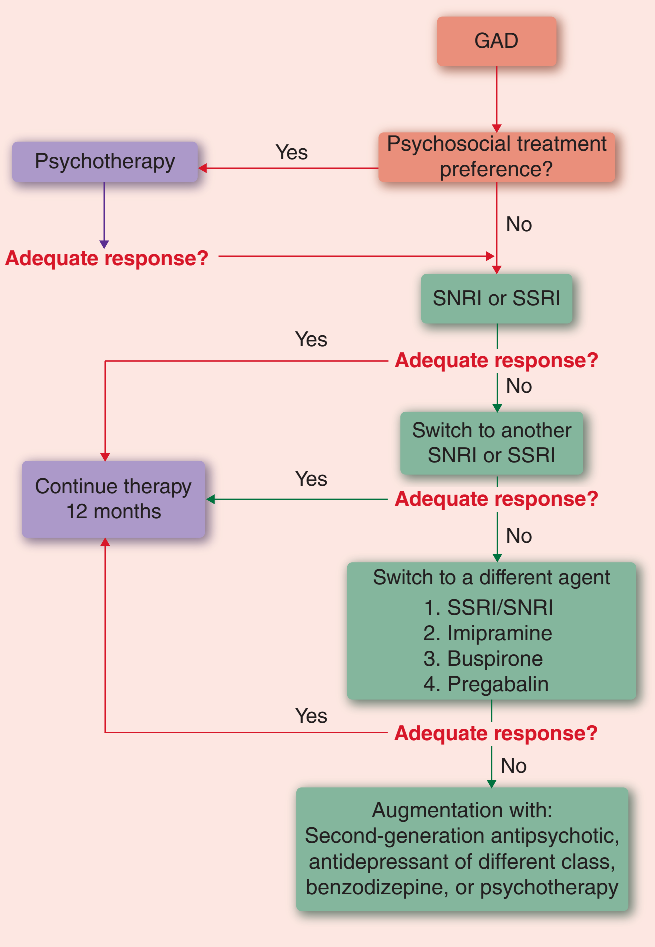
GAD
Psychosocial treatment preference?
Yes
Psychotherapy
No
Adequate response?
SNRI or SSRI
Yes
Adequate response?
No
Switch to another SNRI or SSRI
Continue therapy 12 months
Yes
Adequate response?
No
Switch to a different agent
1. SSRI/SNRI
2. Imipramine
3. Buspirone
4. Pregabalin
Yes
Adequate response?
No
Augmentation with: Second-generation antipsychotic, antidepressant of different class, benzodizepine, or psychotherapy

FIGURE 41–2. Treatment algorithm for generalized anxiety disorder (GAD). (SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.) (Data from Refs. 12, 20, 25, 29.)

The SSRIs are better tolerated than TCAs, and tolerability is similar to that of SNRIs. Sertraline, fluoxetine, and fluvoxamine have demonstrated benefits in children and adolescents with GAD and are the preferred pharmacologic treatment in this population.[21]

Serotonin-Norepinephrine Reuptake Inhibitors Venlafaxine and duloxetine alleviate anxiety with or without comorbid depression and maintain response with extended treatment.[6,12,25,27] Venlafaxine and duloxetine are effective for GAD in children and adolescents.[21] Common side effects reported in patients with GAD are nausea, somnolence, dry mouth, dizziness, sweating, constipation, and anorexia.

Tricyclic Antidepressants Imipramine demonstrated similar rate of remission of anxiety symptoms as treatment with trazodone or diazepam.[6] TCAs are limited by bothersome adverse effects (eg, sedation, orthostatic hypotension, anticholinergic effects, and weight gain). TCAs have narrow therapeutic indices and are lethal in overdose due to atrioventricular block.

Novel Antidepressants The efficacy of mirtazapine, an α_2-adrenergic antagonist and postsynaptic 5-HT$_2$ and 5-HT$_3$ receptor antagonist, for anxiety disorders has been limited to small sample sizes.[28] It is not associated with sexual dysfunction but is associated with sedation and weight gain. Bupropion, a DA and NE reuptake inhibitor, lacks the common antidepressant side effects of weight gain and sexual dysfunction. Bupropion has not been studied or used extensively in anxiety disorders. However, a small controlled trial comparing bupropion XL with escitalopram found bupropion to have comparable anxiolytic efficacy and tolerability.[6,12] Vortioxetine, a multimodal SSRI with blockade of serotonin reuptake transporter, antagonist activity at 5-HT$_{1D}$, 5-HT$_3$, and 5-HT$_7$ receptors and partial agonist activity at 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors has been evaluated in the treatment of GAD with conflicting results.[28] Vilazodone, a SSRI and 5-HT$_{1A}$ receptor partial agonist, has shown benefit compared to placebo in several short-term randomized controlled trials in GAD.[29] Neither of these two agents appear to have advantages over generically available SSRIs/SNRIs.[28]

▶ *Benzodiazepines*

KEY CONCEPT Benzodiazepines are recommended for acute treatment of GAD when short-term relief is needed, as an adjunct during initiation of antidepressant therapy, or patients who have three treatment failures.[6,12,27] Benzodiazepines should be used for short-term treatment with scheduled dosing, as opposed to as-needed.[6,12] They are more effective for somatic symptoms than psychic symptoms.[20] Major benzodiazepine disadvantages are lack of effectiveness for depression; risk for withdrawal and potential need for taper; and potential interdose rebound anxiety, especially with short-acting benzodiazepines. They are cautioned in older adults due to fall and fracture risk.[12] Benzodiazepines have a risk for dependency and abuse and should be avoided in patients with current or past substance use disorder(s).[6,12,27]

Benzodiazepines enhance transmission of the inhibitory neurotransmitter GABA through interaction with the GABA$_A$-receptor complex.[6,29] All benzodiazepines are expected to provide equivalent benefit when given in comparable doses. They differ substantially in their pharmacokinetic properties and potency for the GABA$_A$-receptor (Table 41–4).

Benzodiazepines are metabolized by hepatic oxidation (CYP3A4) and glucuronide conjugation. Because lorazepam and oxazepam bypass hepatic oxidation and are conjugated only, they are preferred agents for patients with reduced hepatic function secondary to aging or disease (eg, cirrhosis). Many benzodiazepines are metabolized to long-acting metabolites (Table 41–4) that provide long-lasting anxiety relief. Drugs that either inhibit or induce CYP450 isozymes or glucuronidation can cause drug interactions.

The most common side effects of benzodiazepine therapy include central nervous system (CNS) depressant effects (eg, drowsiness, sedation, psychomotor impairment, and ataxia) and cognitive effects (eg, poor recall and anterograde amnesia). Anterograde amnesia is more likely with high-potency benzodiazepines such as alprazolam.[30] Some patients may be disinhibited and experience confusion, irritability, aggression, and excitement.[20,29] Discontinuation of benzodiazepines may be associated with withdrawal, rebound anxiety, and recurrence of anxiety symptoms.[20] Higher doses of benzodiazepines and a longer duration of therapy increase the severity of withdrawal and risk of seizures after abrupt or rapid discontinuation. Patients should be tapered to avoid withdrawal symptoms. The duration of the taper should increase with extended duration of benzodiazepine therapy.[6,29] A general approach to the taper is to reduce the dose by 25% every 5 to 7 days until reaching half the original dose and then decreasing by 10% to 12% per week until discontinued. Patients should expect minor withdrawal symptoms and discomfort even when tapering. Rebound symptoms (eg, return of original symptoms at increased intensity) are transient. The patient should be educated that rebound anxiety is not a relapse.

Table 41–3

Pharmacotherapy for the Treatment of Generalized Anxiety Disorder[19,46]

Medication Class Drug Name (Brand Name)	Recommended Starting Dose (mg/day)	Usual Therapeutic Dosage Range (mg/day)	Hepatic Insufficiency	Renal Insufficiency
Antidepressants				
SSRIs				
Citalopram[a] (Celexa)	20	20–40	Maximum, 20 mg/day	
Escitalopram[b] (Lexapro)	10	10–20	Maximum, 10 mg/day	
Fluoxetine (Prozac)	20	20–80	Titrate with caution	
Fluvoxamine (Luvox)	50	100–300	Titrate with caution	
Paroxetine (Paxil)[b]	20	20–50	Titrate with caution	
Paroxetine CR (Paxil CR)	25	25–62.5	Maximum, 50 mg/day	Maximum, 50 mg/day
Sertraline (Zoloft)	50–100	50–200	Reduce dose	
SNRIs				
Venlafaxine XR[b] (Effexor XR)	75	75–225	Reduce dose by 50%	Reduce dose 25%–50%
Desvenlafaxine (Pristiq)	50	50–100	Maximum, 100 mg/day	Maximum, 50 mg/day; CrCl < 30 mL/min (0.50 mL/s), dose once every other day
Duloxetine[b,c](Cymbalta)	30	60–120	Use not recommended	CrCl < 30 mL/min (0.50 mL/s) Use not recommended
TCAs				
Imipramine (Tofranil)	50	75–200	Titrate with caution	
Other Agents				
Hydroxyzine (Atarax)	25–50 four times daily	200–400		Reduce dose by 50% GFR < 50 mL/min (0.83 mL/s)
Azapirones				
Buspirone (Buspar)	7.5 mg twice daily	15–60	Not recommended in severe hepatic impairment	Not recommended in severe renal impairment
Anticonvulsants				
Pregabalin (Lyrica)	150	150–600		Reduce dose[c]
Second-Generation Antipsychotic				
Quetiapine XR (Seroquel XR)	50	150–300		

[a]Maximum daily dose of citalopram is 20 mg/day when used in the elderly or when given concomitantly with CYP2C19 inhibitors.

[b]Food and Drug Administration approved for use in generalized anxiety disorder.

[c]Dose reduction recommended for CrCl < 60 mL/min (1 mL/s) and again for CrCl, 30 mL/min (0.50 mL/s) and 15 mL/min (0.25 mL/s).

CR, controlled release; CrCl, creatinine clearance; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; XR, extended release.

▶ *Pregabalin*

Pregabalin is a calcium channel modulator, and its anxiolytic properties are attributed to its selective binding to the α_2-delta subunit of voltage-gated calcium channels. Pregabalin reduces anxiety with a similar onset to alprazolam.[12,27,31] Compared with venlafaxine and placebo, pregabalin was safe, well tolerated, and efficacious in GAD, and results were seen 1 week sooner than with venlafaxine.[12] Pregabalin reduces the risk of relapse during maintenance treatment.[12,27,31] It has a short elimination half-life and must be dosed two to three times daily. It is excreted renally with a low risk of drug–drug interactions. Pregabalin is a schedule V controlled substance owing to a propensity to cause euphoria and may cause withdrawal symptoms if discontinued abruptly. It should be used cautiously in patients with a current or past history of substance use.

▶ *Alternative Agents*

Hydroxyzine, buspirone, and SGAs are alternative agents. Hydroxyzine may be effective for acute reduction of somatic symptoms of anxiety[6] but not for psychic features of anxiety, depression, or other common comorbid anxiety disorders. Buspirone, a 5-HT$_{1A}$ partial agonist, is thought to exert its anxiolytic effects by reducing presynaptic 5-HT firing.[32] Unlike benzodiazepines, it does not have abuse potential, cause withdrawal symptoms, or potentiate alcohol and sedative-hypnotic effects. It has a gradual onset of action (ie, 2 weeks) and does not provide immediate anxiety relief. Data are inconsistent regarding its efficacy in chronic GAD or GAD with comorbid depression.[6,12,27,31] It may be less effective in patients who have been treated previously (4 weeks–5 years) with benzodiazepines.[6]

Buspirone is well tolerated, and most common side effects include dizziness, nausea, and headaches. Buspirone elimination is affected significantly by drugs that inhibit (eg, verapamil, diltiazem, itraconazole, fluvoxamine) or induce (eg, rifampin) CYP3A4.[33] Buspirone may increase blood pressure when coadministered with a monoamine oxidase inhibitor (MAOI).

The SGA quetiapine XR has demonstrated benefit in GAD. In three large placebo-controlled trials, quetiapine in daily doses

Table 41–4

Comparison of Benzodiazepines[46-48]

Drug Name (Brand Name)	Metabolite	Time to Peak Concentration (hours)	Half-Life Range (hours)	Approved Dosage Range (mg/day)	Dose Equivalent (mg)
Alprazolam[a,b] (Xanax)		1–2	12–15	1–4 (GAD) 1–10 (PD)	0.5
Chlordiazepoxide[a] (Librium)	*Desmethyldiazepam* *Desmethylchlordiazepoxide* *Demoxepam* *Oxazepam*	1–4	5–30 40–120 18 14–95 5–15	25–100	10
Clonazepam[b] (Klonopin)		1–4	18–50	1–4	0.25
Clorazepate[a] (Tranxene)	*Desmethyldiazepam*[c] *Oxazepam*	1–2	40–120 5–15	7.5–60	7.5
Diazepam[a] (Valium)	*Desmethyldiazepam*[c] *Oxazepam* *Temazepam*	0.5–2	20–80 40–120 5–15 8–15	2–40	5
Lorazepam[a] (Ativan)		2–4	10–20	0.5–10	0.75–1
Oxazepam[a] (Serax)		2–4	5–15	30–120	15

[a] Food and Drug Administration (FDA) approved for use in generalized anxiety disorder.

[b] FDA approved for use in panic disorder.

[c] CYP2C19 genetic polymorphisms resulting in little or no enzyme activity are present in 15% to 20% of Asians and 3% to 5% of Black and White patients, resulting in reduced clearance of desmethyldiazepam.[33]

GAD, generalized anxiety disorder; PD, panic disorder.

of 50 to 300 mg resulted in 26% greater likelihood of treatment response (effect size, ~0.3).[34] Quetiapine had similar outcomes paroxetine 20 mg/day and escitalopram 10 mg/day.[34] Quetiapine is still considered a second-line option for GAD due to safety concerns.[12] The SGAs quetiapine, risperidone, olanzapine, and aripiprazole have limited evidence as adjunctive treatment in patients with inadequate response to initial pharmacotherapy.[12] SGAs are associated with a risk of weight gain, glucose intolerance, sedation, fatigue, and extrapyramidal symptoms that limit their use.

Clinical Presentation and Diagnosis of PD

General

Typically presents in late adolescence or early adulthood. Onset in older adults should prompt investigation of medical or substance-induced causes. Laboratory evaluation would be driven by any positive findings during the patient history and physical examination.

Symptoms[1]

Recurrent, unexpected panic attacks. A panic attack is an abrupt surge of intense fear or discomfort peaking within minutes and with four or more of the following symptoms:

- Palpitations or rapid heart rate
- Sweating
- Trembling or shaking
- Sensation of shortness of breath or smothering
- Feeling of choking
- Chest pain or discomfort
- Nausea or abdominal distress
- Feeling dizzy or light-headed
- Chills or hot flushes
- Paresthesias
- Derealization or depersonalization
- Fear of dying
- Fear of losing control or "going crazy"

At least one of the attacks has been followed by 1 month or more of one or both:

- Persistent concern or worry about additional attacks
- Significant maladaptive change in behavior related to the attacks (eg, avoidance)

Differential Diagnosis

Rule out underlying medical or psychiatric disorders and medications that may cause anxiety (Tables 41–1 and 41–2)

Laboratory Evaluation

- Urine drug screen
- Basic metabolic panel and HbA$_{1C}$
- Thyroid-stimulating hormone
- Electrocardiogram

OUTCOME EVALUATION

Assess patients for improvement of anxiety symptoms and return to baseline of occupational, social, and interpersonal functioning. Brief questionnaires like the Generalized Anxiety Disorder 7-Item (GAD-7) may be used to monitor changes in symptoms and measure response to treatment.[35] With effective treatment, patients should have no or minimal symptoms of anxiety or depression. With initiation of drug therapy, evaluate patients frequently for tolerability and response. Monitor for suicidal ideation and behaviors for children, adolescents, and young adults (24 years of age or less) initiated on antidepressants.[21,36,37] Increase the dose in patients exhibiting a partial response after 2 to 4 weeks on an antidepressant or 2 weeks on a benzodiazepine. Individualize the duration of treatment as some patients require up to 1 year of treatment.[6,12,27]

TREATMENT: PANIC DISORDER

Desired Outcomes

The goals of therapy for PD are to reduce the severity and frequency of panic attacks, reduce anticipatory anxiety and avoidant behavior, and minimize symptoms of depression or other comorbid disorders.[38] The long-term goal is to achieve and maintain remission and restore overall functioning.

General Approach to Treatment

Treatment options include medication, psychotherapy, or a combination of both. In some cases, pharmacotherapy will follow psychotherapy treatments when full response is not realized. Patients with panic symptoms without comorbid agoraphobia may respond to pharmacotherapy alone. Agoraphobic symptoms generally take longer to respond than panic symptoms. **KEY CONCEPT** The acute phase of PD treatment lasts about 12 weeks and should markedly reduce or eliminate panic attacks and minimize anticipatory anxiety and phobic avoidance. Treatment should be continued to prevent relapse for an additional 12 to 24 months before attempting discontinuation.[6,12,38] For patients who relapse after discontinuation, therapy should be resumed.[38]

Nonpharmacologic Therapy

Patients with PD should avoid stimulating agents (eg, decongestants, diet pills, and caffeine) that may precipitate a panic attack. CBT generally includes psychoeducation, self-monitoring, countering anxious beliefs, exposure to fear cues, and modification of anxiety-maintaining behaviors.[6,38] Exposure therapy is useful for patients with phobic avoidance.[8,38] CBT is considered a first-line treatment of PD, with efficacy similar to that of pharmacotherapy. Some studies suggest lower risk of relapse after CBT versus drug therapy.[38] Similarly to GAD, iCBT has shown to be effective for PD with effects maintained up to 6 months.[39] CBT in combination with antidepressant treatment is more effective than either treatment alone.[2]

Pharmacologic Therapy

Patients with PD may be treated with SSRIs, SNRIs, TCAs, or MAOIs, as well as benzodiazepines[6,12,38] (Table 41–5) with similar effectiveness, but SSRIs are the treatment of choice. Benzodiazepines often are used concomitantly with antidepressants,

Table 41–5

Antidepressants Used in the Treatment of Panic and Social Anxiety Disorder[6,25,38]

Medication Class	Recommended Starting Dose (mg/day)	Usual Therapeutic Dosage Range (mg/day)	Advantages	Disadvantages
SSRIs/SNRIs			**SSRIs (in General)**	**SSRIs (in General)**
Citalopram	10	20–40	Antidepressant activity; antianxiety activity; single daily dosing (all but fluvoxamine); low toxicity	Activation; delayed onset of action; may precipitate mania; sexual side effects; GI side effects
Escitalopram[b]	5–10	10–20		
Fluoxetine[a]	5–10	20–60		
Fluvoxamine	25	100–300		
Paroxetine[a,b]	10	20–60		
Sertraline[a,b]	25	50–200		
Venlafaxine XR[a,b]	37.5	75–225		
Duloxetine	30	60		
TCAs			**TCAs (in General)**	**TCAs (in General)**
Clomipramine	25 mg	75–250	Established efficacy	Activation; sedation; anticholinergic effects; cardiovascular effects; delayed onset of action; may precipitate mania; sexual side effects; toxic in overdose; weight gain
Imipramine[a]	10–25	75–300		
MAOI				
Phenelzine	15	45–90	Antidepressant effects	Dietary restrictions; drug interactions; weight gain; orthostasis; may precipitate mania

[a] Food and Drug Administration approved for use in panic disorder.

[b] Food and Drug Administration approved for use in social anxiety disorder.

GI, gastrointestinal; MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant, XR=extended release.

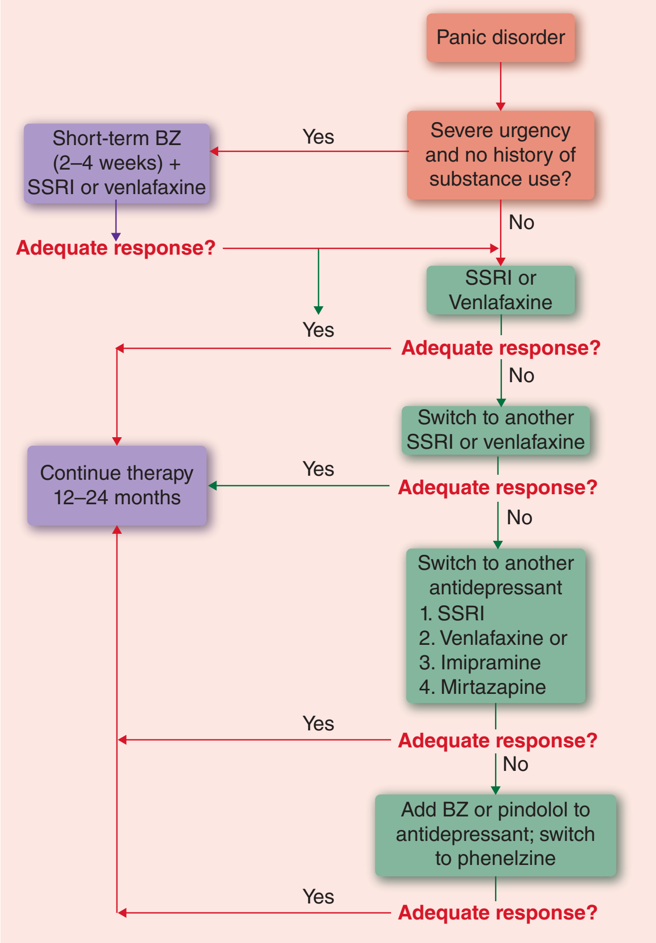
Panic disorder
Severe urgency and no history of substance use?
Yes
Short-term BZ (2–4 weeks) + SSRI or venlafaxine
No
Adequate response?
SSRI or Venlafaxine
Yes
Adequate response?
No
Switch to another SSRI or venlafaxine
Continue therapy 12–24 months
Yes
Adequate response?
No
Switch to another antidepressant
1. SSRI
2. Venlafaxine or
3. Imipramine
4. Mirtazapine
Yes
Adequate response?
No
Add BZ or pindolol to antidepressant; switch to phenelzine
Yes
Adequate response?

FIGURE 41–3. Algorithm for the pharmacotherapy of panic disorder. (BZ, benzodiazepine; SSRI, selective serotonin reuptake inhibitor.) (Adapted from Young AS, Klap R, Sherbourne CD, Wells KB. The quality of care for depressive and anxiety disorders in the United States. Arch Gen Psychiatry. 2001;58:55–61 and Bruce SE, Yonkers SE, Otto MW, et al. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. Am J Psychiatry. 2005;162:1179–1187, with permission.)

especially early in treatment, or as monotherapy to acutely reduce panic symptoms. Benzodiazepines are not preferred for long-term treatment but may be used when patients fail several antidepressant trials.[6,12,38] Patients with comorbid depression should be treated with an antidepressant. An algorithm for pharmacologic management of PD appears in Figure 41–3.

▶ *Antidepressants*

Antidepressants typically require 4 weeks for onset of antipanic effect, with optimal response at 6 to 12 weeks. Reduction of anticipatory anxiety and phobic avoidance generally follows improvement in panic symptoms. **KEY CONCEPT** Patients with PD are more likely to experience stimulant-like side effects of antidepressants than patients with major depression. Antidepressants should be initiated at lower doses (Table 41–5) in patients with PD than in depressed patients. Target doses are similar to those used for depression. **KEY CONCEPT** Antidepressants should be tapered when treatment is discontinued to avoid withdrawal symptoms, including irritability, dizziness, headache, and dysphoria.

Selective Serotonin and Serotonin-Norepinephrine Reuptake Inhibitors SSRIs and SNRIs are the medications of choice for patients with PD. All SSRIs have demonstrated effectiveness in controlled trials, with 60% to 80% of patients achieving a panic-free state.[6,12,38] Similarly, venlafaxine XR, in dosages of 75 to 225 mg/day, reduced panic and anticipatory anxiety in short-term controlled trials and prevented relapse with extended treatment over 6 months.[12,38] Duloxetine has limited evidence for efficacy and is considered a third-line option.[12] Given lack of head-to-head trials and similar efficacy between agents, drug selection is generally based on pharmacokinetics, drug interactions, side effects, and cost differences (see Chapter 39).

Tricyclic Antidepressants Treatment with imipramine has resulted in 45% to 70% of patients achieving a panic-free state. Clomipramine also has demonstrated effectiveness in PD. TCAs are considered second- or third-line therapeutic options because of poorer tolerability and toxicity upon overdose, which may be fatal.[6,38] Owing to their side effect profile, TCAs are associated with a higher rate of treatment discontinuation than SSRIs.[38] PD patients taking TCAs may experience anticholinergic effects, orthostatic hypotension, sweating, sleep disturbances, dizziness, fatigue, sexual dysfunction, and weight gain.

Monoamine Oxidase Inhibitors MAOIs have not been evaluated systematically for treatment of PD under the current diagnostic classification. In general, they are reserved for patients who are refractory to other treatments.[38] They have significant side effects that limit adherence coupled with restrictions to avoid tyramine-containing foods and sympathomimetic drugs to prevent hypertensive crisis (see Chapter 39).

Other Antidepressants Mirtazapine is considered a second-line option.[17] There is insufficient evidence to support the use of bupropion, trazodone, or nefazodone for treatment of PD.[6,12,38]

▶ *Benzodiazepines*

Benzodiazepines are effective antipanic agents with significant effects on anticipatory anxiety and phobic behaviors. Alprazolam, the most studied benzodiazepine for PD, is associated with significant panic reduction after 1 week of therapy (eg, 55%–75% panic free).[38,39] Benzodiazepines achieve outcomes similar to antidepressants over extended treatment, but benzodiazepine-treated patients are more likely to relapse when the drugs are discontinued.[38] The risk for dependence and withdrawal and lack of efficacy for depression are significant concerns for long-term treatment of patients with PD. There is no evidence that tolerance to therapeutic effect occurs. Patients with PD experience greater rebound anxiety and relapse when discontinuing benzodiazepines than do patients with GAD.[6,38] Tapering should be done at a slower rate and over a longer period of time compared to other anxiety disorders.[6,38]

Alprazolam and diazepam, when given in equivalent doses, produce similar treatment benefits.[6,38] Doses should be titrated to response (see Table 41–4). The use of extended-release alprazolam or clonazepam may minimize breakthrough panic symptoms that are sometimes observed with immediate-release alprazolam.[40]

▶ *Adjunctive Treatment*

Pindolol, a mixed β-adrenergic/serotonergic medication, has limited evidence as adjunctive treatment with an SSRI (fluoxetine) for treatment resistant PD.[2] Propranolol, a nonselective β-blocker, is not effective for acute treatment of PD and is not recommended.[2]

Clinical Presentation and Diagnosis of SAD

General

Individuals have marked fear or anxiety about one or more social situations where they are exposed to possible scrutiny or negative evaluation (eg, common social interactions, conversation, eating, drinking, or performing). In children, the anxiety must be present in peer settings, not just in interactions with adults.

Symptoms[1]

- The individual fears acting in a way or showing anxiety that will be negatively evaluated (ie, they will be humiliated or embarrassed, others will be reject them, others will be offended))
- Social situations almost always provoke fear or anxiety and are avoided or endured with intense fear or anxiety. Children may express fear or anxiety by crying, tantrums, freezing, clinging, or failing to speak in social situations.
- The fear or anxiety is
  - Out of proportion to the actual threat posed by the social situation
  - Persistent, typically lasting for 6 months or more
  - Causes clinically significant distress or impairment in social, occupational, or other areas of functioning
  - Not attributable to physiologic effects of a substance or another medical condition
  - Not better explained by the symptoms of another mental disorder (eg, panic disorder, body dysmorphic disorder, or autism spectrum disorder)

Differential Diagnosis

Rule out underlying medical or psychiatric disorders and medications that may cause anxiety (see Tables 41–1 and 41–2).

Laboratory Evaluation

Laboratory investigation is of limited value and should be pursued only in context of other history or physical examination findings.

Outcome Evaluation

Monitor patients weekly during acute treatment (eg, initiation and titration of pharmacotherapy) and monthly once stabilized. With effective therapy, patients should experience significant reductions in the frequency and intensity of panic attacks, anticipatory anxiety, and phobic avoidance with resumption of normal activities. Rating scales, such as the Panic Disorder Symptom Scale (PDSS), can be useful in measuring symptom change over time. Assess patients for comorbidities (eg, depression) as well as suicidal ideation. Alter the therapy of patients who do not achieve a significant reduction in panic symptoms after 6 to 12 weeks on an adequate dose of antidepressant or 3 weeks on a benzodiazepine. Regularly evaluate patients for adverse effects and medication adherence, and educate them about appropriate expectations of drug therapy.

When significant response to drug therapy is achieved, continue treatment for at least 1 year. Evaluate for symptom relapse and adverse effects that may emerge with continued treatment (eg, weight gain and sexual dysfunction). During drug discontinuation, monitor frequently for withdrawal symptoms, rebound anxiety, and relapse.

TREATMENT: SOCIAL ANXIETY DISORDER

Desired Outcomes

Social anxiety disorder is a chronic disorder that begins in adolescence and occurs with significant functional impairment and high rates of comorbidity. The goal of therapy for SAD is to reduce physiologic symptoms of anxiety, fear of social situations, and phobic behaviors. Patients with comorbid depression should have a significant reduction in depressive symptoms. The long-term goal is to restore social functioning and improve the patient's quality of life.

General Approach to Treatment

Patients with SAD may be managed with pharmacotherapy or psychotherapy. There is insufficient evidence to recommend one treatment over the other, and data are lacking on the benefits of combining treatment modalities. Pharmacotherapy often is the first choice of treatment owing to relative greater access and reduced cost compared with psychotherapy.[41,42] Children with SAD should be offered psychotherapy first.[12,41,42] Many patients will not achieve a full response.

Nonpharmacologic Therapy

Patient education on disease course, treatment options, and expectations is essential. CBT is effective for reducing anxiety and phobic avoidance, and may lead to a greater likelihood of maintaining response after treatment discontinuation than does pharmacotherapy.[12,41] CBT targets avoidance-learning and negative-thinking patterns associated with social anxiety. iCBT- or CBT-based supported self-help are alternatives when access to face-to-face CBT is a barrier or declined.[12,42]

Pharmacologic Therapy

Several pharmacologic agents have demonstrated effectiveness in SAD, including the SSRIs, venlafaxine, phenelzine, benzodiazepines, gabapentin, and pregabalin (Table 41–5). **KEY CONCEPT** The SSRIs are considered first line based on their tolerability and efficacy for SAD and comorbid depression, if present. The onset of response for antidepressants may be as long as 8 to 12 weeks.[6,43] Patients responding to medication should be continued on treatment for at least 1 year.[6,12,42] Many patients relapse when medication is discontinued, and there are no clear predictive factors for who will maintain response.[43] Some patients may elect more long-term treatment owing to fear of relapse. A suggested treatment algorithm is shown in Figure 41–4.

▶ *Selective Serotonin Reuptake Inhibitors and Venlafaxine*

The efficacy of paroxetine, sertraline, escitalopram, fluvoxamine, and venlafaxine was established in large controlled trials.[6] SSRIs and SNRIs improve social anxiety and phobic avoidance and reduce overall disability. Approximately 50% of patients achieve response during acute treatment. SSRIs reduce the risk of relapse with extended treatment.[44] Limited data support the effectiveness of citalopram and fluoxetine in SAD.[44]

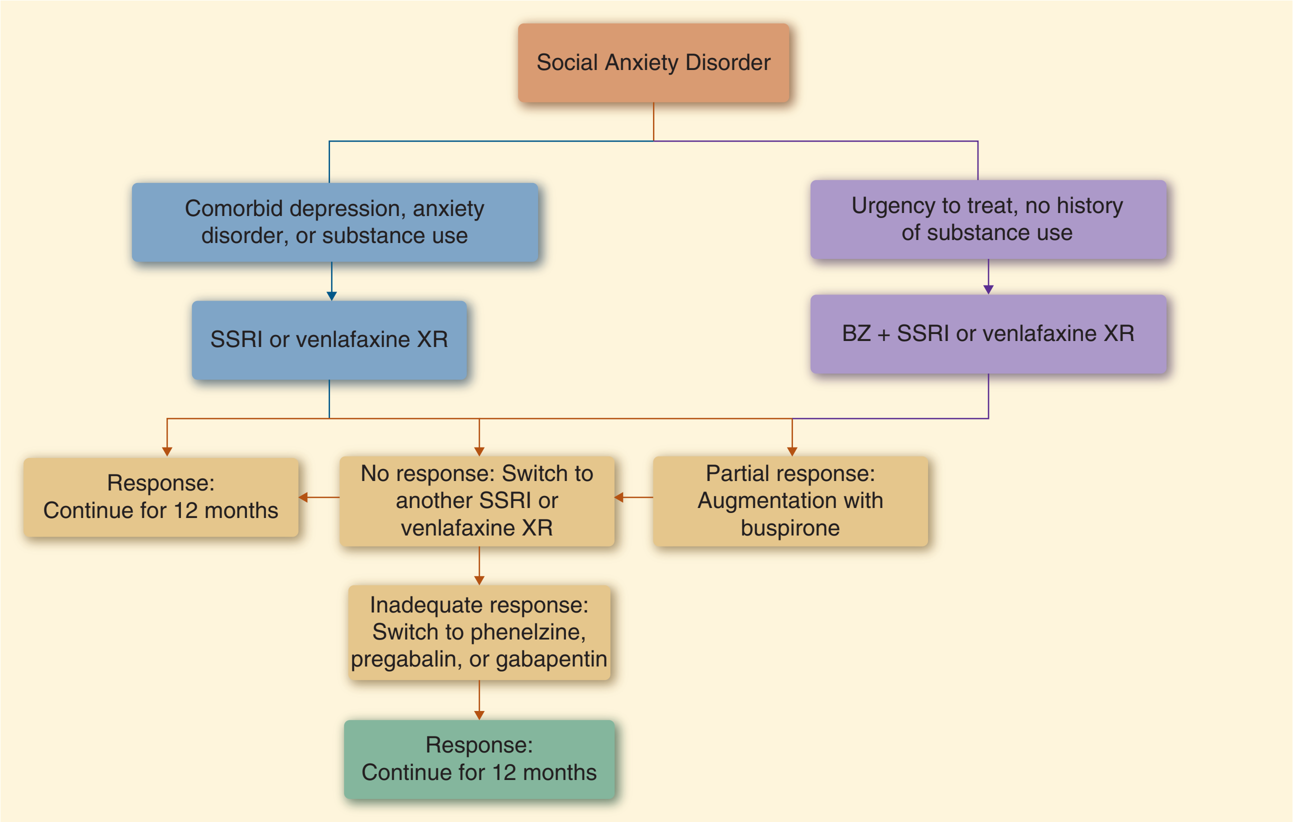
Social Anxiety Disorder
Comorbid depression, anxiety disorder, or substance use
Urgency to treat, no history of substance use
SSRI or venlafaxine XR
BZ + SSRI or venlafaxine XR
Response: Continue for 12 months
No response: Switch to another SSRI or venlafaxine XR
Partial response: Augmentation with buspirone
Inadequate response: Switch to phenelzine, pregabalin, or gabapentin
Response: Continue for 12 months

FIGURE 41–4. Algorithm for the pharmacotherapy of social anxiety disorder. (BZ, benzodiazepine; SSRI, selective serotonin reuptake inhibitor; XR, extended release.) (Adapted from Melton ST, Kirkwood CK. Anxiety disorders I: generalized anxiety, panic and social anxiety disorders. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 8th ed. New York, NY: McGraw-Hill; 2011:1209–1227, with permission.)

The initial dose of SSRIs and venlafaxine is similar to that used in depression. Patients should be titrated as tolerated to response. Patients with comorbid PD should be started on lower doses (see Table 41–6). When discontinuing SSRI/SNRIs, the dose should be tapered slowly to avoid withdrawal symptoms. Relapse rates may be as high as 50%, and patients should be monitored closely for several weeks.[42] Side effects of SSRI/SNRIs in SAD are similar to those seen in depression.

▶ *Monoamine Oxidase Inhibitors*

Phenelzine is generally reserved for treatment-refractory patients owing to dietary restrictions, drug interactions, and side effects.[12]

▶ *Alternative Agents*

Benzodiazepines Benzodiazepines may be useful for acute relief of physiologic symptoms of anxiety when used concomitantly with antidepressants or psychotherapy.[6] Benzodiazepines can also be used as second-line options if the patient does not have a history of substance use.[12] Long-term treatment is not desirable for many SAD patients because of the risk of withdrawal and difficulty with discontinuation, cognitive side effects, and lack of effect on depressive symptoms.

Anticonvulsants Gabapentin and pregabalin, structurally similar anticonvulsants, have each demonstrated modest benefit in a randomized, placebo-controlled trial.[6,12,44] Gabapentin was titrated to a maximum dose of 3600 mg/day and pregabalin to 600 mg/day. While both medications have good tolerability, they should be considered for patients with inadequate response to SSRI/SNRIs, due to better efficacy for comorbid conditions.[17]

β-Blockers β-Blockers decrease the physiologic symptoms of anxiety and are useful for reducing performance anxiety (eg, speech, interview). Propranolol or atenolol should be administered 1 hour before a performance situation. β-Blockers are not useful for management of SAD.[43,44]

Patient Encounter 2, Part 1

A 39-year-old woman experienced a motor vehicle accident about 4 months ago. After the accident she was in the hospital for 1 week with a broken leg. She does not remember much of the accident, except seeing headlights heading straight to her and then paramedics removing her from the car. Since the accident, she has not been able to drive. She has had nightmares for the past few months almost every night. Since the accident, she hasn't volunteered at her daughter's school or attended her weekly book club meeting. She has struggled at work, missing multiple deadlines due to trouble finishing tasks.

Med:

Levothyroxine 75 mcg one tablet daily

Her medical workup is noncontributory, and she is diagnosed with PTSD and recommended to start fluoxetine 20 mg daily.

What symptoms are consistent with a PTSD diagnosis?

What psychotherapy treatment would you recommend for her?

Clinical Presentation and Diagnosis of PTSD

General

Individuals have exposure to a traumatic event (actual or threatened death, serious injury, sexual violence). The patient's exposure to the event can be through direct experience, witnessing, learning about an event to a close family or friend, or repeated exposure or extreme exposure (eg, first responders).

Symptoms[1]

- Intrusion symptoms
  - Recurrent, intrusive distressing memories of the trauma
  - Recurrent, disturbing dreams related to the trauma
  - Reliving the traumatic event (eg, dissociative reaction)
  - Reminders of the trauma result in a physiologic reaction and/or psychological distress
- Stimuli avoidance
  - Memories, thoughts, or feelings related to the trauma
  - External reminders that trigger memories, thoughts, or feelings related to the trauma
- Persistent negative alterations in thinking and mood
  - Inability to remember key features of the traumatic event
  - Inability to feel pleasurable emotions (eg, happiness, love)
  - Isolating from others
  - Loss of interest in activities
  - Negative thoughts about the world or oneself
  - Distorted beliefs about traumatic event resulting in blaming self or others
  - Negative emotions (eg, fear, anger, guilt)
- Hyperarousal symptoms
  - Irritability or anger outbursts expressed as physical aggression
  - Self-destructive behavior
  - Hypervigilance
  - Startle easily ("jumpy")
  - Difficulty concentrating
  - Sleep disturbances
- Symptoms last more than 1 month
- Causes clinically significant distress or impairment in social, occupational, or other areas of functioning
- Not attributable to physiologic effects of a substance or another medical condition

Differential Diagnosis

Rule out underlying medical (traumatic brain injury) or psychiatric disorders (other trauma and stress-related disorders, psychotic disorders, personality disorders, other anxiety disorders, major depressive disorder) and medications that may cause anxiety (see Table 41–2).

OUTCOME EVALUATION

KEY CONCEPT Pharmacotherapy for patients with SAD should lead to improvement in anxiety and fear, functionality, and overall well-being.[6,42] Many patients will experience significant improvement in symptoms but may not achieve full remission. Monitor patients weekly during acute treatment (eg, initiation and titration of pharmacotherapy) and monthly once stabilized. Inquire about adverse effects, SAD symptoms, suicidal ideation, and symptoms of comorbid psychiatric conditions at each visit. Ask patients to keep a diary to record fears, anxiety levels, and behaviors in social situations.[6] Administer the Liebowitz Social Anxiety Scale (LSAS) to rate SAD severity and change, and the Social Phobia Inventory can be used as a "self-assessment" tool.[41] Counsel patients on appropriate expectations of pharmacotherapy in SAD, including gradual onset of effect and the need for extended treatment of at least 6 months following response.

TREATMENT: POSTTRAUMATIC STRESS DISORDER

Desired Outcomes

The goals of therapy for PTSD are to reduce the severity and duration of symptom clusters and restore overall functioning. The long-term goal is to achieve and maintain remission. With a positive response to treatment, comorbid mood or anxiety symptoms should be minimized.

General Approach to Treatment

Patients with PTSD may be managed with pharmacotherapy or psychotherapy. **KEY CONCEPT** Trauma-focused psychotherapy is preferred over pharmacotherapy or other psychotherapy treatments. Pharmacotherapy or non–trauma-focused psychotherapy are both first-line options if trauma-focused psychotherapy is not available.[45]

Nonpharmacologic Therapy

First-line treatment for PTSD is trauma-focused psychotherapy. Trauma-focused therapy involves engaging with the trauma memory for a prolonged period of time and identifying it as benign. This type of therapy includes prolonged exposure (PE), cognitive processing therapy (CPT), and eye movement desensitization and reprocessing (EMDR).[12,45] If trauma-focused psychotherapy is not available, non–trauma-focused therapy is recommended.[45] Treatment effects have been seen for up to 10 years posttreatment.[17]

Pharmacologic Therapy

Several pharmacologic agents have demonstrated effectiveness in PTSD, including some SSRIs, venlafaxine, TCAs, mirtazapine, nefazodone, prazosin, and phenelzine (Table 41–6). **KEY CONCEPT** Sertraline, fluoxetine, and paroxetine are considered the drugs of choice based on their tolerability and efficacy for PTSD and comorbid depression if present.[12,45] Patients responding to medication should be continued on treatment 6 to 12 months.[12,45] A suggested treatment algorithm is shown in Figure 41–5.

▶ *First- and Second-Line Options for Core Symptoms of PTSD*

Antidepressants The efficacy of fluoxetine, paroxetine, sertraline, and venlafaxine has been established in large controlled trials.[6]

The initial dose of first-line agents is similar to that used in depression. Patients should be titrated as tolerated to response. When discontinuing therapy, the dose should be tapered slowly

Table 41–6

Antidepressants for Posttraumatic Stress Disorder[2,12,45]

First-Line Options

Medication	Recommended Starting Dose (mg/day)	Usual Therapeutic Dosage Range (mg/day)
Fluoxetine	10–20	20–80
Paroxetine[a]	10–20	20–60
Sertraline[a]	25	50–200
Venlafaxine XR	37.5	75–225
Second-Line Options		
Phenelzine	15 three times daily	15 mg daily; 60–90 in divided doses
Nefazodone	25–100 twice daily	150–600 in 2 divided doses
Imipramine	25–75	100–300 in 1 or 2 divided doses

[a]Food and Drug Administration approved for use in posttraumatic stress disorder. XR=extended release

to avoid withdrawal symptoms. Side effects of therapy are similar to those seen in depression or anxiety disorders. Limited data support the effectiveness of citalopram, escitalopram, or desvenlafaxine for PTSD.[45]

Phenelzine use is limited due to dietary restriction, tolerability, and drug–drug interaction. The effectiveness of phenelzine for PTSD has been demonstrated in small placebo and comparator (imipramine) studies.[6,12]

Imipramine is limited due to tolerability and concern in overdose. Imipramine for PTSD treatment has shown effectiveness versus placebo and equal efficacy to phenelzine in trials.[6,12]

Effectiveness of mirtazapine as monotherapy and combination therapy with sertraline have been shown in randomized trial and open label trials.[6,12] Although nefazodone use is limited due to hepatoxicity, it has shown efficacy in older studies[2,45] and is included in Department of Veterans Affairs clinical practice guideline for PTSD.[45]

▸ *Adjunctive Therapy for Symptoms of PTSD*

Prazosin has historically been used for the treatment of nightmares associated with PTSD based on limited effectiveness data.

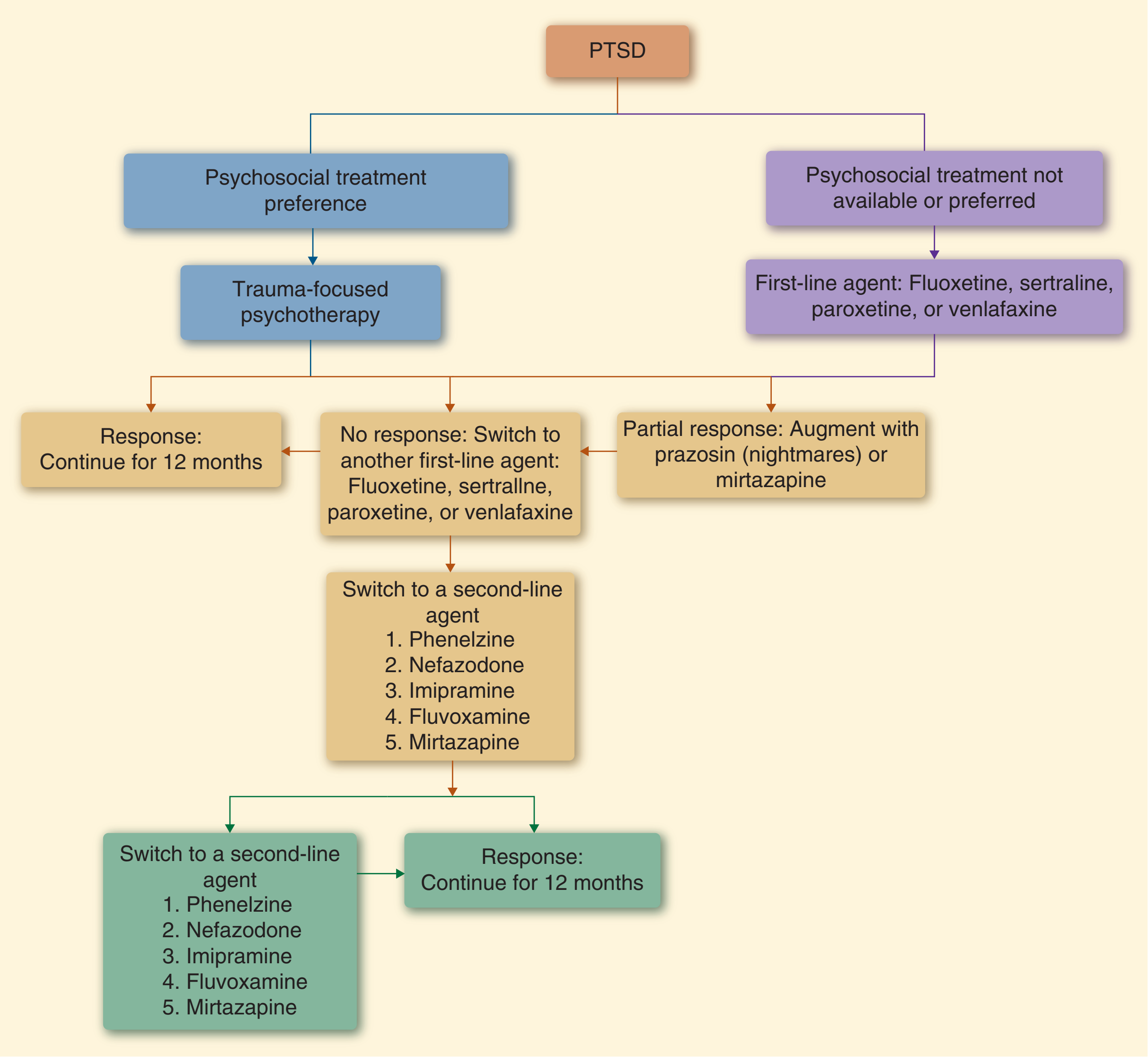
PTSD
Psychosocial treatment preference
Psychosocial treatment not available or preferred
Trauma-focused psychotherapy
First-line agent: Fluoxetine, sertraline, paroxetine, or venlafaxine
Response: Continue for 12 months
No response: Switch to another first-line agent: Fluoxetine, sertrallne, paroxetine, or venlafaxine
Partial response: Augment with prazosin (nightmares) or mirtazapine
Switch to a second-line agent 1. Phenelzine 2. Nefazodone 3. Imipramine 4. Fluvoxamine 5. Mirtazapine
Switch to a second-line agent 1. Phenelzine 2. Nefazodone 3. Imipramine 4. Fluvoxamine 5. Mirtazapine
Response: Continue for 12 months

FIGURE 41–5. Algorithm for the pharmacotherapy of posttraumatic stress disorder (PTSD). (Data from Refs. 2, 12, 45.)

Patient Encounter 2, Part 2

Patient returns to clinic 2 months after starting fluoxetine 20 mg daily. She is currently on fluoxetine 60 mg daily with no response to treatment. Her symptoms have persisted for the last 2 months. She continues to take levothyroxine 75 mcg daily.

What change in treatment is needed for this patient?

What tool could be used to monitor her response to treatment?

It continues to be included in guidelines for this use, although the newest Veteran's Administration guidelines for PTSD could not recommend for or against its use.[2,6,12,45]

The SGAs, risperidone, aripiprazole, and quetiapine have limited evidence for intrusion symptoms associated with PTSD and refractory PTSD. Prior to initiating SGA therapy for PTSD symptoms, the benefit of treatment needs to be weighed against the adverse effects associated with their use.[12]

Benzodiazepines have limited evidence for PTSD symptoms and are not recommended for the symptoms specific to PTSD.[7,12,45]

Outcome Evaluation

Pharmacotherapy for patients with PTSD should lead to improvement in PTSD symptoms, functionality, and overall well-being. Monitor patients weekly during acute treatment (eg, initiation and titration of pharmacotherapy) and monthly once stabilized. Inquire about adverse effects, PTSD symptoms, suicidal ideation, and symptoms of comorbid psychiatric conditions at each visit. Administer the PTSD Checklist for *DSM-5* (PCL-5) to rate PTSD severity and treatment response.[45] Counsel patients on appropriate expectations of pharmacotherapy in PTSD and the need for extended treatment of at least 6 months following response. If pharmacotherapy is being discontinued, educate patient about tapering medication and how to return for treatment in the future if needed.

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Patient Care Process

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. Identify allergies to medications.
- Review medical history and physical examination findings.
- Review mental status examination and screen for depression, anxiety, and substance use.
- Interview the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect treatment access or preference.

Assess the Information:

- Determine whether the patient is taking any medication or substance that could cause or worsen anxiety (Table 41–2).
- Review relevant laboratory tests (eg, urine toxicology, thyroid-stimulating hormone).
- Document pertinent family medical and mental health history (eg, depression, anxiety, substance use, suicide).
- Based on clinical presentation, mental status examination, and screening tools (eg, GAD-7), determine whether the patient is experiencing symptoms of sufficient intensity and duration to warrant treatment.
- Document current symptom severity using a valid measurement-based tool (eg, GAD-7, LSAS, PDSS).
- Identify comorbidities that will affect treatment choice (eg, depression, substance use).
- Assess the efficacy, safety, and adherence of current pharmacotherapy, if applicable.
- Identify any significant adverse drug effects or drug interactions.

Develop a Care Plan:

- Select lifestyle modifications and antianxiety medications that are likely to be effective and safe.
- Use shared decision making for selection of behavioral and pharmacotherapy treatment intervention(s).
- Choose medications and doses that are optimal for the patient based on age, anxiety disorder, and comorbid conditions (see Tables 41–3, 41–4, and 41–6).

Implement the Care Plan:

- Educate the patient about antianxiety medication effectiveness, onset and expected time to benefit, administration, and common adverse effects.
- Address any patient concerns about anxiety and its management.
- Discuss the importance of lifestyle modifications to reduce anxiety (eg, social support, substance use, exercise).
- Determine whether the patient has access to recommended medication or behavioral treatment (eg, insurance, medication on formulary, CBT provider nearby).

Follow-up: Monitor and Evaluate:

- Follow up at monthly intervals or more frequently during acute treatment to assess effectiveness and tolerability until treatment goal achieved.
- Review medication adherence and anxiety symptom control.
- Use appropriate rating scales to assess symptom change over time.
- Once anxiety is controlled and baseline function restored, determine the appropriateness of treatment beyond 1 year based on the patient's previous treatment and comorbid conditions.

Abbreviations Introduced in This Chapter

CBT	Cognitive-behavioral therapy
CNS	Central nervous system
DA	Dopamine
FDA	Food and Drug Administration
GABA	γ-Aminobutyric acid
GAD	Generalized anxiety disorder
HPA	Hypothalamic–pituitary–adrenal
5-HT	Serotonin
iCBT	Internet-based cognitive-behavioral therapy
LC	Locus ceruleus
LSAS	Liebowitz Social Anxiety Scale
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder
NCS-R	National Comorbidity Survey, Replication
NE	Norepinephrine
NPY	Neuropeptide Y
OCD	Obsessive-compulsive disorder
OTC	Over-the-counter
PD	Panic disorder
PDSS	Panic Disorder Symptom Scale
PTSD	Posttraumatic stress disorder
RAS	Reticular activating system
SAD	Social anxiety disorder
SGA	Second-generation antipsychotic
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

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42

Sleep Disorders

Jessa Marie Koch and Azita Alipour

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. List the sequelae of undiagnosed or untreated sleep disorders and appreciate the importance of successful treatment of sleep disorders.
2. Describe the pathophysiology and characteristic features of the sleep disorders covered in this chapter, including insomnia, narcolepsy, restless legs syndrome (RLS), obstructive sleep apnea (OSA), and parasomnias.
3. Assess patient sleep complaints, conduct sleep histories, and evaluate sleep studies to recognize daytime and nighttime symptoms and characteristics of common sleep disorders.
4. Recommend and optimize appropriate sleep hygiene and nonpharmacologic therapies for the management and prevention of sleep disorders.
5. Recommend and optimize appropriate pharmacotherapy for sleep disorders.
6. Describe the components of the patient care process to implement and assess safety and efficacy of pharmacotherapy for common sleep disorders.
7. Educate patients about preventive behavior, appropriate lifestyle modifications, and drug therapy required for effective treatment and control of sleep disorders.

INTRODUCTION

Individuals with normal sleep patterns sleep up to one-third of their lives and spend more time sleeping than in any other single activity. Despite this, our understanding of the full purpose of sleep and the mechanisms regulating sleep homeostasis remain incomplete. Sleep is necessary to allow one to maintain wakefulness and good health. Disruption of normal sleep is a major cause of societal morbidity, lost productivity, reduced quality of life, and contributes to the development and progression of comorbid medical conditions.[1]

Sleep is governed and paced by the suprachiasmic nucleus in the brain that regulates circadian rhythm. There are two main types of sleep: rapid eye movement (REM) sleep, during which eye movements and dreaming occur, but the body is mostly paralyzed, and nonrapid eye movement (NREM) sleep, which consists of three substages (stages 1–3). Stage 1 serves as a transition between wake and sleep and is NREM sleep. This stage of sleep typically lasts several minutes. Most of the time being asleep is spent in stage 2 NREM sleep and is a period of light sleep. Stage 3 is referred to as *deep sleep*, or *delta sleep*, because prominent delta waves are seen on the electroencephalogram (EEG) during this stage of sleep. Stage 3 is considered to be restorative sleep and is needed to feel refreshed in the morning. REM sleep occurs about every 90 minutes upon falling asleep.

EPIDEMIOLOGY AND ETIOLOGY

Approximately 50% of adults will report a sleep complaint over the course of their lifetime.[2] In general, sleep disturbances increase with age and may vary among genders. The full extent and impact of disordered sleep on our society is not known because many patients' sleep disorders remain undiagnosed. Normal sleep, by definition, is "a reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment."[3] Individuals with sleep disorders exhibit or complain about consequent symptoms (eg, excessive daytime sleepiness [EDS]) or a bed partner often observes hallmark characteristics of the sleep disorder. Insomnia, restless legs syndrome (RLS), and sleep-related breathing disorders are the most common sleep disorders.

Insomnia

Nearly one-third of all adults report symptoms of insomnia with around 10% of those individuals meeting *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-5*) criteria for insomnia disorder. The prevalence of insomnia is greater among females compared to males. In females, onset of insomnia is often associated with the birth of a child as well as with menopause.[4] **KEY CONCEPT** Diagnostic criteria for insomnia specify that difficulty initiating sleep, maintaining sleep or early morning awakenings occur at least three times per week for a minimum duration of at least 3 months. It is estimated that 50% to 75% of individuals with comorbid psychiatric (eg, depression, anxiety) and/or chronic pain disorders have accompanying insomnia.[2] Insomnia is frequently triggered by acute stress and resolves when the stress resolves. Numerous coexisting medical conditions (eg, pain, thyroid abnormalities, asthma, gastroesophageal reflux) and medications (eg, selective serotonin reuptake inhibitors [SSRIs], steroids, stimulants, diuretics, β-agonists) can lead to secondary insomnia.

Narcolepsy

In comparison to insomnia, narcolepsy is much less prevalent. It is estimated that 0.02% to 0.04% (or about 1 in 2000) of the population have narcolepsy. The onset of narcolepsy symptoms generally occurs in childhood and adolescence with diagnosis taking 5 to 15 years.[4] Narcolepsy is further classified into type 1 (narcolepsy with cataplexy and low orexin levels) and type 2 (narcolepsy without cataplexy and normal orexin levels).[5,6] Around 75% of patients with narcolepsy have narcolepsy type 1.[7]

Restless Legs Syndrome

The prevalence of RLS ranges from 5% to 15% of which around 2.5% of individuals require medical treatment.[4,8] Prevalence increases with age and in various medical conditions, such as end-stage renal disease, pregnancy, and iron deficiency.[9] RLS appears to be more common in women than in men and has a genetic link in a majority of patients.[10]

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) affects between 2% and 15% of adults who are middle-aged, with risk increasing with older age to greater than 20%. There is a higher prevalence of OSA in males, with a male: female ratio of up to 4:1. This ratio decreases in older age, possibly due to the frequency increasing in females after menopause. In addition, there is a strong association between OSA and obesity.[4]

Individuals with OSA experience repetitive upper airway collapse during sleep, which decreases or stops airflow, with subsequent arousal from sleep to resume breathing. Severity is determined by polysomnography (PSG) or home sleep study and is graded by the number of episodes of apnea (total cessation of airflow) and hypopnea (partial airway closure with blood oxygen desaturation) experienced during sleep. Severity is expressed as the respiratory disturbance index (RDI), quantified in events per hour.

Parasomnias

NREM parasomnias have variable prevalence rates depending on patient age and comorbid diagnoses. Sleep talking, bruxism, sleepwalking, sleep terrors, and enuresis occur more frequently in childhood than in adulthood. For instance, sleepwalking occurs at least once in 10% to 30% of children and has a lifetime prevalence in adults of 29.2%.[4] Nightmares appear to occur with similar frequency in adults and children whereas sleep terror episodes occur in 36.9% in individuals of 18 months of age as opposed to 2.2% in adults.[4] REM sleep behavior disorder (RBD), a REM sleep parasomnia, has a reported prevalence of 0.5%, is more common in elderly men and is frequently associated with concomitant neurologic conditions.[4,11]

PATHOPHYSIOLOGY

Although the neurophysiology of sleep is complex, certain neurotransmitters promote sleep and wakefulness in different areas of the central nervous system (CNS). Whereas serotonin is thought to control NREM sleep, cholinergic and adrenergic transmitters mediate REM sleep. Dopamine, norepinephrine, hypocretin (also referred to as orexin), substance P, and histamine all play a role in wakefulness. Perturbations of various neurotransmitters are responsible for some sleep disorders and explain why various treatments are beneficial.

Insomnia

There is no single pathophysiologic explanation for the manifestations of insomnia. Current hypotheses focus on a combination of possible models that incorporate physiologic, cognitive, and cortical arousal. Most models focus on hyperarousal and its interference with the initiation or maintenance of sleep.

Narcolepsy

The exact pathophysiology of narcolepsy is not entirely known. Although individuals with type 1 or type 2 narcolepsy share phenotypic features of the disorder, the underlying cause is believed to differ between the two types. Type 1 narcolepsy is caused by a loss of neurons in the hypothalamus that produce orexin. Type 2 narcolepsy may also be caused by injury or damage to these neurons, but to a much lesser degree due to the normal levels of orexin seen in type 2.[5,6] Genetics also play a significant role in type 1 narcolepsy with 98% of individuals with this subtype carrying HLA-DQB1∗06:02 compared to about 50% of those with type 2 narcolepsy.[12] Another interesting aspect to the disease is onset of symptoms. Symptoms more commonly present in the late spring, which may suggest an autoimmune process from infection such as group A streptococcal infection or influenza that then triggers the attack to the orexin-producing neurons.[13]

Restless Legs Syndrome

RLS is a neurologic medical condition characterized by an irresistible desire to move the limbs. The two main theories surrounding the pathophysiology of RLS center around iron and dopamine pathologies.[8] Dopaminergic dysfunction in individuals with RLS is supported by the dopaminergic medications that reduce RLS symptoms in patients. Likewise, individuals with RLS have been found to have reduced serum ferritin levels. Iron and H-ferritin concentrations, along with transferrin receptor and iron transporter numbers, have been found to be reduced in the substantia nigra of patients with RLS.[14] It is hypothesized that iron abnormalities lead to dysfunction of dopaminergic transmission in the substantia nigra.[15]

Obstructive Sleep Apnea

At least 20 muscles and soft tissue structures control patency of the upper airway. Patients with OSA may have differences in upper airway muscle activity during sleep and may have smaller airways, predisposing them to upper airway collapse and consequent apneic episodes during sleep. The inability of the upper airway to contend with factors that promote collapse, including fat deposition in the neck, negative pressure in the airway during inspiration, and a smaller lower jawbone, also may play a role in the pathogenesis of OSA. Patients with sleep apnea often are obese and may be predisposed to weight gain.

Poor sleep architecture and fragmented sleep secondary to OSA can cause EDS and neurocognitive deficits. These sequelae can affect quality of life and work performance and may be linked to occupational and motor vehicle accidents. OSA is also associated with systemic disease such as hypertension, arrhythmias, heart failure, stroke, and ischemic heart disease.[16,17] Hypertension frequently occurs in OSA and may be a contributing cause of increased cardiovascular conditions found in this population.[18] Furthermore, when hypertension is present, it is often resistant to antihypertensive therapy. Breathing against a closed upper airway during sleep causes intermittent and repetitive episodes of hypoxemia and hypercapnia, dramatic changes in intrathoracic pressure, and activation of the sympathetic nervous system. These responses can produce acute hemodynamic and humoral responses.[19]

Parasomnias

The pathogenesis of both NREM and REM parasomnias (eg, sleepwalking, enuresis, sleep talking) is variable, poorly described, and involves state dissociation, whereby two states of being overlap

Clinical Presentation and Diagnosis

KEY CONCEPT Patients with sleep complaints should have a careful sleep history performed to assess their possible sleep disorder in order to guide diagnostic and therapeutic decisions.

Daytime Symptoms and Associated Characteristics

EDS is the primary symptom described by patients with sleep disorders. It is usually described as not waking up refreshed in the morning or falling asleep or fighting the urge to sleep during the day despite a night of sleep. Other daytime characteristics of sleep disorders include:

- Irritability, fatigue, or depression
- Confusion or impaired performance at work or school
- Cataplexy
- Hypertension

Nighttime Sleep Complaints

Depending on the sleep disorder, patients may exhibit or experience various nocturnal complaints during sleep. Some complaints can be uncovered by clinical history alone (eg, hallucinations, RLS, snoring), but others can be diagnosed during sleep studies (eg, OSA, nighttime awakenings, somnambulism [sleepwalking], etc). Frequent complaints include:

- Inability to fall asleep, nighttime awakenings
- Sleepwalking (somnambulism), sleep talking (somniloquy)
- Cessation of breathing (apnea), snoring
- Sleep paralysis or hallucinations when waking or falling asleep
- Restlessness and periodic limb movements of sleep

simultaneously. For example, abnormal activation of the central pattern generator of the spinal cord that produces motor movements is hypothesized to underlie sleepwalking behavior. In RBD, active inhibition of motor activity in the perilocus coeruleus region is lost, resulting in loss of paralysis and dream enactment.

CLINICAL PRESENTATION AND DIAGNOSIS

KEY CONCEPT Although the clinical history guides diagnosis and therapy, only PSG, home sleep studies, and/or multiple sleep latency tests (MSLTs) can definitively diagnose and guide therapy for OSA and narcolepsy. All patients presenting with sleep complaints should have a thorough interview and history to inventory their sleep habits and sleep hygiene.

Sleep Diagnostics

Complete PSG is the "gold standard" for diagnosing and identifying sleep-disordered breathing, parasomnias, and nocturnal sleep irregularities related to narcolepsy. Sleep is observed and monitored in a controlled setting, recording sleep onset, arousals, sleep stages, eye movements, leg and jaw movements, heart rhythm, airflow, respiratory effort, and oxygen desaturations. Home sleep studies are increasingly used to diagnose sleep apnea due to their reduced cost and increased patient convenience.[1,4,16]

The MSLT is a commonly performed test to assess daytime sleepiness. During the MSLT, the patient attempts to take a 20-minute nap every 2 hours during the day beginning 2 hours after morning awakening (after a normal night's sleep) to evaluate physiologic sleepiness. The patient is instructed not to resist the urge to fall asleep. Sleep latency of less than 5 minutes is considered pathologic hypersomnolence. The occurrence of a REM onset period during two naps with short sleep latency is indicative of a diagnosis of narcolepsy.[1,4]

Insomnia

Insomnia is often characterized by difficulty falling asleep, frequent nocturnal awakenings, and early morning awakenings, which may result in daytime impairments in concentration and school or work performance. In some situations, social factors (eg, family difficulties, bereavement), medications (eg, antidepressants, β-agonists, corticosteroids, decongestants), and coexisting medical or psychiatric conditions (eg, depression, bipolar disorder) may help to explain difficulties in initiating and maintaining sleep.

Narcolepsy

The hallmark of narcolepsy is EDS and may also include disrupted nighttime sleep. Many patients with narcolepsy experience a tetrad of symptoms: EDS, cataplexy, sleep paralysis, and hypnagogic/hypnopompic hallucinations (dream-like images that appear at sleep–wake transitions).

Restless Legs Syndrome

Although RLS symptoms can vary, patients commonly report "creepy-crawly," burning, tingling, or achy feelings in the legs or arms. These sensations create a desire to move the limbs and may produce motor agitation. Symptoms begin to get worse in the evening and are almost exclusively present at rest, with temporary relief with movement.[4] Symptoms also can occur during sleep and often lead to semirhythmic periodic limb movements of sleep. Periodic limb movements of sleep are objective findings during PSG recorded by leg electrodes and present in most patients with RLS but may occur independently.

Obstructive Sleep Apnea

Common characteristics of OSA include snoring, choking, gasping for air, nocturnal reflux symptoms, and morning headaches.[4] A bed partner or roommate may observe these apneic episodes where the patient stops breathing. Patients with large neck sizes (> 45 cm [~18 in] neck circumference) and a body mass index (BMI) of 30 kg/m^2 or greater are at higher risk for OSA. OSA should always be considered and evaluated in hypertensive patients who are resistant to therapy.

Parasomnias

Parasomnias are characterized by undesirable physical or behavioral phenomena that occur during sleep (eg, sleepwalking, sleep eating, sleep talking, bruxism [grinding of teeth], enuresis, night terrors, and RBD). People with RBD act out their dreams during sleep, often in a violent manner.

TREATMENT

Desired Outcomes and General Approach to Treatment

KEY CONCEPT Treatment goals vary among different sleep disorders but generally include restoration of normal sleep patterns, elimination of daytime sequelae, improved quality of life, and prevention of complications and adverse effects from therapy.[1,4]

Table 42–1

Nonpharmacologic Therapies for Insomnia

Sleep Hygiene
- Keep a regular sleep schedule.
- Exercise frequently but not immediately before bedtime.
- Avoid alcohol and stimulants (caffeine, nicotine) in the late afternoon and evening.
- Maintain a comfortable sleeping environment that is dark, quiet, and free of intrusions.
- Avoid consuming large quantities of food or liquids immediately before bedtime.

Stimulus Control
- Go to bed only when sleepy.
- Avoid daytime naps.
- If you cannot sleep within approximately 20 minutes, get out of bed and go to another room—only return to your bed when you feel the need to sleep.
- Bed is for sleep and intimacy only (no eating or watching TV on bed).
- Always wake up at the same time each day.

Relaxation Training
- Reduce somatic arousal (muscle relaxation).
- Reduce mental arousal (eg, attention-focusing procedures, imagery training, meditation).
- Use biofeedback (visual or auditory feedback to reduce tension).

Cognitive Therapy
- Alter beliefs, attitudes, and expectations about sleep.

Insomnia

KEY CONCEPT Psychological and behavioral interventions for insomnia are effective for adults of all ages. First-line therapy for the treatment of insomnia is nonpharmacological: cognitive-behavioral therapy for insomnia (CBT-I).[2] A number of nonpharmacologic interventions for insomnia are outlined in Table 42–1. Sleep hygiene should be reinforced in all patients; however, insufficient evidence supports its use alone.[2] Rather, good sleep hygiene principles should be combined with behavioral, cognitive, and stimulus-control interventions. Pharmacologic treatment with short-term hypnotic use should be adjunctive to nonpharmacologic therapies.[2] An algorithm for the initial assessment and first treatment step of EDS is provided in Figure 42–1.

In referring to pharmacologic treatment for insomnia, the ideal hypnotic medication would be effective at reducing sleep latency, maintaining sleep, increasing total sleep time, and would be free of unwanted adverse effects. **KEY CONCEPT** Pharmacologic treatment of insomnia is considered a second-line intervention. Treatment guidelines vary slightly regarding which medication is recommended for what primary complaint or patient population. In general, intermediate-acting NBRAs, eszopiclone or zolpidem, or the benzodiazepine, temazepam, may be preferable in patients with complaints of sleep onset difficulty as well as difficulty with sleep maintenance.[2] In individuals solely with sleep onset difficulty, zaleplon, ramelteon, or triazolam may be the best options to consider due to their improvement in reducing sleep latency.[2] For those with complaints of difficulty maintaining sleep, doxepin or suvorexant may be best given evidence to support reduction in time spent awake after sleep onset, improvement in total sleep time, and sleep efficiency.[2] Guidelines are not clear on duration of treatment but will vary depending on pharmacologic medication selected. Eszopiclone, zolpidem CR, and ramelteon have been studied for use up to a 6-month duration whereas zaleplon use should be limited to 30 days.[20-24]

Patient Encounter, Part 1

A 58-year-old woman with a history of chronic insomnia complains of worsened symptoms over the last 2 months: excessive daytime sleepiness, difficulty falling asleep (sleep latency of 2 hours), and frequent nighttime awakenings. She has been followed by a therapist for CBT-I and taking melatonin 3 mg nightly. She reports doing well for 2 months following this treatment plan. Her other medications include sertraline 100 mg daily, furosemide 20 mg daily, lisinopril 10 mg daily, and carvedilol 6.25 mg twice daily.

What additional information do you need to know in your assessment of this patient?

What could contribute to worsening insomnia in this patient?

▶ *Benzodiazepines*

Although all benzodiazepines have sedative-hypnotic properties, only five are FDA approved for the treatment of insomnia: estazolam, temazepam, triazolam, flurazepam, and quazepam. Key pharmacokinetic differences between these five agents help to guide selection, depending on patient considerations and specific sleep complaints (Table 42–2). The benzodiazepines work by binding to a site on the γ-aminobutyric acid (GABA) type A receptor complex, resulting in opening of chloride channels that facilitate GABA inhibition and promote sleepiness.[25] In turn, benzodiazepines decrease sleep latency, increase stage 2 sleep, reduce delta sleep and REM sleep, and some may increase total sleep time.[25]

▶ *Nonbenzodiazepine Receptor Agonists*

NBRAs have a very similar mechanism of action to the BZDs with some subtle differences in exact binding affinities, limiting their efficacy as sedative-hypnotics only.[25] One way in which the NBRAs differ from the BZDs is selectivity for the α_1 subtype of the α subunit on GABA_A. This subtype is known to produce sedation. The BZDs are not as selective and bind to four of the α subtypes on the α subunit on GABA_A.[25] The three NBRAs include eszopiclone, zaleplon, and zolpidem.

Patients should be instructed to take BZDs/NBRAs at bedtime and avoid activities requiring alertness after ingestion. Although BDZs and NBRAs are generally well-tolerated, mild-to-moderate adverse effects can occur, and precautions are warranted.

Precautions and Safety The most common adverse effects associated with BZDs and NBRAs include residual sedation into the waking hours after sleep, grogginess, and psychomotor impairment.[25] Selection of a hypnotic with a duration of action matching the patient's budgeted sleep time can help minimize the risk of residual sedation. BZDs and NBRAs should be initiated at low doses and should ideally be avoided in elderly patients for a number of reasons, but one being an increased risk for falls.[26,27] BZDs may cause anterograde amnesia, defined as memory loss of activities and interactions after ingestion of the drug.[27] Additionally, the BZDs carry a black box warning regarding concomitant use with opioids. The use of BZDs with opioids may result

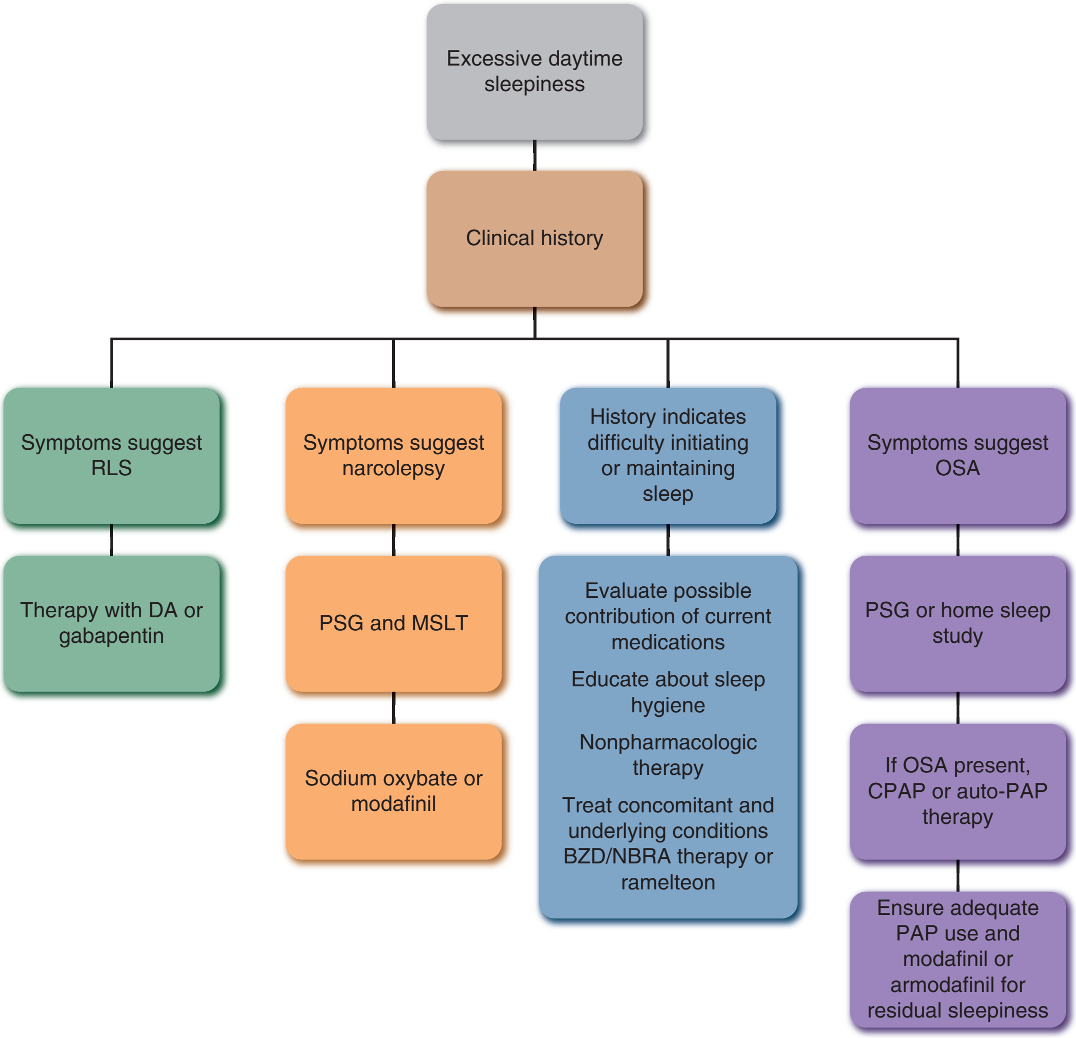
Excessive daytime sleepiness
Clinical history
Symptoms suggest RLS
Therapy with DA or gabapentin
Symptoms suggest narcolepsy
PSG and MSLT
Sodium oxybate or modafinil
History indicates difficulty initiating or maintaining sleep
Evaluate possible contribution of current medications
Educate about sleep hygiene
Nonpharmacologic therapy
Treat concomitant and underlying conditions BZD/NBRA therapy or ramelteon
Symptoms suggest OSA
PSG or home sleep study
If OSA present, CPAP or auto-PAP therapy
Ensure adequate PAP use and modafinil or armodafinil for residual sleepiness

FIGURE 42–1. Primary assessment and initial treatment for complaint of excessive daytime sleepiness. (BZD, benzodiazepine; CPAP, continuous positive airway pressure; DA, dopamine agonist; MSLT, multiple sleep latency test; NBRA, nonbenzodiazepine receptor agonist; PSG, polysomnography; OSA, obstructive sleep apnea; PAP, positive airway pressure; RLS, restless legs syndrome.)

Patient Encounter, Part 2: Medical History, Physical Examination, and Diagnostic Test

The patient undergoes further evaluation for her worsening insomnia symptoms.

PMH: Chronic insomnia × 10 years, major depressive disorder × 2 years, generalized anxiety disorder × 1 year, congestive heart failure × 4 years

FH: Noncontributory

SH: Married, no children. No tobacco or alcohol intake

Meds:

- Melatonin 3 mg nightly (patient purchases over the counter)
- Sertraline 100 mg daily
- Furosemide 20 mg daily
  - Of note, this medication was started about 3 months ago. Patient takes at bedtime to minimize bathroom use during the day
- Lisinopril 10 mg daily
- Carvedilol 6.25 mg twice daily

ROS: (+) daytime sleepiness; (+) symptoms of anxiety (Generalized Anxiety Disorder 7-Item Scale score: 19 out of 21, indicating severe symptoms of anxiety)

PE: Complete physical examination was unremarkable

VS: BP 122/68 mm Hg, P 72 beats/min, RR 16 breaths/min, T 37°C (98.6°F); BMI 21 kg/m^2

Labs: All within normal limits

Given this additional information, summarize what is occurring with this patient.

Identify your treatment goals and therapy recommendations for the patient.

What nonpharmacologic and pharmacologic alternatives are available for this patient?

Table 42–2

Pharmacokinetics and Dosing of Prescription Medications[a] Approved to Treat Insomnia

Generic Name (Brand)	Class	Parent t½ (hours)	Daily Dose Range (mg)	Recommended Daily Dose in Elderly (mg)[b]	Dose or Action in Hepatic Impairment	Comments
Doxepin (Silenor)	Antidepressant	15.3	3–6	3	3 mg	Effective for sleep maintenance difficulties only. Noncontrolled substance
Estazolam (Prosom)	BZD	2	1–2	0.5[e]	Dose ↓ may be needed	Moderate duration. CIV
Eszopiclone (Lunesta)	NBRA	6	2–3	1–2[e]	1 mg in severe impairment	Can be used up to 6 months for chronic insomnia. CIV
Flurazepam (Dalmane)	BZD	8	15–30	15[e]	No change necessary	High risk of hangover and residual effects. CIV
Lemborexant (Dayvigo)	Orexin receptor antagonist	17–19	5–10	5	5 mg maximum in moderate hepatic impairment	Novel mechanism of action. CIV
Quazepam (Doral)	BZD	2	7.5–15	7.5–15[e]	Dose ↓ may be needed	High risk of hangover and residual effects. CIV
Ramelteon (Rozerem)	Melatonin receptor agonist	1–2.6	8	No specific recommendations	Do not use in severe hepatic impairment	Noncontrolled substance; may be useful in patients with a history of substance abuse
Suvorexant (Belsomra)	Orexin receptor antagonist	12	10–20	No specific recommendations	No change necessary	Novel mechanism of action. CIV.
Temazepam (Restoril)	BZD	10–15	7.5–30	7.5	No change necessary	Moderate duration, well-tolerated, inexpensive. CIV
Triazolam (Halcion)	BZD	2	0.125–0.25	0.125[e]	0.125 mg	Short acting; little residual hangover. CIV
Zaleplon (Sonata)	NBRA	1	5–10	5[e]	5 mg	Short acting; only for difficulty falling asleep. CIV
Zolpidem (Ambien)	NBRA	2–2.6	5–10[d]	5[e]	5 mg	Short-to-moderate duration; no effects on sleep architecture. CIV
Zolpidem CR (Ambien CR)	NBRA	2.8	6.25–12.5[d]	6.25[e]	6.25 mg	Longer duration of action than regular-release zolpidem. CIV
Zolpidem sublingual (Intermezzo)	NBRA	2.5	1.75–3.5[d]	1.75[e]	1.75 mg	Approved for middle-of-the-night insomnia taken more than 4 hours before awakening. CIV

[a] In 2007, the Food and Drug Administration required additional information added to the safety labeling of sedative–hypnotic drugs concerning potential risks, including severe allergic reactions and complex sleep-related behaviors, which may include sleep driving. Sleep driving is defined as driving while not fully awake after ingestion of a sedative–hypnotic product with no memory of the event.

[b] If a dosing range is displayed, the first dose listed should be the starting dose.

[c] Data not available.

[d] For zolpidem, recommended dose for women is 5 mg, 6.25 mg for zolpidem CR, and 1.75 mg for sublingual zolpidem.

[e] These agents are all included on the updated 2019 Beers criteria and should be avoided in the elderly when possible.

BZD, benzodiazepine; CIV controlled substance schedule IV, CR, controlled release; NBRA, nonbenzodiazepine receptor agonist

in greater levels of sedation, respiratory depression, coma, and death. BZDs should not be used in conjunction with other sedating medications or alcohol due to concern for increased CNS depression.

On discontinuation of BZDs and NBRAs, patients may experience rebound insomnia that may last for a few nights. Rebound insomnia occurs more frequently after discontinuation of shorter-acting BZDs and NBRAs compared with longer-acting BZDs and NBRAs. Intermittent hypnotic therapy with the lowest dose possible reduces the likelihood of tolerance, dependence, and withdrawal when therapy is stopped. Patients should be counseled that rebound insomnia is not necessarily a return of their original symptoms, and it may take a few nights for rebound symptoms to subside. In general, eszopiclone, zaleplon, and zolpidem appear to be associated with lower risk of tolerance, rebound insomnia, and withdrawal than traditional benzodiazepines.[28] The NBRAs, however, are associated with complex sleep-related behaviors (eg, sleep eating, sleep driving, etc), and all carry a boxed warning regarding this risk. Female patients have reduced zolpidem clearance compared to males, and the maximum dose of zolpidem is 5 mg for female patients.[22]

► *Sedating Antidepressants*

Sedating antidepressants (eg, trazodone, amitriptyline, mirtazapine, doxepin) are commonly used for insomnia and may be an appealing option in patients with concomitant depression. However, at the doses frequently used for sleep, only mirtazapine exhibits significant antidepressant activity. Furthermore, quality clinical studies demonstrating efficacy for insomnia are lacking.[2,29] Adverse effects from antidepressants can be frequent, including next day sedation, grogginess, anticholinergic effects, and weight gain. Tricyclic antidepressants (TCAs; eg, amitriptyline, doxepin) should be used with caution in the elderly and patients with cardiovascular and hepatic impairment. Doxepin is approved for treatment of sleep maintenance insomnia at low doses (3–6 mg). Mirtazapine can cause daytime sedation, dizziness, and weight gain; trazodone can cause orthostatic hypotension and dizziness.

▶ *Miscellaneous Agents*

Ramelteon, a melatonin receptor agonist, is indicated for insomnia characterized by difficulty with sleep onset. Ramelteon is not a controlled substance and can be a viable option for patients with a history of substance abuse.[30] Suvorexant and lemborexant, orexin receptor antagonists, are the first medications that turn off wakefulness mechanisms instead of stimulating pathways that induce sleepiness. Suvorexant and lemborexant are both indicated for insomnia characterized by both difficulty initiating and maintaining sleep, and like BZD and NBRA are classified as Schedule IV controlled substances.[31,32] Both suvorexant and ramelteon have documented safety in those with mild-to-moderate chronic obstructive pulmonary disease and OSA while evidence for lemborexant in this population is limited at this time.[31-34]

▶ *Over-the-Counter Agents*

Over-the-counter first-generation antihistamines, such as diphenhydramine and doxylamine, are frequently used for difficulty sleeping. Diphenhydramine and doxylamine are FDA approved for the treatment of insomnia and can be effective at reducing sleep latency. However, first-generation antihistamine medications produce undesirable anticholinergic effects and carryover sedation that limit their use, especially in the elderly. Additionally, rapid tolerance can develop to antihistamines, thus use beyond 10 days is not recommended.[35]

Melatonin is an endogenous hormone that is secreted by the pineal gland to regulate the body's circadian rhythm and is available exogenously as a supplement. Doses of 8 mg or less seem to be safe for use for up to 6 months; however, there is limited evidence to support its use for insomnia in individuals.[36] Valerian root is a herb that has inconsistent effects on sleep but may reduce sleep latency and increase efficiency at commonly used doses of 400 to 900 mg valerian extract.[37]

Patient Encounter, Part 3: Modifying the Treatment Plan

The patient returns to the clinic 3 months later. The provider previously decided to increase the dose of the patient's sertraline to better control her symptoms of anxiety and changed the furosemide schedule to morning. She was also started on zolpidem 5 mg to take nightly as needed if insomnia persists. At the visit today, the patient reports that her anxiety is well-controlled and she is no longer having nighttime awakenings to use the restroom. She takes the zolpidem about five nights/week with benefit but is very concerned about staying on the zolpidem. She requests a different sleep aid that is not controlled and may be safer to take as she ages.

Based on the information presented, recommend therapy and a plan for the patient.

Narcolepsy

Therapy for narcolepsy involves two key principles: (a) treatment of EDS with scheduled naps, CNS stimulants or sodium oxybate and (b) suppression of cataplexy and REM sleep abnormalities with aminergic signaling drugs or sodium oxybate.

▶ *Excessive Daytime Sedation*

Modafinil/or sodium oxybate are the first-line treatments recommended for EDS due to narcolepsy.[38] Modafinil and armodafinil (the active R-isomer of modafinil) are Schedule IV medications, and these may have fewer peripheral and cardiovascular effects than traditional stimulants due to a slightly different mechanism of action. Most recently, solriamfetol was FDA approved as an additional medication to improve wakefulness in individuals with EDS secondary to narcolepsy. Solriamfetol is a dopamine and norepinephrine reuptake inhibitor and is also a Schedule IV medication.[39] Pitolisant is a histamine-3 receptor antagonist/inverse agonist that works to increase histamine levels and thereby increasing wakefulness; it has been FDA approved for EDS and is not a controlled substance.[40]

Sodium oxybate is a first-line treatment indicated for both EDS and cataplexy. The exact mechanism of action for sodium oxybate is not known but is believed to improve nocturnal sleep via CNS depression and GABA-B agonist activity. The improvement in nocturnal sleep thereby decreases EDS and improves alertness. Due to illicit use and abuse, sodium oxybate is Schedule III and only dispensed by one pharmacy in the nation. Sodium oxybate has a short duration of action, requiring patients to take two doses per night, one at bedtime and one follow-up dose taken 2.5 to 4 hours later.[41]

▶ *Cataplexy*

The most effective medication for the treatment of cataplexy is sodium oxybate. Other treatment options consist of aminergic signaling antidepressants.[38] These include TCAs and certain selective serotonin reuptake inhibitors (eg, sertraline) and serotonin norepinephrine reuptake inhibitors (eg. venlafaxine).

Restless Legs Syndrome

KEY CONCEPT RLS treatment involves suppression of abnormal sensations and leg movements and consolidation of sleep. Dopaminergic medications are prescribed commonly to treat RLS. Dopamine agonists (DAs) offer many advantages over levodopa–carbidopa, including longer half-lives to cover overnight symptoms, flexible dosing, and a reduced incidence of symptom augmentation. Up to 80% of patients who take levodopa–carbidopa will experience symptom **augmentation**: RLS symptoms appear earlier in the day, previously unaffected body parts become involved, duration of relief gets shorter, and higher doses of medication are required to control symptoms.[42] Augmentation should be managed by tapering and discontinuing dopaminergic medications, repleting body iron stores (if low), and switching to alternative medications such as gabapentin. Additionally, use of longer-duration DAs may reduce symptom augmentation.[43] Ropinirole, pramipexole, and rotigotine are FDA approved for the treatment of RLS and are available in sustained-release products. Treatment guidelines recommend pramipexole and rotigotine as first-line therapy with ropinirole as an alternative option.[44]

Table 42–3

Frequently Used Medications for Restless Legs Syndrome

Generic Name (Brand Name)	Half-Life (hours)	Dose Range (mg/day)[a]	Potential Side Effect or Disadvantage
Dopaminergic Agents[b]			
Levodopa–carbidopa (Sinemet)	1.5–2	100–200 of levodopa	Nausea or vomiting; high incidence of symptom augmentation
Pramipexole (Mirapex)	8–12[c]	0.125–0.5	Nausea or vomiting; risk of compulsive behaviors[d]
Ropinirole (Requip)	6[e]	0.25–3	Nausea or vomiting; risk of compulsive behaviors[d]
Rotigotine (Neupro)	5–7	1–3	Application site reactions with patch; risk of compulsive behaviors[d]
Anticonvulsants			
Gabapentin (Neurontin, Horizant)	5–7[c]	300–3600	Dizziness, ataxia, weight gain
Pregabalin (Lyrica)	5–6.5[c]	50–300	Weight gain, daytime sedation

[a] Usual range.

[b] Dopaminergic agents are frequently given at bedtime or 2 hours before bedtime or the anticipated onset of RLS symptoms.

[c] May be longer in patients with renal dysfunction.

[d] Compulsive behaviors such as gambling, shopping, sexual behaviors, and eating have been reported in patients taking dopamine agonists.

[e] May be longer in patients with hepatic dysfunction.

Gabapentin is an effective treatment for RLS, particularly in patients with painful symptoms.[8] The gabapentin prodrug (gabapentin enacarbil) is FDA approved for RLS at a recommended dose of 600 mg taken with food at dinnertime.[45,46] Although not FDA approved for RLS, pregabalin has demonstrated similar or greater efficacy compared to DAs for RLS treatment.[47] Low iron levels may exacerbate RLS symptoms. Iron supplementation should be prescribed in patients who are iron deficient. Iron supplementation in patients with serum ferritin concentrations of less than 50 to 75 mcg/L (ng/mL; 112–169 pmol/L) have been shown to improve RLS symptoms. Medications frequently used for RLS are shown in Table 42–3.[44]

Obstructive Sleep Apnea

KEY CONCEPT The main therapy for OSA is nasal continuous positive airway pressure **(CPAP)** therapy, which alleviates sleep-disordered breathing by producing a positive pressure column in the upper airway using room air. A flexible tube connects the CPAP machine to a mask that covers the nose. CPAP therapy has a favorable impact on blood pressure and attenuates some of the potential hemodynamic and neurohumoral responses that may link OSA to systemic disease.[16,18]

Not all individuals tolerate CPAP therapy, in part because patients must wear a mask during sleep, and therapy can dry and irritate the upper airway. In some individuals, these barriers for adherence may be reduced by properly fitting the mask, adding humidity to therapy, using bilevel positive airway pressure (BiPAP) or autotitrating continuous positive airway pressure (AutoPAP) therapy. BiPAP therapy applies a variable pressure into the airway during the inspiratory phase of respiration but, unlike CPAP, reduces the applied pressure during the expiratory phase. AutoPAP machines are set for a pressure range and individualize the pressure based on breath-to-breath analysis of the necessary pressure to keep the airway open.[16,48]

Obesity can worsen sleep apnea; thus weight management should be implemented for all overweight patients with OSA. In obese patients with mild OSA, weight loss alone can be effective, with studies showing reduced severity of OSA following bariatric surgery.[16,18] For patients who cannot tolerate CPAP, oral appliances can be used to advance the lower jawbone and to keep the tongue forward to enlarge the upper airway. For individuals who have OSA only when on their backs during sleep, positional therapies may be effective.[16]

Medication is not first- line for OSA but may be considered in select patients. Modafinil, armodafinil, and solriamfetol are wake-promoting medications approved by the FDA to treat EDS due to OSA. Initiation of these medications should be attempted only after patients are using optimal CPAP therapy to alleviate sleep-disordered breathing. The need for treating residual sleepiness in this population is not clear because it may not be related to the OSA and is similar to sleepiness in the general population.[49]

Parasomnias

NREM parasomnias usually do not require treatment. If needed, low-dose BZDs such as clonazepam can be prescribed for bothersome episodes. Clonazepam reduces the amount of sleep time spent in stage 3 of NREM sleep, when most NREM parasomnias occur. For treating RBD, clonazepam 0.5 to 2 mg at bedtime is the drug of choice, although melatonin 3 to 12 mg at bedtime also may be effective.[50] Patients with RBD also should have dangerous objects removed from the bedroom and environmental accommodations made to reduce the chance of injury from breakthrough episodes.

Drug–Disease and Drug–Drug Interactions

KEY CONCEPT It is important to review medication profiles for drugs that may aggravate sleep disorders. Patients should be monitored for adverse drug reactions and potential drug–drug interactions and assessed for treatment adherence. Pharmacotherapy for sleep disorders should be individualized. Often medications can treat several concomitant sleep disorders. Conversely, medication therapy may be effective for one sleep disorder and exacerbate another. For example, antidepressants may alleviate depressive symptoms but exacerbate symptoms of RLS. Medications that block dopaminergic transmission may worsen RLS symptoms. The orexin receptor antagonists are contraindicated in patients with narcolepsy. Alcohol and CNS depressants, including opioids,

Patient Care Process

Collect Information:

- Perform a detailed history of prescription, nonprescription, and complementary or alternative medication use.
- Based on patient nighttime and daytime complaints and bed partner report, determine the suspected sleep problem and its consequences.
- Review objective and subjective data regarding sleepiness, nighttime sleep quality and limb movements, sleep disordered breathing, and parasomnias.
- Evaluate concomitant sleep and medical conditions that influence therapy decisions.

Assess the Information:

- Evaluate effectiveness, safety, adherence, and adverse effects of therapy.
- Assess whether patient is taking any medications that may contribute to sleep complaint and/or daytime complaints.
- Determine whether the patient has insurance coverage for prescribed medications.
- Review relevant laboratory parameters for sleep (eg, serum thyroid-stimulating hormone [TSH], ferritin).

Develop a Care Plan:

- If patient requires sedative-hypnotic medication therapy, determine best agent based on timing of sleep complaint (difficulty initiating and/or maintaining sleep).
- For treatment of insomnia, try to ensure the lowest possible doses are prescribed and used for the shortest possible time period.
- If patient complaints are not entirely improved, consider increasing dose or adding a complementary agent.
- Ensure sleep hygiene (see Table 42–1) and drug therapy are appropriate for each sleep complaint.
- Determine if medication doses are optimal for treatment of various sleep disorders (see Tables 42–2 and 42–3).
- For insomnia, select medications whose duration of action matches the timing of the difficulty sleeping (eg, difficulty initiating or maintaining sleep).

Implement the Care Plan:

- Educate patient about medication changes, sleep hygiene, and importance of proper medication use and adherence.
- Address patient concerns about the sleep medication and possible adverse effects.

Follow-up: Monitor and Evaluate:

- Evaluate improvement in the specific sleep complaint (eg, how therapy affected sleep latency or sleep maintenance).
- Monitor daytime sleepiness, sleep diaries, and diaries of sleep events (periodic limb movements of sleep [PLMS], hallucinations, snoring, apneas, etc) and monitor cataplexy and other daytime symptoms to determine if therapy is effective.
- Make appropriate changes to therapy to address inadequately controlled symptoms and reported adverse effects.

sedatives (such as BZDs), and muscle relaxants, can worsen OSA, even in small doses, by reducing respiratory drive and relaxing the upper airway muscles responsible for maintaining patency. CNS depressants should be avoided, and if they are necessary, they should not be administered before sleep. Medication therapy for sleep disorders should be patient specific, and careful consideration should be given to coexisting diseases, concomitant medications, and potential drug–drug and drug–disease interactions to optimize patient care and treatment.

OUTCOME EVALUATION

Evaluate whether the treatment plan restored normal sleep patterns, reduced daytime sequelae, and improved quality of life without causing adverse effects. Schedule patients for follow-up within 3 weeks for insomnia and within 3 months for other sleep disorders. Perform a detailed clinical history to determine the patient's perception of treatment progress and symptoms along with medication effectiveness and adverse effects.[2,16,38,44,50]

Instruct patients to keep sleep diaries (number of hours, number of awakenings, and worsening or improved sleep) and daytime symptoms, along with documentation of episodes such as cataplexy or RBD. Increase medication to effective doses, and if necessary, start additional therapy to control symptoms. Perform a detailed history of prescription, nonprescription, and complementary or alternative medications and review the patient's sleep diary, daytime symptoms, and nonpharmacologic therapies on a regular basis.[2,16,38,44,50]

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Abbreviations Introduced in This Chapter

AutoPAP	Autotitrating continuous positive airway pressure
BiPAP	Bilevel positive airway pressure
BMI	Body mass index
BZD	Benzodiazepine
CBT-I	Cognitive-behavioral therapy for insomnia
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CRD	Circadian rhythm disorder
DA	Dopamine agonist
EDS	Excessive daytime sleepiness
EEG	Electroencephalogram
ESS	Epworth sleepiness scale
FDA	Food and Drug Administration
GABA	γ-Aminobutyric acid
MSLT	Multiple sleep latency test
NBRA	Nonbenzodiazepine receptor agonist
NREM	Nonrapid eye movement
OSA	Obstructive sleep apnea
PLMS	Periodic limb movements of sleep
PSG	Polysomnography
RBD	REM sleep behavior disorder

RDI	Respiratory disturbance index
REM	Rapid eye movement
RLS	Restless legs syndrome
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

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43 Attention-Deficit/Hyperactivity Disorder

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain accepted criteria necessary for the diagnosis of attention-deficit/hyperactivity disorder (ADHD).
2. Recommend a therapeutic plan, including drug selection, initial doses, dosage forms, and monitoring parameters, for a patient with ADHD.
3. Differentiate among the available pharmacologic agents used for ADHD with respect to pharmacology and pharmaceutical duration of action.
4. Recommend alternative agents and/or adjunctive agents as clinically indicated.
5. Address potential cost–benefit issues associated with pharmacotherapy of ADHD.
6. Recommend strategies for minimizing adverse effects of ADHD medications.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is characterized by a persistent pattern of inattention and/or hyperactivity–impulsivity. It can have a severe impact on a patient's ability to function in both academic and social environments. Early diagnosis and appropriate treatment are essential to compensate for areas of deficit.

EPIDEMIOLOGY AND ETIOLOGY

KEY CONCEPT This disorder usually begins in young children and must occur before 12 years of age to meet current diagnostic criteria. In the United States, ADHD is the most common neurobehavioral disorder that affects children.[1] ADHD has been diagnosed in approximately 11% of school-aged children.[2] ADHD occurs more than twice as often in school-aged boys than girls.[3]

Although ADHD generally is considered a childhood disorder, symptoms can persist into adolescence and adulthood. The prevalence of adult ADHD is estimated to be 2.5%; majority of adults with ADHD have symptoms that manifested in childhood.[3,4] Furthermore, problems associated with ADHD (eg, social, marital, academic, career, anxiety, depression, smoking, and substance abuse problems) increase with the transition of patients into adulthood. Untreated adults with ADHD have high rates of psychopathology, substance abuse, and social and occupational dysfunction.

PATHOPHYSIOLOGY

KEY CONCEPT The exact pathologic cause of ADHD has not been identified. ADHD is generally thought of as a disorder of self-regulation or **response inhibition** and **cognitive deficits**.[5] Patients who meet the diagnostic criteria for ADHD have difficulty maintaining self-control, resisting distractions, concentrating on ideas, and often alternate between inattentiveness to overexcitement.[3,6]

KEY CONCEPT Dysfunction of the **neurotransmitters** is thought to key in the pathology of ADHD. Norepinephrine is responsible for maintaining alertness and attention; dopamine is responsible for regulating learning, motivation, goal setting, and memory. Both of these neurotransmitters predominate in the frontal subcortical system, an area of the brain responsible for maintaining attention and memory. Genetics is a risk factor for developing ADHD with children having a 50% chance of developing ADHD if a parent has ADHD. An association has been made between the development of ADHD and fetal alcohol syndrome, lead poisoning, maternal smoking, and hypoxia.[3,6]

CLINICAL PRESENTATION AND DIAGNOSIS

KEY CONCEPT ADHD is often misdiagnosed and is generally associated with comorbid conditions.[1] Males are more likely to have oppositional defiant disorder and conduct disorders, where females are more likely to have anxiety and depression.[6] It is important to identify and appropriately treat coexisting conditions in patients with ADHD.

According to most recent diagnostic guidelines, all patients 4 to 18 years of age presenting with inattention, hyperactivity, impulsivity, academic, and/or behavioral problems should be evaluated for ADHD. Additional behavior information from various settings should be gathered from the patient, family, and teachers. The age of onset, frequency, severity, and duration of symptoms should be documented.[3,6]

The most useful diagnostic criteria for ADHD is the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-5*).[3] The *DSM-5* defines three presentations of ADHD: (a) predominately inattentive; (b) predominantly hyperactive–impulsive; and (c) combined, in which both inattentive and hyperactive or impulsive symptoms are evident.[3,6] It is recommended that parents and teachers complete a standardized rating scale based on the *DSM-5* criteria.[3] Rating scales (Vanderbilt, Conners) are not by themselves diagnostic but are diagnostic aids when added to a careful history and interview.[7]

Clinical Presentation and Diagnosis of ADHD Based on DSM-5 Criteria

General

Patients with ADHD can present with inattention, hyperactivity–impulsivity, or both. ADHD is typically encountered with comorbid conditions.

Symptoms

- A persistent pattern of inattention and/or hyperactivity–impulsivity that interferes with functioning or development, as characterized by inattention and/or hyperactivity and impulsivity:
  - Inattention: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
    - Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (eg, overlooks or misses details, work is inaccurate.)
    - Often has difficulty sustaining attention in tasks or play activities (eg, has difficulty remaining focused during lectures, conversations, or lengthy reading).
    - Often does not seem to listen when spoken to directly (eg, mind seems elsewhere, even in absence of any obvious distraction).
    - Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workspace (eg, starts tasks but quickly loses focus and is easily sidetracked).
    - Often has difficulty organizing tasks and activities (eg, difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
    - Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (eg, schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
    - Often loses things necessary for tasks or activities (eg, school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
    - Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
    - Is often forgetful in daily activities (eg, doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).
  - Hyperactivity and impulsivity: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities: Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
    - Often fidgets with or taps hands or feet or squirms in seat.
    - Often leaves seat in situations when remaining seated is expected (eg, leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
    - Often runs about or climbs in situations where it is inappropriate. (Note: In adolescents or adults, may be limited to feeling restless.)
    - Often unable to play or engage in leisure activities quietly.
      - Is often "on the go," acting as if "driven by a motor" (eg, is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
    - Often talks excessively.
    - Often blurts out an answer before a question has been completed (eg, completes people's sentences; cannot wait for turn in conversation).
    - Often has difficulty waiting his or her turn (eg, while waiting in line).
    - Often interrupts or intrudes on others (eg, butts into interrupts conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

Diagnostic Criteria

- Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.
- Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).
- There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
- The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

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TREATMENT

Desired Outcomes

KEY CONCEPT The primary therapeutic objectives in ADHD are to (1) improve behavior; (2) increase attention; or (3) response inhibition. The secondary goals of treatment are to (1) improve interpersonal relationships and academic performance; (2) decrease disruptive behavior; (3) increase independence; and (4) minimize adverse effects of therapy.

Nonpharmacologic (Behavioral) Therapy

Behavioral therapy can be useful; however, it is generally not recommended as first-line monotherapy except in preschool-aged children (4–5 years of age).[3,6] KEY CONCEPT Studies have demonstrated pharmacotherapy alone is superior to behavioral intervention alone in improving attention. However, combined behavioral and stimulant therapy is better at improving opposition and aggression in school-aged children.[8] Behavioral modification involves training caregivers and teachers to change environmental factors and establish a reward/consequence system.[6] Success of behavioral modifications depends on the cooperation of the caregivers and teachers.

Pharmacologic Therapy

The proposed mechanism of ADHD pharmacotherapy is to modulate neurotransmitter function in order to improve academic and social functioning. Pharmacotherapy can be divided into two categories—stimulants and nonstimulants.

▶ *Stimulants*

KEY CONCEPT Psychostimulants (eg, methylphenidate and amphetamines) are the most effective agents in treating ADHD. Following a diagnosis of ADHD, a stimulant medication should be considered first-line therapy in patients 6 years of age or older. Stimulants theoretically exert their primary effect by blocking the reuptake of dopamine and norepinephrine. In preschool-aged children, methylphenidate can be added to the patient's treatment if behavioral modification monotherapy is not sufficient.[6] Generally, a trial of at least 3 months on a stimulant is appropriate, and this includes dose titration to response as tolerated.[6] **KEY CONCEPT** If treatment with the first stimulant formulation fails, it is recommended to switch to a different stimulant class.[3,6] For example, if the patient was started on methylphenidate but could not tolerate the side effects, switching to dextroamphetamine with or without amphetamine is appropriate. Most patients who fail one stimulant will respond to an alternative stimulant medication.[6] **KEY CONCEPT** If the patient fails two adequate trials of different stimulant medications, a third stimulant formulation or second-line nonstimulant such as atomoxetine, guanfacine, or clonidine can be considered. The diagnosis of ADHD should be revalidated as well.

Stimulants should be initiated at recommended starting doses and titrated up using a consistent dosing schedule until appropriate response, minimizing side effects (Table 43–1). Stimulant medications have been shown to decrease fidgeting and finger tapping, increase on-task classroom behavior and positive interactions at home and in social environments, and ameliorate conduct and anxiety disorders.[9] Generally, stimulants should not be used in patients who have glaucoma, severe hypertension or cardiovascular disease, hyperthyroidism, severe anxiety, or previous illicit or stimulant drug abuse.

Stimulant drug formulations can be divided into short-, intermediate-, and long-acting preparations (see Table 43–1). Initial response to short-acting stimulant formulations (eg, methylphenidate and dextroamphetamine) is seen within 30 minutes and can last for 4 to 6 hours.[6] Thus short-acting stimulant formulations must frequently be dosed at least twice daily, increasing the chance of missed doses and nonadherence. Patients using any stimulant formulation, but especially short-acting formulations, can experience a rebound effect of ADHD symptoms as the stimulant wears off.[9]

Most intermediate-acting stimulants release the medication in a slow, continuous fashion without any early release (except Dexedrine Spansules). The onset of action for this category of stimulants (typically 60–90 minutes) may be inadequate for some patients. Some practitioners prescribe a short-acting stimulant concurrently with an intermediate-acting stimulant to curtail the delay in onset of action of the intermediate-acting stimulant. However, this practice can increase patient copay costs.

To minimize rebound symptoms associated with short-acting formulations and still achieve early stimulant release, long-acting formulations with rapid onsets have been developed. These formulations release medications early and deliver a delayed release of stimulant in either a pulsed (Adderall XR, Focalin XR, Metadate CD, Quillivant XR, and Ritalin LA) or continuous manner (Concerta). Formulations available as capsules contain coated beads that can be opened and sprinkled on semisolid food. Concerta tablets have an immediate-release overcoat and an oral osmotic controlled release that delivers methylphenidate in an extended manner. Patients should be educated that the empty tablet shell of Concerta can be seen in the stool.

Three long-acting stimulants, Daytrana, Vyvanse, and Jornay PM, have slower onsets of action than the other long-acting stimulants with a rapid release. Daytrana transdermal patches have a delayed onset of 2 hours and are to be applied for only 9 hours per day; their effects persist for 3 hours after being removed. Some patients report skin sensitization and irritation. Vyvanse is a prodrug that is hydrolyzed to its active form, dextroamphetamine, after oral ingestion. Inhalation or injection abuse potential is minimized because of impeded hydrolysis by these routes. Onset of action for Vyvanse has been reported to be 2 hours.[10] Jornay PM beads are formulated with two different coatings, the first is a delayed-release coating which prevents release of medication for 8 to 10 hours after ingestion, the second coating is an extended-release coating which allows for release of medication throughout the day.[11]

Adverse effects of stimulants can be generalized to the whole class (Table 43–2). Most side effects can be managed by changing the dosing routine (ie, giving with food, dividing daily dose, or giving the dose earlier in the day). Serious side effects (eg, hallucinations and abnormal movements) require discontinuation of medication.[9] To avoid potential drug–food interactions and absorption issues, stimulants should be given 30 to 60 minutes before eating.

Patient Encounter, Part 1

An 11-year-old boy who described is reported to having difficulties with focusing and sitting still in class. He often has difficulty sustaining his attention at school. His parents and teacher indicate that he is restless, and often requires reminders to help him stay on task. He is described as "constantly running around" and presenting with difficulties listening and following instructions. His teacher indicates that he often blurts out answers and interrupts other students in the classroom. He recognizes this tendency in himself but says that he can't stop in spite of his best intentions. The patient is diagnosed with ADHD using the Vanderbilt scale.

Wt: 47.2 kg or 104 lb (90th percentile)

Allergies: None known

Ht: 152 cm or 5′0″ (90th percentile)

BP: 95/63 mm Hg

P: 100 beats/min

Which of the patient's symptoms are suggestive of ADHD?

What other information should be collected before recommending therapy for ADHD?

What treatment recommendations could you make for this patient?

Table 43–1

Selected Medications for ADHD[a]

Drug, Generic (Brand Name)	Initial Dose	Titration Schedule Increments	Typical Dosing Range (Maximum Dose)	Cost[e]
Stimulants				
Short Acting				
Methylphenidate[b] (Methylin, Ritalin)	5 mg twice daily	5–10 mg/day in weekly intervals	5–20 mg two to three times daily (60 mg/day)	Brand—$$ Generic—$
Dexmethylphenidate[b] (Focalin)	2.5 mg twice daily	2.5–5 mg/day in weekly intervals	5–10 mg twice daily (20 mg/day)	Brand—$ Generic—$
Dextroamphetamine[b] (Zenzedi)	2.5–5 mg every morning	2.5–5 mg/day in weekly intervals	5–20 mg twice daily (40 mg/day)	Brand—$ Generic—$
Intermediate Acting				
Methylphenidate[b,f] (Methylin ER)	10 mg once daily	10 mg/day in weekly intervals	20–40 mg every morning (60 mg/day)	Generic—$
Dextroamphetamine–amphetamine[b] (Adderall)	2.5–5 mg once to twice daily	2.5–5 mg/day in weekly intervals	10–30 mg every morning or 5–20 mg twice daily (40 mg/day)	Brand—$$$ Generic—$
Dextroamphetamine[b,f] (Dexedrine Spansule)	5 mg every morning	5 mg/day in weekly intervals	5–30 mg daily or 5–15 mg twice daily (40 mg/day)	Generic—$$
Long Acting				
Methylphenidate[b]				
(Concerta[f])	18 mg every morning	9–18 mg/day in weekly intervals	18–54 mg every morning (54 mg/day in children)	Brand—$$$ Generic—$
(Daytrana[f])	10 mg every morning (2 hours before effect needed)	Patch dosage strength in weekly intervals	30–60 mg every morning	Brand—$$$
(Metadate CD)	20 mg every morning	10–20 mg/day in weekly intervals	20–40 mg daily every morning (60 mg/day)	Brand—$$$ Generic—$
(Ritalin LA[f])	20 mg every morning	10 mg/day in weekly intervals	20–40 mg every morning (60 mg/day)	Brand—$$$ Generic—$
(Quillivant XR)[c]	20 mg every morning	10–20 mg/day in weekly intervals	20–40 mg every morning (60 mg/day)	Brand—$$$
(Aptensio XR[f])	10 mg every morning	10 mg/day in weekly intervals	10–60 mg every morning (60 mg/day)	Brand—$$$ Generic—$$
(Cotempla XR-ODT)	17.3 mg every morning	8.6–17.3 mg/day in weekly intervals	17.3–51.8 mg every morning (51.8 mg/day)	Brand—$$$
(Adhansia XR[f])	25 mg every morning	10–15 mg/day in ≥ 5 day intervals	25–85 mg every morning (85 mg/day)	Brand—$$$
(Jornay PM[f])	20 mg every evening between 6:30 and 9:30 PM	20 mg/day in weekly intervals	20–100 mg every evening (100 mg/day)	Brand—$$$
Dextroamphetamine/amphetamine[b] (Adderall XR[f])	5–10 mg every morning (children); 20 mg once daily (adults)	5–10 mg/day in weekly intervals	10–30 mg every morning or 5–15 mg twice daily (30 mg/day, children) (60 mg/day, adult)	Brand—$$$ Generic—$
Dexmethylphenidate[b] (Focalin XR[f])	5 mg every morning (children); 10 mg every morning (adults)	5 mg/day in weekly intervals	10–20 mg daily in the morning (20 mg/day)	Brand—$$$ Generic—$$
Lisdexamfetamine[b] (Vyvanse[f])	30 mg every morning (children and adults)	10–20 mg/day in weekly intervals	30–70 mg every morning (70 mg/day)	Brand—$$$
Amphetamine[b]				
(Dyanavel XR)	2.5–5 mg every morning	2.5–10 mg/day every 4–7 days	2.5–20 mg every morning (20 mg/day)	Brand—$$$
(Adzenys XR-ODT)	6.3 mg every morning	3.1–6.3 mg/day in weekly intervals	6.3–18.8 mg every morning depending on age (ages 6–12 years—18.8 mg/day; ages 13–18 years—12.5 mg/day)	Brand—$$$
(Evekeo)	2.5 mg every morning (3–5 years) or 5 mg every morning or twice daily (6 years or older)	2.5 mg/day (3–5 years) or 5 mg/day (6 years or older) in weekly intervals	2.5–40 mg daily in a single morning or twice daily divided dose (40 mg/day)	Brand—$$$ Generic—$$
(Mydayis[f])	12.5 mg every morning (13-17 years of age)	12.5 mg/day at weekly intervals	12.5–25 mg every morning (25 mg/day)	Brand—$$$
Nonstimulants				
Atomoxetine[b,d,f] (Strattera)	≤ 70 kg: 0.5 mg/kg/day divided once to twice daily > 70 kg: 40 mg once daily	To target dose of 1.2 mg/kg/day after 3 days 40 mg/day after 3 days (may ↑ to total of 100 mg/day after 2–3 weeks)	40–60 mg/day every morning (1.4 mg/kg or 100 mg/day, whichever is less) 40–80 mg/day divided once to twice daily (100 mg/day)	Brand—$$$ Generic—$

(Continued)

Table 43–1

Selected Medications for ADHD[a] (*Continued*)

Drug, Generic (Brand Name)	Initial Dose	Titration Schedule Increments	Typical Dosing Range (Maximum Dose)	Cost[e]
Clonidine (Catapres)	0.05 mg once daily	0.05 mg/day every 3–7 days	0.1 mg 1 to 4 times daily (0.4 mg/day)	Brand—$$
(Kapvay)[b,f]	0.1 mg at bedtime	0.1 mg/day in weekly intervals	0.1–0.2 mg twice daily (0.4 mg/day)	Generic—$
Guanfacine (Tenex)	0.5 mg at bedtime	0.5 mg every 3–14 days	1.5–3 mg/day divided into 2–3 doses (4 mg/day)	Generic—$
(Intuniv)[b,f]	1 mg once daily	No more than 1 mg/week	1–4 mg daily (4 mg/day)	

[a] Pediatric dosing except when adult dosing specified.

[b] Approved by the US FDA for the treatment of ADHD.

[c] Oral extended-release suspension.

[d] Dose adjustment required in patients with hepatic insufficiency.

[e] Cost based on brand regimen specified without a dispensing fee or discount for a 30-day supply.

[f] Do not crush, chew, or cut.

CD, extended release (biphasic immediate release with extended release); ER, extended release; LA, long acting; ODT, orally disintegrating tablet; SR, sustained release; XL, extended release; XR, extended release.

(From GoodRx.com or various online State Maximum Allowable Costs [SMAC]); $, less than $60; $$, $60–$140; $$$, greater than $140.

Table 43–2

Patient Monitoring and Management of Selected Adverse Effects of ADHD Medications

Drug	Adverse Effects	Management	Monitoring
Stimulants			
Methylphenidate Dexmethylphenidate Dextroamphetamine Amphetamine Lisdexamfetamine	GI upset, nausea, decreased appetite, potential growth delay	Administer after breakfast and lunch Encourage high-calorie meals/beverages and snacks after dinner Divide dose Change to shorter-acting stimulant Discontinue on weekends and during holidays	Height, weight, blood pressure, pulse ECG if warranted Eating and sleeping patterns Evaluate every 2–4 weeks until stable dose is achieved; then evaluate every 3 months
	Insomnia	Move dose(s) earlier in the day and discontinue later day dose if problem persists Change to a shorter-acting stimulant Consider adjunct hypnotic (eg, melatonin) or alternate medication (eg, guanfacine)	
	Headache	Decrease dose Change to longer-acting stimulant or nonstimulant (eg, atomoxetine) Consider analgesic (eg, acetaminophen)	
	Irritability, dysphoria, agitation	Early onset (peak related): Decrease dose or change to longer-acting stimulant Late onset (withdrawal related): Change to longer-acting stimulant Evaluate for comorbidity and treat if present	
	Tics	Decrease dose if stimulant caused Change to a different stimulant or a nonstimulant (eg, guanfacine, atomoxetine) Add an antipsychotic (eg, risperidone)	
Nonstimulants			
Atomoxetine	Increased blood pressure and pulse, nausea, vomiting, fatigue, and insomnia	Decrease dose or change to another medication (eg, guanfacine)	Same as above but with baseline and routine liver function tests for hepatotoxicity
	Hepatotoxicity, suicidal thoughts	Discontinue, reevaluate patient and consider a change to another medication	
Clonidine and guanfacine	Sedation	Decrease dose Administer closer to bedtime	Same as above

ECG, electrocardiogram; GI, gastrointestinal.

Growth suppression or delay is a major concern for parents of children taking stimulants. Height appears to be decreased by 1 to 2 cm; these effects are diminished after 3 years of treatment and do not appear to rebound.[12] Another concern is risk of substance abuse with stimulant use. A diagnosis of untreated ADHD increases the risk of substance abuse in adolescents and adults.[13] Two prospective observational studies concluded that ADHD treatment in children does not increase or decrease the likelihood of developing substance abuse in adulthood.[14,15]

The choice of ADHD medication should be made based on the patient's symptoms, prescriber's familiarity with the medications, ease of administration, and cost. Stimulants should be used as first-line agents in most ADHD patients, although studies in groups of patients have shown no clear advantage of one stimulant over another.[4]

▶ *Nonstimulants*

Atomoxetine Atomoxetine is approved for the treatment of ADHD in both children and adults. In clinical studies it demonstrated superior efficacy over placebo and either equivalent efficacy compared with a suboptimal immediate-release methylphenidate dose or inferior to Concerta.[16] **KEY CONCEPT** Atomoxetine may be used first line if there are concerns with using stimulant medications; however, atomoxetine is less effective than stimulants in treatment of ADHD.

Atomoxetine selectively inhibits the reuptake of adrenergic neurotransmitters, principally norepinephrine.[16] Atomoxetine is metabolized through the cytochrome P450 (CYP) 2D6 pathway. Concurrent use of CYP2D6 inhibitors may necessitate slower dose titration of atomoxetine. Approximately 5% to 10% of the population are CYP2D6 poor metabolizers, and atomoxetine's half-life is increased significantly in this population.[17] The recommended dosing for atomoxetine depends on patient weight and is given once or twice daily[17] (see Table 43–1). In poor metabolizers, atomoxetine should be dosed once daily at 25% to 50% of the dose typically used in normal metabolizers.[17] Onset of therapeutic effect of atomoxetine may take up to 2 to 8 weeks, significantly longer than with stimulants.[18] Common side effects (headache, decreased appetite) of atomoxetine are similar to those of stimulants.[16] It can slow growth rate and cause weight loss; thus, height and weight should be monitored routinely in children[16] (see Table 43–2). Atomoxetine's labeling includes warnings about severe hepatotoxicity and increased association with suicidal thinking.

Atomoxetine can be given once daily in many patients. It appears to lack any abuse potential and is not a controlled substance.[19] One big disadvantage of atomoxetine is cost compared with other ADHD medications, despite a generic being approved by the FDA in May 2017 (see Table 43–1).

Because of the high cost, lack of long-term efficacy data, and few comparison studies with stimulants, atomoxetine should be advocated only if the patient has failed or is intolerant to stimulant therapy or has history or risk factors for substance use.

Clonidine and Guanfacine Clonidine and guanfacine are central α_2-adrenergic agonists that inhibit the release of norepinephrine presynaptically. Both of these agents are less effective than stimulants in treating ADHD but typically are used as adjuncts to stimulants to control disruptive or aggressive behavior and alleviate insomnia.[20] The effects of immediate-release guanfacine typically last 3 to 4 hours longer than immediate-release clonidine, and the drug requires less frequent dosing. Extended-release formulations of guanfacine (Intuniv) and clonidine (Kapvay) were developed to minimize dosing frequency and improve treatment of anger, hostility, and irritability in patients with ADHD. Similar to other nonstimulants, these two dosage forms can also be used in patients who are intolerant to stimulants. However, use of these dosage forms is limited because of a lack of comparative trials to stimulants. Common side effects with clonidine and guanfacine are low blood pressure and sedation. Sedation generally subsides after 2 to 3 weeks of therapy.[21,22] Rarely, severe side effects such as bradycardia, rebound hypertension, irregular heartbeats, and sudden death have been reported.

Patient Encounter, Part 2

He has been on Focalin (dexmethylphenidate) 5 mg BID for the past 3 months with only a moderate change in symptoms. He has also lost 10 lb (4.5 kg) (currently 76th percentile for weight) in the last 3 months and reports trouble sleeping.

What changes to the patient's ADHD medication therapy would you recommend?

What important education points would you discuss with the patient and his caregivers about his ADHD medications?

Pharmacoeconomic and Treatment Adherence Considerations

Annual healthcare costs for people with ADHD was almost 60% higher than people without ADHD.[20] The financial burden of ADHD is attributed to the direct cost of pharmacotherapy, office visits, diagnostic measurements, therapy monitoring, and indirect costs (eg, lost work time and productivity). When selecting a treatment, the cost burden to the patient's family should be considered. Short-acting stimulants may be more cost effective compared with longer-acting stimulant formulations (see Table 43–1), but in certain circumstances, longer-acting stimulant formulations may provide a greater benefit owing to increased adherence to the medication and prolonged control of symptoms of ADHD. All intermediate-acting and various long-acting (Concerta, Ritalin LA, Metadate CD, Focalin XR, and Adderall XR) stimulant formulations are now available as generic products, making them potentially more affordable. In addition, some nonstimulant ADHD medications (eg, immediate-release α_2-adrenergic agonists) appear to be less costly than many stimulant formulations; however, these agents have not been consistently proven to have superior efficacy over stimulants. Decisions on selection of

Patient Encounter, Part 3

Patient returns 3 months later having been on Concerta titrated to 36 mg daily. He is reporting being able to focus better, improvement in grades, no reported insomnia, and evening appetite has normalized; however, he still struggles with no appetite in the morning after taking his medication.

What monitoring parameters should be followed in order to assess efficacy and safety of treatment?

What education could you provide to the patient and caregivers regarding his lack of appetite in the morning?

Patient Care Process

Collect Information:

- Current and past medication use including prescription and nonprescription products
- Identify allergies
- Medication history, physical assessment (blood pressure, pulse, height, and weight), ECG (baseline and periodically in children with known or suspected cardiac disease) neurologic assessment, home assessment
- Signs and symptoms of hyperactivity, impulsivity, and/or inattention from patient, parents, teachers, and/or other people spending significant amount of time with the patient utilizing established ADHD rating scales (Vanderbilt, Conners)
- Patient and family lifestyle habits (poor academic performance, poor sleep hygiene, inadequate nutrition), belief system, functional goals, socioeconomic factors (insurance vs ability to pay for prescriptions)

Assess the Information:

- Determine if medications or lifestyle habits could be contributing to signs and symptoms of ADHD
- Evaluate medications for indication, side effects, adherence and effectiveness, interactions, and drug-related problems
- Assess overall health status, signs, and symptoms of ADHD
- Identify patient/family cost effectiveness/burden of therapy and ability to remain adherent to therapy

Develop a Care Plan:

- Address any drug-related problems, interactions, adherence issues
- Patients < 6 years old, consider behavioral modification before pharmacotherapy
- Patients ≥ 6 years old, consider low-dose stimulant (see Table 43–1)
- If initial stimulant therapy is not effective after 2 to 4 weeks, consider switching to a different stimulant medication (see Table 43–1)
- Try at least two stimulant medications before considering nonstimulant pharmacotherapy
- Reevaluate the diagnosis if all pharmacotherapy treatment attempts fail

Implement the Care Plan:

- Initiate medication at appropriate dose (see Table 43–1) and titrate to effect as tolerated (see Table 43–2), while considering cost (see Table 43–1)
- Emphasize medication adherence
- Educate patient/family on effectiveness and safety (see Table 43–2)

Follow-up: Monitor and Evaluate:

- Evaluate effectiveness and safety of stimulant therapy monthly for the first 3 months
- Evaluate every 3 months once on maintenance dose
- Monitor height and weight in children and blood pressure in adults quarterly
- Evaluate for improvement in function, use rating scales for consistent evaluation

specific ADHD medications should not be based solely on cost but also on efficacy and safety along with adherence to the prescribed regimen.

OUTCOME EVALUATION

Carefully document core ADHD symptoms at baseline to provide a reference point from which to evaluate effectiveness of treatment. Improvement in individualized patient outcomes is desired, such as (a) family and social relationships, (b) disruptive behavior, (c) completing required tasks, (d) self-motivation, (e) appearance, and (f) self-esteem. Elicit evaluations of the patient's behavior from family, school, and social environments in order to assess these outcomes. Using standardized rating scales (eg, Conners Rating Scales—Revised, Child Behavior Checklist-Attention Problem scale, and Conners Abbreviated Symptoms Questionnaire, Vanderbilt) leads to favorable diagnostic precision.[23] Assess eating and sleeping patterns, height, weight, pulse, and blood pressure at baseline and after initiation of pharmacotherapy every 2 to 4 weeks to determine efficacy of treatment and potential effects on growth and cardiac system. Use physical examinations or liver function tests as appropriate to monitor for adverse effects. In children with known or suspected cardiac disease obtain baseline and follow-up electrocardiograms (ECGs) to monitor for safety of stimulant therapy.[24] Recent evidence suggests that overall cardiac risk with ADHD pharmacotherapy is low, but presence of risk factors is associated with increased risk of serious cardiac events.[25] Typically, therapeutic benefits will be seen within days of initiating stimulants and within 1 or 2 months of starting atomoxetine. When a maintenance dose has been achieved, schedule follow-up visits every 3 months. At these visits, assess height and weight, and screen for possible adverse drug effects. If a patient has failed to respond to multiple agents, reevaluate for other possible causes of behavior dysfunction. Educate patients and their families that treatment generally is long term. Typically, appropriately treated patients learn to better control their ADHD symptoms as adults.

Abbreviations Introduced in This Chapter

ADHD	Attention-deficit hyperactivity disorder
CYP	Cytochrome P450
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition,
ECG	Electrocardiogram

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44

Diabetes Mellitus

Julie M. Sease and Elizabeth W. Blake

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Discuss the incidence of diabetes mellitus (DM).
2. Distinguish clinical differences in type 1, Latent Autoimmune Diabetes of Adulthood, type 2, and gestational diabetes.
3. List screening and diagnostic criteria for DM.
4. Discuss therapeutic goals for blood glucose (BG) and blood pressure (BP) for a patient with diabetes.
5. Recommend nonpharmacologic therapies, including meal planning and physical activity, for patients with diabetes.
6. Compare oral agents used in treating diabetes by their mechanisms of action, time of action, side effects, contraindications, and effectiveness.
7. Select appropriate insulin therapy based on onset, peak, and duration of action.
8. Discuss the signs, symptoms, and treatment of hypoglycemia.
9. Define *diabetic ketoacidosis* and discuss treatment goals.
10. Develop a comprehensive therapeutic monitoring plan for a patient with diabetes based on patient-specific factors.

INTRODUCTION

Diabetes mellitus (DM) describes a group of chronic metabolic disorders. **KEY CONCEPT** DM is characterized by hyperglycemia that may result in long-term **microvascular** and neuropathic complications that contribute to DM being the leading cause of (a) new cases of blindness among adults, (b) end-stage renal disease, and (c) nontraumatic lower limb amputations. Macrovascular complications (coronary artery disease, peripheral vascular disease, and stroke) are also associated with DM.

EPIDEMIOLOGY

DM affects an estimated 34.2 million persons in the United States, or 10.5% of the population.[1] Although an estimated 23.1 million persons have been diagnosed, another 7.2 million have DM but are unaware they have the disease.[1] DM is characterized by a complete lack of insulin, a relative lack of insulin, or **insulin resistance**, as well as disorders of other hormones. These defects result in an inability to use glucose for energy. The increasing prevalence of DM is partly caused by three influences: lifestyle, ethnicity, and age.

Lifestyle

A sedentary lifestyle coupled with greater consumption of high-fat, high-carbohydrate foods, and larger portion sizes have resulted in increasing rates of obesity. Current estimates indicate that 42.4% of US adults are obese when obesity is defined as body mass index (BMI) of greater than 30 kg/m^2.[2] Over 15% of adults throughout the country report being physically inactive, defined as self-report of no leisure-time physical activity within the past month.[3]

Ethnicity

Certain ethnic groups are at disproportionately high risk for developing type 2 DM (T2DM). Prevalence of DM is 14.7% among American Indian/Alaska Native individuals, 12.5% among persons of Hispanic ethnicity, and 11.7% among non-Hispanic Black individuals, whereas among non-Hispanic White individuals, prevalence is only 7.5%.[1] Socioeconomic status, when examined as a function of education level, also plays a role in development of DM. Rate of DM is 13.3% for persons with less than a high school education versus 7.5% for those with education beyond high school.[1]

Age

The third factor contributing to increased prevalence of T2DM is age. In 2018, it was estimated that 11.5 million Americans aged 65 or older had been diagnosed with DM compared with 3.6 million between the ages of 18 and 44.[1] As the population ages, incidence of T2DM is expected to increase. **KEY CONCEPT** T2DM accounts for approximately 90% to 95% of all diagnosed cases of DM, is progressive in its development, and often preceded by an increased risk for diabetes, known as **prediabetes**. A combination of insulin deficiency, insulin resistance, and other hormonal irregularities, primarily involving **glucagon**, are key problems with T2DM. The majority of people with T2DM are overweight, and an increasing number of cases in children have been observed. Type 1 DM (T1DM) is usually diagnosed before age 30 years but can develop at any age. As a result, patients over 30 years of age who newly develop T1DM may be misdiagnosed as having T2DM.

ETIOLOGY

T1DM is an autoimmune disease in which the insulin-producing β-cells of the pancreas are destroyed, leaving the individual insulin deficient.[4] T1DM develops on a variable, but predictable continuum through three stages. In Stage 1, patients have two or more islet autoantibodies but normal glucose values and no classic symptoms of DM. In Stage 2, β-cell autoimmunity is present, dysglycemia (impaired fasting glucose [IFG] or impaired glucose tolerance [IGT]) has begun, but the patient remains asymptomatic. In Stage 3, classic symptoms including polyuria, polydipsia, weight loss, polyphagia, fatigue, and blurred vision are present. It was once a commonly held belief that, at the time of diagnosis of T1DM, most patients have over 80% loss of β-cell function.[5] This belief has become contested by more recent data suggesting residual β-cell mass up to 40% may be present in those diagnosed in adolescence and may also be variable based on degree and cellular profile of the individual's insulitis. The concept of remaining β-cell function at diagnosis is supported by the observation that, once provided insulin, patients with T1DM may have a temporary and spontaneous partial or even full remission. Duration of this so-called honeymoon period is variable, lasting anywhere from weeks to, in rare cases, years.

Maturity onset diabetes in the young (MODY) is seen in approximately 1.2% to 4% of pediatric diabetes patients.[4] Often misdiagnosed as T1DM and treated with insulin, MODY should be considered in patients presenting without the presence of diabetes-associated islet cell autoantibodies to insulin. Autoantibodies include islet cell cytoplasmic, glutamic acid decarboxylase, and tyrosine phosphatase autoantibodies. C-peptide, a surrogate marker for insulin secretion, may be used to establish or verify diagnosis of T1DM. While variable in MODY, C-peptide will be decreased or absent in T1DM. Diagnosing MODY correctly has implications for the patient as well as their family. Testing for various genetic mutations associated with the disorder is available. The calculator found at https://www.diabetesgenes.org/exeter-diabetes-app/ModyCalculator may be useful in determining which individuals should undergo genetic testing.

KEY CONCEPT Latent autoimmune diabetes in adults (LADA) is a form of autoimmune diabetes hallmarked by a milder autoimmune process and slower progression of β-cell failure as compared with T1DM.[6] Criteria for diagnosis of LADA include adult age at onset, presence of islet autoantibodies, and insulin dependence. Patients with LADA often are mistakenly thought to have T2DM because the person is an adult at onset and exogenous insulin is usually not required during the first 6 to 12 months following diagnosis. The presence of glutamic acid decarboxylase antibodies is a key indicator of LADA as it is more prevalent in LADA than T1DM.

Prediabetes is a commonly used term to describe those at highest risk for development of T2DM and cardiovascular disease. Prediabetes encompasses the following conditions: IFG, IGT, or hemoglobin A_{1c} (A_{1c}) between 5.7% and 6.4% (0.057 and 0.064; 39 and 46 mmol/mol hemoglobin [Hgb]).[7] IFG is defined as having a fasting blood glucose (FBG) level between 100 and 125 mg/dL (5.6 and 6.9 mmol/L).[7] IGT is defined by a postprandial blood glucose (BG) level between 140 and 199 mg/dL (7.8 and 11.0 mmol/L).[7]

T2DM is usually slow and progressive in its development. Risk factors include:[7]

- First-degree family history of DM (ie, parents or siblings)
- Overweight or obese
- Habitual physical inactivity
- Race or ethnicity (Native American, Latino or Hispanic American, Asian American, African American, and Pacific Islander)
- Previously identified IFG, IGT, or A_{1c} between 5.7% and 6.4% (0.057 and 0.064 or 39 and 46 mmol/mol Hgb)
- Hypertension (greater than or equal to 140/90 mm Hg or on therapy for hypertension)
- High-density lipoprotein (HDL) cholesterol less than 35 mg/dL (0.91 mmol/L) and/or a triglyceride level greater than 250 mg/dL (2.83 mmol/L)
- History of gestational diabetes
- History of cardiovascular disease
- History of polycystic ovarian syndrome
- Other conditions associated with insulin resistance (eg, acanthosis nigricans)

Gestational DM (GDM) is defined as glucose intolerance in women during pregnancy. Clinical detection of and therapy for GDM are important because blood sugar levels within normal range produces significant reductions in adverse maternal, fetal, and neonatal outcomes.

Diabetes insipidus is unrelated to DM despite the similar nomenclature.[8] Four types of diabetes insipidus exist including central, nephrogenic, dipsogenic, and gestational. Central diabetes insipidus results from damage to a patient's hypothalamus or pituitary causing irregular production, storage and/or release of vasopressin leading to excessive elimination of fluid by the kidneys. Nephrogenic diabetes insipidus occurs when the kidneys no longer respond appropriately to the action of vasopressin. Dipsogenic diabetes insipidus results from hypothalamic dysfunction which causes increased thirst and liquid intake in the affected patient. Gestational diabetes insipidus occurs during pregnancy and results either from placental destruction of the mother's vasopressin or from prostaglandin's action on the kidneys causing them to lose sensitivity to the action of vasopressin.

DM from other causes includes genetic defects in β-cell function and genetic defects in insulin action, both related to neonatal diabetes; diseases of the exocrine pancreas such as cystic fibrosis; and drug- or chemical-induced diabetes.[7] Drugs which have been associated with development of diabetes include those thought to cause insulin resistance/decreased insulin sensitivity such as atypical antipsychotics, glucocorticoids, first-generation protease inhibitors, nicotinic acid, and statins; those that cause insulin deficiency such as β-adrenergic antagonists, didanosine, pentamidine, and thiazide diuretics; and those that cause insulin resistance such as β-adrenergic agonists and megestrol.[9]

PATHOPHYSIOLOGY

Normal Carbohydrate Metabolism

Glucose, the body's fuel source, is required for both aerobic and anaerobic cellular respiration.[10] Cells metabolize glucose through glycolysis and the citric acid cycle, producing energy as adenosine triphosphate (ATP). Glucose is stored in the liver and muscles as glycogen. Glycogenolysis converts stored glycogen back to glucose. Glucose may also be stored in adipose tissue, which subsequently undergoes lipolysis to yield free fatty acids.[11] In the fasting state, free fatty acids supply much of the energy needs for the body except the central nervous system, which requires glucose to function normally. Glucose is primarily supplied to the brain by liver glycogen stores during fasting, though conversion of lactate, alanine, and glycerol to glucose also provides energy for the brain when no exogenous glucose supply is available. During exercise, most glucose is supplied through hepatic gluconeogenesis which is stimulated by the catecholamines epinephrine and norepinephrine.

Insulin and glucagon are produced in the pancreas by cells in the pancreatic islets. β-cells produce insulin and amylin, whereas α-cells produce glucagon. The main function of insulin is to decrease BG, and an elevated BG is necessary for insulin release above basal levels. Glucagon and other counterregulatory hormones such as epinephrine and norepinephrine increase BG levels. Although BG levels vary, the opposing actions of insulin and glucagon, along with the counterregulatory hormones, normally maintain fasting values below 100 mg/dL (5.6 mmol/L).[11]

▶ *Normal Insulin Action*

Insulin is necessary for glucose to move into cells where it can be utilized to create energy. Without adequate insulin, glucose remains extracellular and BG remains high. In persons without diabetes, a constant, lower amount of insulin is produced by the pancreas to maintain fasting BG within normal levels.[12] This is referred to as basal insulin production. After food is consumed, BG levels rise, and the insulin-secretion response occurs in two phases.[13] An initial burst, known as the *first phase,* lasts for only minutes while the *second phase* occurs over the course of an hour or more. The pulsatile release of insulin appears to be particularly important for suppressing hepatic glucose production and stimulating glucose disposal in adipose tissue.

Amylin is a naturally occurring hormone cosecreted from β-cells with insulin. People with T1DM have either a relative or complete lack of amylin. Amylin has three major mechanisms of action: suppression of postmeal glucagon secretion; regulation of the rate of gastric emptying from the stomach to the small intestine, which increases satiety; and stimulation of glycogenolysis and glycolysis in muscle.

▶ *Impaired Insulin Secretion*

A pancreas with normal β-cell function is able to adjust insulin production to maintain normal BG levels.[11] In T2DM, the β-cell becomes less sensitive to glucose and other stimuli,[13] resulting in slowed, insufficient release of insulin and subsequent hyperglycemia, particularly after meals. Additionally, insufficient insulin production results in insufficient suppression of glucose production by the liver as the result of a meal. The typical course of T2DM is characterized by increasing therapy requirements to maintain adequate glucose control. The progressive nature of T2DM is thought to be related to an ongoing loss of both β-cell mass and function.

Table 44–1

Five Components of Metabolic Syndrome[14]

Risk Factor	Defining Level
1. Abdominal obesity	Based on ethnic group[a]
Plus any two of the following:	
2. Triglycerides	≥ 150 mg/dL (1.70 mmol/L) or treated
3. HDL cholesterol	
• Men	< 40 mg/dL (1.03 mmol/L) or treated
• Women	< 50 mg/dL (1.29 mmol/L) or treated
4. Blood pressure	≥ 130 or ≥ 85 mm Hg or treated
5. Fasting glucose	≥ 100 mg/dL (5.6 mmol/L) or diagnosed type 2 diabetes

[a]102 cm (40 in) for males and 88 cm (35 in) for females likely to be used clinically.

HDL, high-density lipoprotein.

▶ *Insulin Resistance*

The initial hyperglycemia which occurs in T2DM causes the body to react with an exaggerated second-phase hyperinsulinemia response. This initial hyperinsulinemia downregulates insulin receptors on the liver, muscles, and adipose tissue,[11,13] resulting in insulin resistance which is the inability of target tissues to respond as expected to circulating insulin. Insulin resistance in the liver is particularly problematic as it results in the liver continuing glucose production even during nonfasting periods.[11] Insulin resistance may exist for years prior to diabetes diagnosis. Attempts by the pancreas to increase insulin production to overcome insulin resistance will eventually result in β-cell exhaustion and decreased insulin production. The combination of insulin resistance and reduced β-cell mass and function results in T2DM.

▶ *Metabolic Syndrome*

Insulin resistance has been associated with a number of other cardiovascular risks. The clustering of these risk factors has been termed the metabolic syndrome. Criteria defining the metabolic syndrome as established by the International Diabetes Federation are summarized in Table 44–1.[14] Patients having these additional risk factors are at much higher cardiovascular risk than would be expected from individual components of the syndrome.

Clinical Presentation and Diagnosis

Characteristic	T1DM	T2DM	LADA
Usual age of onset	Childhood or adolescence	Adult	Over 30
Speed of onset	Abrupt	Gradual	Gradual
Family history	Negative	Positive	Positive
Body type	Thin	Obese	Thin
Metabolic syndrome	No	Often	No
Autoantibodies	Present	Rare	Present
Symptoms	Polyuria, polydipsia, polyphagia, rapid weight loss	Asymptomatic	Polyuria, polydipsia, polyphagia, rapid weight loss
Ketones at diagnosis	Present	Uncommon	Dependent upon β-cell function at time of diagnosis
Acute complications	Diabetic ketoacidosis (DKA)	Rare	DKA possible
Microvascular complications at diagnosis	Rare	Common	Dependent on length of disease at time of diagnosis
Macrovascular complications at or before diagnosis	Rare	Common	Dependent on length of disease at time of diagnosis

▶ *Incretin Effect*

When nutrients enter the stomach and intestines, incretin hormones are released, which stimulate insulin secretion to a greater degree than what is secreted when glucose is administered intravenously.[15,16] This so-called incretin effect is mediated by two hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). GLP-1 is secreted by the L cells of the ileum and colon primarily, and GIP is secreted by the K cells. GLP-1 secretion is stimulated when nutrients enter the gastrointestinal (GI) tract.[16] Within minutes of food ingestion, GLP-1 levels rise rapidly. A glucose-dependent release of insulin occurs, and the dipeptidyl peptidase-4 (DPP-4) enzyme cleaves GLP-1 rapidly to an inactive metabolite. Much of the research on glucose-lowering products involves prolonging the action of GLP-1. Other glucose-lowering effects of GLP-1 include suppression of glucagon, slowing gastric emptying, and increasing satiety.

▶ *Selective Sodium-Dependent Glucose Cotransporter-2 (SGLT2)*

Rather than allowing glucose to be dumped into the urine to assist with correction of hyperglycemia in the blood, the kidney functions to hold onto glucose. Glucose filtered by the kidneys is completely reabsorbed when blood glucose values are normal, though once blood glucose levels exceed 180 mg/dL (10.0 mmol/L), glucose does begin being spilled into excreted urine.[17] The SGLT2 transporter reabsorbs the majority (80%–90%) of the filtered glucose in the early section of the proximal tubule and the remaining glucose in the more distal portions of the proximal tubule.[17] The SGLT2 transporter has become an important target for newer antidiabetic drug therapy since inhibition of this transporter results in excretion of glucose by the kidney, thereby lowering glucose concentrations in the plasma.

CLINICAL PRESENTATION AND DIAGNOSIS

Screening

Currently, the American Diabetes Association (ADA) recommends routine screening for T2DM every 3 years in all adults starting at 45 years of age.[7] Testing for T2DM should be considered, regardless of age, in adults who have a BMI greater than or equal to 25 kg/m^2 (or BMI greater than or equal to 23 kg/m^2 for Asian Americans) and one or more additional risk factors.[7] The ADA does not currently recommend widespread screening for T1DM, although measurement of islet autoantibodies may be appropriate for high-risk individuals, including those who have relatives with T1DM. See Table 44–2[7] for complete screening guidelines.

Table 44–2

American Diabetes Association (ADA) Screening Recommendations for Diabetes[7]

Asymptomatic Type 1

The ADA does not recommend screening for T1DM because of low incidence in the general population and due to acute presentation of symptoms

Asymptomatic Type 2

1. The ADA recommends screening for T2DM every 3 years in all adults beginning at 45 years of age
2. Testing should be considered for persons younger than 45 years of age or more frequently in individuals who are overweight (BMI ≥ 25 kg/m^2 for the general population and ≥ 23 kg/m^2 for Asian Americans) and have additional risk factors:
   - Habitually inactive
   - First-degree relative with diabetes
   - Member of a high-risk ethnic population (eg, African American, Latino or Hispanic American, Native American, Asian American, Pacific Islander)
   - Previous diagnosis of GDM
   - Hypertensive (≥ 140/90 mm Hg or on therapy)
   - HDL cholesterol level < 35 mg/dL (0.91 mmol/L) and/or triglyceride level > 250 mg/dL (2.83 mmol/L)
   - Polycystic ovary syndrome
   - Previous IGT or IFG or A_{1c} ≥ 5.7% (0.057 or 39 mmol/mol Hgb)
   - Other clinical conditions associated with insulin resistance (eg, acanthosis nigricans)
   - History of cardiovascular disease

Type 2 in Children and Adolescents

Criteria:
- Overweight (BMI ≥ 85th percentile for age and sex) or obesity (BMI ≥ 95th percentile for age and sex)

And one or more of the following risk factors:
- Family history of T2DM in first- or second-degree relatives
- Race or ethnicity (Native American, African American, Latino or Hispanic American, Asian American, Pacific Islander)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary disease, small-for-gestational-age birth weight)
- Maternal history of diabetes or GDM during child's gestation

Age of initiation:
Age 10 years or at onset of puberty, if puberty occurs at a younger age
Frequency of testing:
Every 3 years
Test method: A_{1c}, FPG, or OGTT (FPG or OGTT possibly more suitable than A_{1c})

GDM

1. Screen for undiagnosed T2DM at first prenatal visit in those with risk factors using standard criteria
2. All women not already known to have diabetes should be screened with an OGTT between weeks 24 and 28 of gestation

A_{1c}, hemoglobin A_{1c}; BMI, body mass index; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; Hgb, hemoglobin; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Gestational Diabetes

All pregnant women who have risk factors for T2DM should be screened for undiagnosed T2DM at their first prenatal visit using standard diagnostic criteria. Any woman found to have diabetes at that early point in pregnancy is considered to have T2DM, not GDM. All other pregnant women not currently known to have DM should be screened for GDM. Two possible strategies exist for GDM screening. They are a "one-step" fasting 2-hour 75-g oral glucose tolerance test (OGTT) and a "two-step" process that include a 1-hour 50-g nonfasting screen followed by a 3-hour fasting 100-g OGTT for those with a 1-hour screening glucose of greater than or equal to 140 mg/dL (7.8 mmol/L). See Table 44–3.[7] The "one-step" test with diagnostic criteria from the International Association of Diabetes and Pregnancy Study Groups is preferred by the ADA given these criteria were based on pregnancy outcomes rather than prediction of subsequent maternal diabetes.[7] Any woman diagnosed with GDM should be retested at four to 12 weeks postpartum using the OGTT with nonpregnant diagnostic criteria.

Table 44–3

One-Step and Two-Step Strategies for Diagnosis of Gestational Diabetes Mellitus[7]

One-Step Strategy		
	Plasma Glucose	
Time	**mg/dL**	**mmol/L**
Fasting	92 or more[a]	5.1 or more[a]
75-g glucose load		
1 hour	180 or more[a]	10.0 or more[a]
2 hours	153 or more[a]	8.5 or more[a]
Two-Step Strategy		
	Plasma Glucose	
Time	**mg/dL**	**mmol/L**
Step 1: Nonfasting		
50-g glucose load		
1 hour	130 or more[b]	7.2 or more[b]
	135 or more[b]	7.5 or more[b]
	140 or more[b]	7.8 or more[b]
Step 2: Fasting		
	95 or more[c]	5.3 or more[c]
100-g glucose load		
1 hour	180 or more[c]	10 or more[c]
2 hours	155 or more[c]	8.6 or more[c]
3 hours	140 or more[c]	7.8 or more[c]

[a] A positive diagnosis of diabetes is made when any of the listed glucose values are exceeded. The test should be done in the morning after an 8-hour fast.

[b] Any threshold could be utilized. Exceeding threshold selected requires follow-up fasting oral glucose tolerance test.

[c] A positive diagnosis of diabetes is made when at least two of the four listed glucose values are exceeded.

Note: These values are based on American Diabetes Association guidelines.

Diagnostic Criteria

Diagnosis of DM includes glycemic outcomes exceeding threshold values with one of three testing options (Table 44–4).[7] For a diagnosis, two abnormal test results are required from either the same sample or two separate samples unless unequivocal symptoms of hyperglycemia exist, such as polydipsia, polyuria, and polyphagia. Either A_{1c}, fasting plasma glucose (FPG), or OGTT are appropriate tests for detecting and confirming DM. Use of the same type of test for initial screening and confirmation is recommended, but diagnostic results from two different testing options can also be used.

The categorization thresholds of glucose status for FPG determination and the OGTT are listed in Table 44–5.[7] IFG and IGT may coexist or may be identified independently. FPG level represents hepatic glucose production during the fasting state, whereas postprandial glucose (PPG) levels in the OGTT may reflect glucose uptake in peripheral tissues, insulin sensitivity, or decreased first-phase insulin response. The OGTT identifies people with either IFG or IGT and, therefore, potentially more people at increased risk for DM and cardiovascular disease. The OGTT is a more cumbersome test to perform than either A_{1c} or

Table 44–4

American Diabetes Association Criteria for Diagnosis of Diabetes[7]

Symptoms of diabetes plus a casual plasma glucose concentration ≥ 200 mg/dL (11.1 mmol/L). *Casual* is defined as any time of day without regard to time since the last meal. Classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

Or

FPG ≥ 126 mg/dL (7.0 mmol/L). *Fasting* is defined as no caloric intake for at least 8 hours.

Or

Two-hour postload glucose ≥ 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water.

Or

A_{1c} ≥ 6.5% (0.065; 48 mmol/mol Hgb). The test should be performed in a laboratory using a method that is NGSP certified to the DCCT assay.

A_{1c}, hemoglobin A_{1c}; DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; Hgb, hemoglobin; NGSP, National Glycohemoglobin Standardization Program; OGTT, oral glucose tolerance test; WHO, World Health Organization.

In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. The OGTT is not recommended for routine clinical use.

Patient Encounter Part 1

A 42-year-old African American woman presents to her provider for a follow-up appointment for hypertension. Upon questioning, she states that she has noticed increased fatigue lately. She has occasional headaches which she treats with moderate success with over-the-counter ibuprofen.

PMH: Hypertension for 3 years

FH: Mother has type 2 diabetes, dyslipidemia, and hypertension and is living at age 65; father has hypertension, dyslipidemia, and a previous myocardial infarction resulting in the placement of two stents at age 51. He is living at age 67. She has three siblings, all of whom have hypertension; one older brother has type 2 diabetes, as well. She has two children without chronic health conditions.

SH: Prior history of smoking one-half pack per day for 10 years, but she quit 10 years ago; denies alcohol or illicit drug use; denies physical activity.

Allergies: Amoxicillin

Meds: Hydrochlorothiazide 25 mg daily; ibuprofen 400 mg PRN headache

VS: BP 146/84 mm Hg, P 78 beats/min, RR 16 breaths/min, T 36.5°C (97.7°F), Ht 5′3″ (160 cm), Wt 185 lb (84 kg)

ROS: (+) Fatigue, (–) N/V/D, headache, SOB, chest pain

What risk factors does this patient have for diabetes?

Based on patient presentation, which type of diabetes is more likely?

What additional information is needed to diagnose this patient with diabetes?

Table 44–5

American Diabetes Association Categorization of Glucose Status[7]

	mg/dL	mmol/L
FPG		
Normal	< 100	< 5.6
IFG (prediabetes)	100–125	5.6–6.9
Diabetes	≥ 126	≥ 7.0
2-hour postload plasma glucose (OGTT)		
Normal	< 140	< 7.8
IGT (prediabetes)	140–199	7.8–11.0
Diabetes	≥ 200	≥ 11.1

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

FPG; however, the efficacy of interventions for primary prevention of T2DM has been demonstrated among patients with IGT, not among those with IFG or specific A_{1c} levels.

TREATMENT

Goals of Therapy

KEY CONCEPT DM treatment goals include reducing, controlling, and managing long-term microvascular, macrovascular, and neuropathic complications; preserving β-cell function; preventing acute complications from high BG levels; minimizing hypoglycemic episodes; and maintaining the patient's overall quality of life. To achieve the majority of these goals, near-normal BG levels are fundamental; thus, glycemic control remains a primary objective in diabetes management. Two landmark trials, the Diabetes Control and Complications Trial (DCCT)[18] and the United Kingdom Prospective Diabetes Study (UKPDS),[19] showed that lowering BG levels decreased the risk of developing chronic complications. A near-normal BG level can be achieved with appropriate patient education, lifestyle modification, and medications.

▶ *Setting and Assessing Glycemic Targets*

KEY CONCEPT Patients and clinicians can evaluate how well a patient's DM is managed by monitoring daily BG values and the A_{1c} quarterly to biannually.[20] Self-monitoring of blood glucose (SMBG) enables patients to obtain their current BG level at any time easily and relatively inexpensively. The A_{1c} test provides a weighted-mean BG level from approximately the previous 3 months.[20]

Self-Monitoring of Blood Glucose SMBG is the standard method for routinely checking BG levels. Most often, a small drop of blood obtained from a fingertip using a lancet device is used for testing. Some home BG meters require very little blood and can be used for alternative site testing, where small samples can be obtained from the palm, forearm, or thigh. Each reading provides a point-in-time evaluation of glucose levels that can vary widely depending on numerous factors including food, exercise, stress, illness, and time of day.

By examining multiple individual points of data, glucose patterns can be established. Therapy can be evaluated from these patterns, and adjustments made to improve overall BG levels. The ADA premeal plasma glucose goals are 80 to 130 mg/dL (4.4–7.2 mmol/L) and peak postprandial plasma glucose goals are less than 180 mg/dL (10.0 mmol/L).[20] For patients using multiple daily insulin injections or insulin pump therapy, SMBG is generally required prior to each meal or snack, at bedtime, prior to exercise, prior to critical tasks like driving, and throughout an episode of hypoglycemia from suspicion of hypoglycemia to restoration of normal glucose levels.[21] Optimal frequency of testing in patients using less frequent insulin injections, noninsulin therapies, or medical nutrition therapy (MNT) is less clear.

Continuous glucose sensors are now available that work with or independently of insulin pumps. These monitors provide BG readings, primarily through interstitial fluid (ISF). A small sterile disposable glucose-sensing device called a sensor is inserted into the subcutaneous tissues. This sensor measures change in glucose in ISF and sends the information to a monitor, which stores the results. Some devices allow analysis of data collected over time to aid in clinical decision-making.

Hemoglobin A_{1c} Glucose interacts spontaneously with Hgb in red blood cells to form glycated derivatives. The most prevalent derivative is A_{1c}. Greater amounts of glycation occur when BG levels increase. Because a red blood cell has a life span of approximately 3 months, levels of A_{1c} provide a marker reflecting the average glucose levels over this timeframe.[20] The ADA goal for persons with DM is less than 7% (0.07; 53 mmol/mol Hgb), whereas the American Association of Clinical Endocrinologists (AACE) supports a goal of less than or equal to 6.5% (0.065; 48 mmol/mol Hgb) if achievable without resultant hypoglycemia.[20,22] A less stringent A_{1c} goal of less than 8% (0.08; 64 mmol/mol Hgb) may be utilized in some patients such as those with limited life expectancy, long-standing diabetes that is otherwise difficult to control, and those with multiple comorbid conditions including advanced microvascular and/or macrovascular complications.[20] Testing A_{1c} levels should occur at least twice a year for patients who are meeting treatment goals and four times per year for patients not meeting goals or those with recent changes in therapy.[20] Table 44–6 presents goals for A_{1c} and monitoring parameters for concomitant conditions associated with DM.[20,23,24]

Ketone Monitoring Diabetic ketoacidosis is a particular concern in people with T1DM but can also occur in GDM and even in patients with T2DM.[25] When there is a lack of insulin, peripheral tissues cannot take up and store glucose. This causes the body to think it is starving, and because of excessive lipolysis, ketones, primarily β-hydroxybutyric acid and acetoacetic acid, are produced as byproducts of free fatty acid metabolism in the liver. Glucose and ketones are osmotically active, and when an excessive amount of ketones is formed, the body gets rid of them through urine, leading to dehydration.

Patients prone to ketosis should test for ketones during stressful events such as acute illness.[20] When marked hyperglycemia is accompanied by ketosis, vomiting, or alterations in consciousness, temporary changes to the patient's treatment regimen are needed, and therefore, immediate contact with the diabetes care team is required. Women with preexisting diabetes before pregnancy or with GDM should be prescribed ketone strips and educated on ketoacidosis prevention and detection.[26] Blood ketone testing methods that quantify β-hydroxybutyric acid, the predominant ketone body, are available and preferred to diagnose and monitor ketoacidosis.[25] Home tests for β-hydroxybutyric acid are available. Specific treatment of DKA may include rehydration, correction of electrolyte imbalances, and insulin administration.[27]

General Approach to Therapy

▶ *Type 1 Diabetes Mellitus*

Treatment of T1DM requires providing exogenous insulin to replace the endogenous loss of insulin from the nonfunctional pancreas. Ideally, insulin therapy mimics normal

Table 44–6

American Diabetes Association Recommended Goals of Therapy in Adults[20,23,24]

Area	Goals
Glycemia	
A_{1c}	< 7% (0.07; 53 mmol/mol Hgb) Evaluate every 3 months until in goal; then every 6 months
Preprandial plasma glucose	80–130 mg/dL (4.4–7.2 mmol/L)
Peak postprandial plasma glucose[a]	< 180 mg/dL (10.0 mmol/L)
Blood Pressure	10-year ASCVD risk ≥ 15%: < 130/80 mmHg 10-year ASCVD risk < 15%: < 140/90 mm Hg Evaluate at every visit
Lipids	No lipid-lowering therapy: Evaluate at diagnosis, then every 5 years thereafter Lipid-lowering therapy: At initiation, 4–12 weeks after initiation or dose change, then annually
Monitoring for Complications	
Eyes	Dilated eye examination every 1–2 years
Feet	Yearly comprehensive foot evaluation Feet should be examined at every visit for those with known sensory loss or history of prior ulcerations or amputation
Urinary microalbumin	Yearly

[a] Peak postprandial glucose measurements should be made 1–2 hours after the beginning of the meal.

A_{1c}, hemoglobin A_{1c}; ASCVD, atherosclerotic cardiovascular disease; Hgb, hemoglobin.

insulin physiology. The basal-bolus approach attempts to reproduce basal insulin response using intermediate- or long-acting insulin, whereas short- or rapid-acting insulin replicates bolus release of insulin physiologically seen around a meal in individuals without diabetes. A number of different regimens have been used through the years to more closely follow natural insulin patterns. As a rule, basal insulin makes up approximately 50% of the total daily dose.[28] The remaining half is provided with bolus doses around three daily meals. Exact doses are individualized to the patient and amount of food consumed. Most people with T1DM use between 0.4 and 1 unit/kg/day.[28]

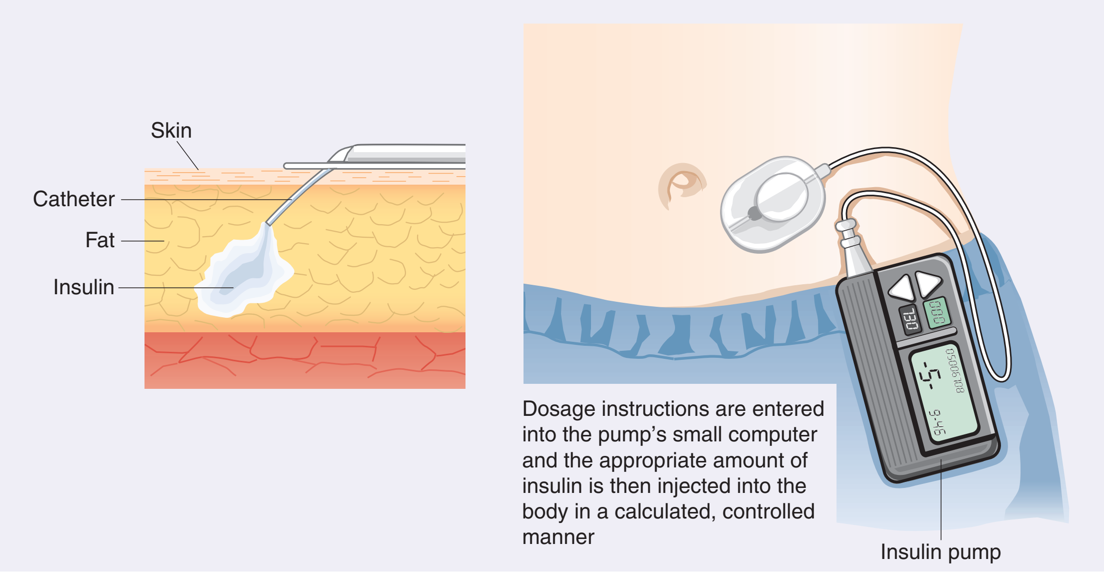
Currently, the most advanced form of insulin delivery is the insulin pump, also referred to as continuous subcutaneous insulin infusion (CSII).[28] See Figure 44–1. Insulin pumps have been linked to improvement in quality of life. Using rapid-acting insulin most often, these pumps are programmed to provide a slow release of small amounts of insulin as the basal portion of therapy, and larger boluses of insulin are administered by the patient to account for consumption of food or correction of hyperglycemia. Insulin pump settings may be adjusted to address exercise, illness, and other factors. Pramlintide, a synthetic analog of the naturally occurring hormone amylin, is another injectable BG–lowering medication that can be used in people with T1DM or in people with T2DM using insulin for treatment.[28] In addition to medication management with insulin, patients with T1DM must also be educated to live a healthy lifestyle including eating a healthy diet and exercising.

▶ *Type 2 Diabetes Mellitus*

Treatment of patients with T2DM has changed dramatically over the past decade with the addition of a number of new drugs and recommendations to maintain tighter glycemic levels.[20,22,28] Technology available to individuals with T1DM can also be used for those with T2DM.[21] However, lifestyle modifications including education, nutrition, and exercise are paramount to managing the disease successfully.[29]

▶ *Gestational Diabetes*

An individualized meal plan consisting of at least 175 g of carbohydrate, 71 g of protein, and 28 g of fiber per day is recommended in all pregnant women.[26] Preventing ketosis, promoting adequate



Dosage instructions are entered into the pump's small computer and the appropriate amount of insulin is then injected into the body in a calculated, controlled manner

FIGURE 44–1. Insulin pump and placement.

growth of the fetus, maintaining satisfactory BG levels, and preventing nausea and other undesired GI side effects are desired goals in these patients. Glucose goals for SMBG for pregnant women as per the ADA include fasting of 95 mg/dL (5.3 mmol/L), 1-hour postprandial of 140 mg/dL (7.8 mmol/L), and 2-hour postprandial of 120 mg/dL (6.7 mmol/L).[26] An abundance of glucose causes excessive insulin production by the fetus, which can lead to development of an abnormally large baby. Infant hypoglycemia at delivery, hyperbilirubinemia, and complications associated with delivery of a large baby also may occur when BG levels are not controlled. The ADA currently advocates for insulin as the primary pharmacotherapeutic choice for GDM.[26] Neither metformin nor glyburide is considered first line owing to the fact that they cross the placenta as well as concerns over inconsistent efficacy data in this population. Insulin should be used when BG levels are not maintained adequately by diet and physical activity. Insulin detemir, insulin aspart, lispro, neutral protamine hagedorn (NPH), and regular insulin all carry the older Food and Drug Administration (FDA) letter category B safety rating which indicates animal studies with the drug have failed to demonstrate risk to a developing fetus.[30]

Nonpharmacologic Therapy

▶ *Medical Nutrition Therapy*

MNT is considered an integral component of DM management and self-management education.[29] People with DM should receive individualized MNT, preferably by a registered dietitian. MNT should be provided as an ongoing dialogue customized to take into account cultural, lifestyle, and financial considerations. The primary focus of MNT for T1DM patients and T2DM patients taking mealtime insulin is matching optimal insulin dosing to carbohydrate consumption while maintaining a healthy balance. In T2DM, the primary focus is portion control and controlling BG, blood pressure (BP), and lipids through individualizing limits of carbohydrates, saturated fats, sodium, and calories.

▶ *Dietary Supplements*

There is insufficient evidence of efficacy for improved BG control for any individual herb or supplement. Herbs and supplements commonly touted to improve glucose control include chromium, curcumin, vitamin D, aloe vera, and cinnamon.[29] Additional information can be found at the National Institutes of Health Office of Dietary Supplements (https://ods.od.nih.gov).

▶ *Weight Management*

Moderate weight loss in patients with T2DM has been shown to reduce cardiovascular risk, as well as delay or prevent onset of DM in those with prediabetes.[31-33] The recommended primary approach to weight loss is therapeutic lifestyle change (TLC), which integrates a 7% reduction in body weight and increase in physical activity.[34] Slow but progressive weight loss of 0.45 to 0.91 kg (1–2 lb) per week is preferred.[34] Individual target caloric goals should be set. In the Diabetes Prevention Program, this was done by estimating daily caloric intake needed to maintain a person's current weight and then subtracting 500 to 1000 Calories per day (about 2100–4200 kJ/day) depending on initial weight.[31] Metabolic surgeries, such as Roux-en-Y gastric bypass, are recommended for patients with T2DM and BMI that is or exceeds 40 kg/m^2 regardless of glycemic control.[35] Metabolic surgery is also recommended in patients with BMI above 35 kg/m^2 but less than 40 kg/m^2 who are unable to achieve sustained weight loss and have comorbidities such as uncontrolled glucose.[35] Four drug therapy options have been approved for weight loss in patients with BMI greater than or equal to 27 kg/m^2 with one or more obesity-related conditions and in patients with BMI greater than or equal to 30 kg/m^2.[35] Options include orlistat (a lipase inhibitor), phentermine/topiramate extended release (a sympathomimetic amine anorectic/antiepileptic combination), naltrexone/bupropion (an opioid antagonist/aminoketone antidepressant combination), liraglutide (a GLP-1 receptor agonist [GLP-1 RA]), and semaglutide (a GLP-1 RA).

▶ *Physical Activity*

Regular physical activity improves BG control by improving insulin sensitivity.[34] Physical activity is associated with long-term maintenance of weight loss and may prevent onset of T2DM in high-risk persons. Before initiating a physical activity program, patients should undergo a detailed physical examination, including screening for microvascular or macrovascular complications that may be worsened by a particular activity.[29] Initiation of physical activities in an individual with a history of a sedentary lifestyle should begin with a modest increase in activity. Walking, swimming, and cycling are examples of low-impact exercises that could be encouraged; gardening and usual housecleaning tasks can be good exercises as well. Recommended physical activity goals for patients with T2DM include 150 min/week of moderate-to-vigorous aerobic exercise spread out during at least 3 days of the week with no more than 2 consecutive days between bouts of aerobic activity and moderate-to-vigorous resistance training at least 2 to 3 days/week.[29] All persons should be encouraged to break up sedentary periods over 30 minutes by getting up to stand, walk, or perform light physical activities.[29]

▶ *Psychological Assessment and Care*

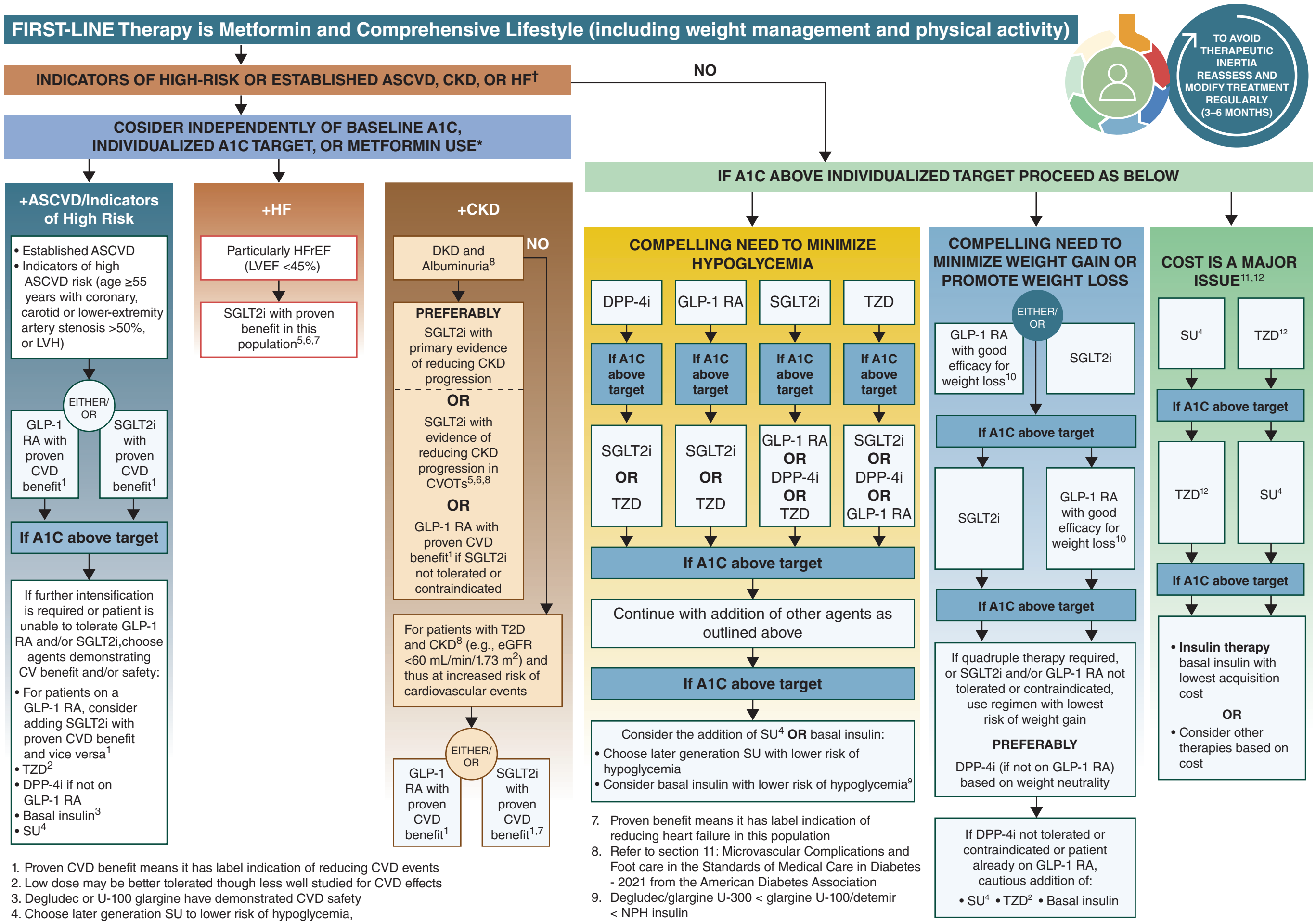
Mental health may impact a patient's ability to carry out DM management care tasks. Clinicians should incorporate psychological assessment and treatment into routine care. The ADA recommends ongoing psychological screening, including determining the patient's attitudes regarding DM; expectations of medical management and outcomes; mood and affect; general and diabetes-related quality of life; and financial, social, and emotional resources.[29] Patients demonstrating poor self-management should be screened for diabetes-related distress, depression, anxiety, an eating disorder, and/or cognitive impairment.[29]

▶ *Immunizations*

Yearly influenza vaccinations are recommended for all patients with DM 6 months of age or older.[36] Pneumococcal vaccination with the 13-valent conjugate vaccine is recommended for children before age 2.[36] The 23-valent polysaccharide vaccine is recommended for patients with DM who are between 2 and 64 years of age as a one-time vaccination.[36] At age greater than or equal to 65 years, patients should receive the pneumococcal polysaccharide vaccine, regardless of prior vaccination history. Whether the patient should receive another dose of the pneumococcal 13-valent conjugate vaccine before receipt of this 23-valent polysaccharide dose should be determined via shared clinical decision making with a healthcare provider. A 2- or 3-dose hepatitis B vaccination series is recommended in unvaccinated patients aged 18 to 59.[36] For those over the age of 60, hepatitis B vaccination may also be considered. Additional vaccinations such as zoster; human papillomavirus; and tetanus, diphtheria, and pertussis are also recommended by the Advisory Committee on Immunization Practices for persons with diabetes as they are for persons without diabetes.

Pharmacologic Therapy

Figure 44–2 summarizes the treatment algorithm for T2DM per the ADA.[28] This algorithm is similar to the AACE algorithm in that both treatment guidelines prioritize treatment options based


FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†
NO
COSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*
IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW
+ASCVD/Indicators of High Risk
• Established ASCVD
• Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower-extremity artery stenosis >50%, or LVH)
EITHER/ OR
GLP-1 RA with proven CVD benefit1
SGLT2i with proven CVD benefit1
If A1C above target
If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i,choose agents demonstrating CV benefit and/or safety:
• For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit and vice versa1
• TZD2
• DPP-4i if not on GLP-1 RA
• Basal insulin3
• SU4
+HF
Particularly HFrEF (LVEF <45%)
SGLT2i with proven benefit in this population5,6,7
+CKD
DKD and Albuminuria8
NO
PREFERABLY
SGLT2i with primary evidence of reducing CKD progression
OR
SGLT2i with evidence of reducing CKD progression in CVOTs5,6,8
OR
GLP-1 RA with proven CVD benefit1 if SGLT2i not tolerated or contraindicated
For patients with T2D and CKD8 (e.g., eGFR <60 mL/min/1.73 m2) and thus at increased risk of cardiovascular events
EITHER/ OR
GLP-1 RA with proven CVD benefit1
SGLT2i with proven CVD benefit1,7
COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
DPP-4i
GLP-1 RA
SGLT2i
TZD
If A1C above target
SGLT2i OR TZD
SGLT2i OR TZD
GLP-1 RA OR DPP-4i OR TZD
SGLT2i OR DPP-4i OR GLP-1 RA
If A1C above target
Continue with addition of other agents as outlined above
If A1C above target
Consider the addition of SU4 OR basal insulin:
• Choose later generation SU with lower risk of hypoglycemia
• Consider basal insulin with lower risk of hypoglycemia9
COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
EITHER/ OR
GLP-1 RA with good efficacy for weight loss10
SGLT2i
If A1C above target
SGLT2i
GLP-1 RA with good efficacy for weight loss10
If A1C above target
If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain
PREFERABLY
DPP-4i (if not on GLP-1 RA) based on weight neutrality
If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:
• SU4 • TZD2 • Basal insulin
COST IS A MAJOR ISSUE11,12
SU4
TZD12
If A1C above target
TZD12
SU4
If A1C above target
• Insulin therapy basal insulin with lowest acquisition cost
OR
• Consider other therapies based on cost

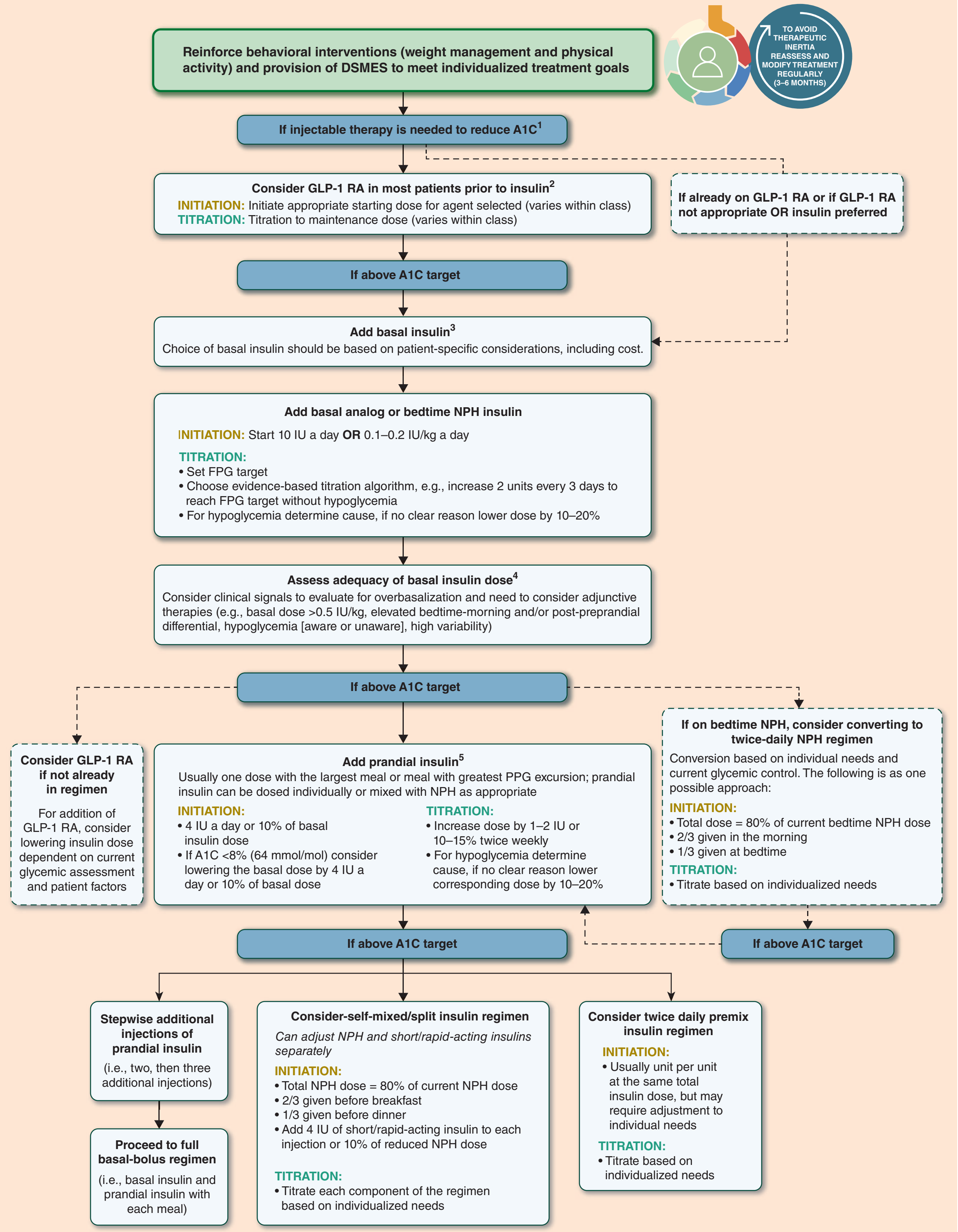
1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia, glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to section 11: Microvascular Complications and Foot care in the Standards of Medical Care in Diabetes - 2021 from the American Diabetes Association
9. Degludec/glargine U-300 < glargine U-100/detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

FIGURE 44–2. Glucose-lowering medication in type 2 diabetes: overall approach as per the American Diabetes Association. (A_{1c}, hemoglobin A_{1c}; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DKD, diabetic kidney disease; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HErEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.) (From American Diabetes Association. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes – 2021. Diabetes Care. 2021;44(suppl 1):S40–S52., with permission.)

on patient specific factors and treatment benefits, particularly for those patients with cardiovascular disease, heart failure, or chronic kidney disease (CKD).[22,28] The AACE guidelines take a more aggressive approach by advocating for consideration of starting a patient on two medications if presenting A_{1c} is greater than or equal to 7.5% (0.075; 58 mmol/mol Hgb).[22] The ADA, on the other hand, recommends dual therapy when the A_{1c} is greater than or equal to 8.5% (0.085; 69 mmol/mol Hgb).[28] While the ADA guidelines include metformin alone as the first-line therapy option for T2DM, the AACE guidelines include six other noninsulin initial therapy options as possibilities, though SGLT2 inhibitors and GLP-1 RAs are preferred in patients with established or high atherosclerotic cardiovascular disease (ASCVD) risk, heart failure with reduced ejection fraction (HFrEF), and/or CKD.[22,28] Because T2DM generally tends to be a progressive disease, BG levels will eventually increase, making insulin therapy the eventual required therapy in many patients, and therefore, insulin should not be used rhetorically as a prophylactic deterrent as this may result in patient trust issues and/or feelings of failure. This is usually done when several agents have been used with inadequate glucose-lowering results. Addition of GLP-1 RA is recognized by the ADA as an alternative to mealtime insulin in those already receiving maximally titrated basal regimens; in addition to GLP-1 RAs, the AACE guidelines also suggest DPP-4 or SGLT2 inhibitors as options in this scenario. Figure 44–3 is one illustration of a way to start insulin therapy in a patient with T2DM.[28]

KEY CONCEPT Oral and injectable agents are available to treat patients with T2DM who are unable to achieve glycemic control through meal planning and physical activity. Table 44–7[22,28,37-39] lists the oral agents, Table 44–8 lists each noninsulin drug class with site of action and mechanism of action, and Table 44–9 lists the expected A_{1c} reduction for each noninsulin antiglycemic drug class.[28,38-40] Various classes of BG-lowering agents target different organs and have different mechanisms of action. Each of these



TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Reinforce behavioral interventions (weight management and physical activity) and provision of DSMES to meet individualized treatment goals

If injectable therapy is needed to reduce A1C[1]

Consider GLP-1 RA in most patients prior to insulin[2]
INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Titration to maintenance dose (varies within class)

If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred

If above A1C target

Add basal insulin[3]
Choice of basal insulin should be based on patient-specific considerations, including cost.

Add basal analog or bedtime NPH insulin

INITIATION: Start 10 IU a day **OR** 0.1–0.2 IU/kg a day

TITRATION:
- Set FPG target
- Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
- For hypoglycemia determine cause, if no clear reason lower dose by 10–20%

Assess adequacy of basal insulin dose[4]
Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose >0.5 IU/kg, elevated bedtime-morning and/or post-preprandial differential, hypoglycemia [aware or unaware], high variability)

If above A1C target

Consider GLP-1 RA if not already in regimen

For addition of GLP-1 RA, consider lowering insulin dose dependent on current glycemic assessment and patient factors

Add prandial insulin[5]
Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

INITIATION:
- 4 IU a day or 10% of basal insulin dose
- If A1C <8% (64 mmol/mol) consider lowering the basal dose by 4 IU a day or 10% of basal dose

TITRATION:
- Increase dose by 1–2 IU or 10–15% twice weekly
- For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10–20%

If on bedtime NPH, consider converting to twice-daily NPH regimen

Conversion based on individual needs and current glycemic control. The following is as one possible approach:

INITIATION:
- Total dose = 80% of current bedtime NPH dose
- 2/3 given in the morning
- 1/3 given at bedtime

TITRATION:
- Titrate based on individualized needs

If above A1C target

If above A1C target

Stepwise additional injections of prandial insulin

(i.e., two, then three additional injections)

Proceed to full basal-bolus regimen

(i.e., basal insulin and prandial insulin with each meal)

Consider-self-mixed/split insulin regimen

Can adjust NPH and short/rapid-acting insulins separately

INITIATION:
- Total NPH dose = 80% of current NPH dose
- 2/3 given before breakfast
- 1/3 given before dinner
- Add 4 IU of short/rapid-acting insulin to each injection or 10% of reduced NPH dose

TITRATION:
- Titrate each component of the regimen based on individualized needs

Consider twice daily premix insulin regimen

INITIATION:
- Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs

TITRATION:
- Titrate based on individualized needs

1. Consider insulin as the first injectable if evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high, or a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RA, cosider: patient preference, A1C lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit. Oral or injectable GLP-1 RA are appropriate.
3. For patients on GLP-1 RA and basal insulin combination, consider use of a fixed-ratio combination product (iDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the patient develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with an AM dose of a long-acting basal insulin.
5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin regimen to decrease the number of injections required.

FIGURE 44–3. Initiation and adjustment of insulin regimens. (A$_{1c}$, hemoglobin A$_{1c}$; CVD, cardiovascular disease; DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; NPH, neutral protamine Hagedorn; PPG, postprandial glucose.) (From American Diabetes Association. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes—2021. Diabetes Care. 2021;44(Suppl 1):S40–S52, with permission.)

Table 44–7

Oral Agents for the Treatment of Type 2 Diabetes Mellitus (T2DM)[22,28,37–39]

	Drugs					Adjustment for Renal Impairment			
Drug Class	**Trade**	**Generic/ Commercially Available**	**Target Area**	**Blood Glucose Affected**	**Dosing Strategy (All Agents Taken Orally)**	**eGFR 30-50 mL/min (0.50–0.83 mL/s)**	**eGFR < 30 mL/min (0.50 mL/s)**	**Adjustment for Hepatic Impairment**	**Common Adverse Drug Reactions**
α-Glucosidase inhibitors	Precose	Acarbose/Y	Brush border of small intestine	Postprandial	25 mg three times daily with first bite of each main meal Advance at 4–8 week intervals to maximum of 100 mg three times daily	SCr > 2 mg/dL (177 μmol/L): Not recommended	SCr > 2 mg/dL (177 μmol/L): Not recommended	No specific dose adjustment recommended; contraindicated in cirrhosis	GI (flatulence, diarrhea)
	Glyset	Miglitol/Y			25 mg three times daily with first bite of each main meal Advance at 4–8 week intervals to maximum of 100 mg three times daily	SCr > 2 mg/dL (177 μmol/L): Not recommended	SCr > 2 mg/dL (177 μmol/L): Not recommended	No adjustment necessary	GI (flatulence, diarrhea)
Meglitinides (should not be used in combination with other insulin secretagogues)	Prandin	Repaglinide/Y	Pancreas	Postprandial	0.5 mg 15–30 minutes before each meal Double preprandial dose every 7 days to maximum of 4 mg/dose or 16 mg/day (To be taken only if eating)	20–40 mL/min (0.33–0.67 mL/s): Initial dose: 0.5 mg with careful titration	< 20 mL/min (0.33 mL/s): Not studied	Use conservative initial and maintenance doses and use longer intervals between dose adjustments	Hypoglycemia (although less risk than with sulfonylureas)
	Starlix	Nateglinide/Y			120 mg three times daily before meals (To be taken only if eating)	No specific dose adjustment recommended	Use with caution in severe dysfunction	No dose adjustment needed in mild impairment; use with caution in moderate-to-severe dysfunction	Hypoglycemia (although less risk than with sulfonylureas)

(Continued)

Table 44–7

Oral Agents for the Treatment of Type 2 Diabetes Mellitus (T2DM)[22,28,37–39] (*Continued*)

	Drugs					Adjustment for Renal Impairment			
Drug Class	Trade	Generic/ Commercially Available	Target Area	Blood Glucose Affected	Dosing Strategy (All Agents Taken Orally)	eGFR 30-50 mL/min (0.50–0.83 mL/s)	eGFR < 30 mL/min (0.50 mL/s)	Adjustment for Hepatic Impairment	Common Adverse Drug Reactions
Second-generation sulfonylureas	Glynase PresTab	Glyburide micronized/Y	Pancreas	Fasting and postprandial	1.5–3 mg/day with breakfast Increase by 1.5 mg weekly to maximum of 12 mg/day	Not recommended	Not recommended	Use conservative dosing and avoid in severe disease	Hypoglycemia, weight gain
	DiaBeta	Glyburide/Y			2.5–5 mg/day with breakfast Increase by 2.5 mg weekly to maximum of 20 mg/day	Not recommended	Not recommended	Use conservative dosing and avoid in severe disease	Hypoglycemia, weight gain
	Glucotrol	Glipizide/Y			2.5 mg/day 30 minutes before a meal Increase by 2.5–5 mg weekly to maximum of 40 mg/day; divide dose if > 15 mg/day	No specific dose adjustment recommended	No specific dose adjustment recommended	Initial dose: 2.5 mg/day	Hypoglycemia, weight gain
	Glucotrol XL	Glipizide ER/Y			2.5-5 mg once daily before a meal Increase by 5–10 mg weekly to maximum of 20 mg/day	No specific dose adjustment recommended	No specific dose adjustment recommended	No specific dose adjustment recommended	Hypoglycemia, weight gain
	Amaryl	Glimepride/Y			1–2 mg with breakfast Increase by 2 mg every 1–2 weeks to maximum of 8 mg/day	No specific dose adjustment recommended	Initial starting dose should be 1 mg < 15 mL/min (0.25 mL/s): Consider alternative	No specific dose adjustment recommended	Hypoglycemia, weight gain

Biguanides	Glucophage	Metformin/Y	Liver	Fasting and postprandial	500 mg/day to twice daily with meals. Advance weekly to maximum of 2000–2550 mg/day	Do not start or, if already taking, continue cautiously if eGFR 30–45 mL/min/1.73 m^2. Consider 50% of maximum doses and monitoring of renal function every 3 months.	Contraindicated	Avoid or use cautiously in patients at risk for lactic acidosis (renal impairment or alcohol abuse)	GI (diarrhea, abdominal pain)
	Glucophage ER, Glumetza, Fortamet	Metformin, ER/Y							
	Riomet	Metformin, solution/Y			500 mg twice daily; dose may be increased by 500 mg weekly or 850 mg every 2 weeks to maximum of 2000 mg/day				
Thiazolidinediones	Actos	Pioglitazone/Y	Peripheral tissue	Fasting and postprandial	15–30 mg/day Increase after 12 weeks to maximum of 45 mg/day	No adjustment necessary	No adjustment necessary	Clearance lower in Child-Pugh grade B/C; do not start if transaminases > 2.5 × ULN and discontinue if ALT rises to and remains at more than three times ULN	Weight gain
	Avandia	Rosiglitazone/Y	Peripheral tissue	Fasting and postprandial	4 mg/day Increase after 8–12 weeks to maximum of 8 mg/day	No adjustment necessary	No adjustment necessary	Do not initiate if active liver disease or ALT > 2.5 times ULN	Weight gain
Dipeptidyl peptidase-4 inhibitors	Januvia	Sitagliptin/N	GI tract (increases GLP-1)	Fasting and postprandial	100 mg/day	50 mg once daily	25 mg once daily	Child-Pugh class A and B: No dosage adjustment necessary Child-Pugh class C: Not studied	Upper respiratory, diarrhea
	Onglyza	Saxagliptin/N			2.5 or 5 mg/daily	2.5 mg once daily	2.5 mg once daily	No dose adjustment necessary	UTI, headache
	Tradjenta	Linagliptin/N			5 mg/day	No dose adjustment necessary	No dose adjustment necessary	No dose adjustment necessary	Headache, arthralgia, nasopharyngitis
	Nesina	Alogliptin/Y			25 mg/day	> 30 mL/min (0.50 mL/s) but < 60 mL/min (1 mL/s): 12.5 mg/day	> 15 mL/min (0.25 mL/s) but < 30 mL/min (0.50 mL/s): 6.25 mg/day < 15 mL/min (0.25 mL/s): 6.25 mg/day	No dose adjustment necessary Child-Pugh class C: Not studied	Headache, increased ALT greater than three times ULN, nasopharyngitis, upper respiratory

(*Continued*)

Table 44–7

Oral Agents for the Treatment of Type 2 Diabetes Mellitus (T2DM)[22,28,37–39] (*Continued*)

	Drugs					Adjustment for Renal Impairment			
Drug Class	**Trade**	**Generic/ Commercially Available**	**Target Area**	**Blood Glucose Affected**	**Dosing Strategy (All Agents Taken Orally)**	**eGFR 30-50 mL/min (0.50–0.83 mL/s)**	**eGFR < 30 mL/min (0.50 mL/s)**	**Adjustment for Hepatic Impairment**	**Common Adverse Drug Reactions**
Selective sodium-dependent glucose cotransporter-2 inhibitor	Invokana	Canagliflozin/N	Kidney	Fasting and postprandial	100 mg/day in the morning; may increase to 300 mg/day	> 45 mL/min/1.73 m^2 (0.43 mL/s/m^2) but < 60 mL/min/1.73 m^2 (0.58 mL/s/m^2): 100 mg/day 30 mL/min/1.73 m^2 (0.29 mL/s/m^2) to 45 mL/min/1.73 m^2 (0.43 mL/s/m^2) with urinary albumin excretion > 300 mg/day: 100 mg/day	< 30 mL/min/1.73 m^2 (0.29 mL/s/m^2): contraindicated	Mild-to-moderate (Child-Pugh class A and B): no adjustment necessary Severe (Child-Pugh class C): not recommended	Hyperkalemia, genitourinary infection, hypovolemia, renal insufficiency, hypotension
	Farxiga	Dapagliflozin/N			5 mg/day in the morning; may increase to 10 mg/day	< 45 mL/min/1.73 m^2 (0.43 mL/s/m^2): not recommended for glycemic control >25 mL/min/1.73 m^2 (0.24 mL/s/m^2) but <45 mL/min/1.73 m^2 (0.43 mL/s/m^2) with heart failure or chronic kidney disease: 10 mg/day	< 25 mL/min/1.73 m^2 (0.24 mL/s/m^2): contraindicated	Mild-to-moderate: No adjustment necessary Severe: not studied	Genitourinary infection, hypovolemia/hypotension, dysuria, polyuria, dyslipidemia, mild hypoglycemia, nasopharyngitis
	Jardiance	Empagliflozin/N			10 mg/day in the morning; may increase to 25 mg/day	No dosage adjustment	< 30 mL/min/1.73 m^2 (0.29 mL/s/m^2): contraindicated	No dose adjustment necessary	Genitourinary infection, hypovolemia/hypotension, dysuria, polyuria, mild hypoglycemia
	Steglatro	Ertugliflozin/N			5 mg/day in the morning; may increase to 15 mg/day	< 60 mL/min (1.0 mL/s): not recommended	< 30 mL/min (0.50 mL/s): contraindicated		Genitourinary infection, hypovolemia, mild hypoglycemia, polyuria, increased LDL cholesterol, renal insufficiency

GLP-1 receptor agonist	Rybelsus	Semaglutide/N	GI tract; pancreas	Fasting and postprandial	3 mg/day in the morning with water 30 minutes before first food, beverage, or other oral medications for 30 days; increase to 7 mg/day; may increase to 14 mg/day after 30 days if additional glycemic control needed	No dose adjustment necessary	No dose adjustment necessary	No dose adjustment necessary	GI effects (nausea, diarrhea, flatulence, abdominal pain), risk of pancreatitis, increased heart rate
Dopamine receptor agonist	Cycloset	Bromocriptine mesylate/N	Hypothalamus	Postprandial	0.8 mg once daily within 2 hours of waking; may increase in weekly intervals to 4.8 mg once daily	No dose adjustment necessary	No dose adjustment necessary	No specific dose adjustment recommended, although adjustment may be necessary because of extensive hepatic metabolism	Nausea, headache
Bile acid sequestrant	Welchol	Colesevelam/Y	Intestinal lumen	Fasting	1.875 g twice daily or 3.75 g once daily	No dose adjustment necessary	No dose adjustment necessary	No dose adjustment necessary	Constipation

ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; ER, extended release; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; LDL, low-density lipoprotein; SCr, serum creatinine; ULN, upper limit of normal; UTI, urinary tract infection.

Table 44–8

Site and Mechanism of Action for Noninsulin Agents[22,38-40]

Site of Action	Drug Class	Mechanism of Action
Pancreas	Sulfonylureas	Enhances insulin secretion
	Nonsulfonylurea secretagogues	Enhances insulin secretion
	GLP-1 agonists	Enhances insulin secretion and suppresses glucagon secretion
	Pramlintide	Suppresses glucagon secretion
Liver	Biguanide	Decreases hepatic glucose production and increases insulin sensitivity
	Thiazolidinedione	Increases insulin sensitivity
Muscle	Biguanide	Increases insulin sensitivity
	Thiazolidinedione	Increases insulin sensitivity
Adipose tissue	Thiazolidinedione	Increases insulin sensitivity
Intestines	GLP-1 agonists	Increases satiety and regulates gastric emptying
	Pramlintide	Increases satiety and regulates gastric emptying
	Dipeptidyl peptidase-4 inhibitors	Increases endogenous GLP-1
	α-Glucosidase inhibitors	Delays absorption of carbohydrates
Kidney	SGLT2 inhibitors	Inhibits glucose reabsorption in the kidney's proximal tubule

GLP-1, glucagon-like peptide-1; SGLT2, sodium-dependent glucose cotransporter-2.

agents may be used individually or in combination with other medications targeting different organs for synergistic effects. In addition to single agent products, there are many combination products marketed as well.

▶ *Sulfonylureas*

Sulfonylureas enhance insulin secretion by blocking ATP-sensitive potassium channels in the cell membranes of pancreatic β-cells. This action results in membrane depolarization, allowing an influx of calcium to cause the translocation of secretory granules of insulin to the cell surface, and enhances insulin secretion in a non–glucose dependent manner. Insulin is then transported through the portal vein to the liver, suppressing hepatic glucose production. These drugs are classified as being either first- or second-generation agents. The vast majority of patients receiving a sulfonylurea are prescribed a second-generation agent.

All sulfonylureas undergo hepatic biotransformation, with most agents being metabolized by the cytochrome P450 2C9 pathway. First-generation sulfonylureas are more likely to cause drug interactions. All sulfonylureas, except tolbutamide, require dosage adjustment or are not recommended in renal impairment.[38] In elderly patients or those with compromised renal or hepatic function, lower starting dosages are necessary.

The BG-lowering effects sulfonylureas can be observed in both fasting and postprandial levels. Monotherapy with these agents generally produces a 1.5% to 2% (0.015–0.02 or 17–22 mmol/mol Hgb) decline in A_{1c} concentrations and a 60 to 70 mg/dL (3.3–3.9 mmol/L) reduction in FBG levels.[40] Secondary failure with these drugs occurs as a result of continued pancreatic β-cell destruction. One limitation of sulfonylurea therapy is the inability of these products to stimulate insulin release from β-cells at extremely high glucose levels, a phenomenon called glucose toxicity. Common adverse effects include hypoglycemia and weight gain. There may be some cross-sensitivity in patients with sulfa allergy. Patients with glucose-6-phosphate dehydrogenase deficiency may experience an increased risk for hemolytic anemia with sulfonylurea use.[38]

▶ *Nonsulfonylurea Secretagogues (Glinides)*

Although producing the same effect as sulfonylureas, nonsulfonylurea secretagogues, meglitinides, have a much shorter onset and duration of action. Meglitinides produce a pharmacologic effect by interacting with ATP-sensitive potassium channels on the β-cells; however, this binding is to a receptor adjacent to those to which sulfonylureas bind. The primary benefit of

Table 44–9

Expected A_{1c} Reduction for Noninsulin Antiglycemic Drug Classes[22,38-40]

Drug Class	Efficacy	A_{1c} Reduction (%)	A_{1c} Reduction (mmol/mol Hgb)
Biguanides	High	1.5%–2% (0.015–0.02)	17–22 mmol/mol Hgb
Sulfonylureas	High	1.5%–2% (0.015–0.02)	17–22 mmol/mol Hgb
GLP-1 agonists	High	0.78%–1.9% (0.0078–0.019)	8.8–20 mmol/mol Hgb
Thiazolidinedione	High	up to 1.5% (0.015)	17 mmol/mol Hgb
Dipeptidyl peptidase-4 inhibitors	Intermediate	0.7%–1% (0.007–0.01)	8–11 mmol/mol Hgb
SGLT2 inhibitors	Intermediate	0.5%–1% (0.005–0.01)	5–11 mmol/mol Hgb
Nonsulfonylurea secretagogues	Intermediate	0.3%–1% (0.003–0.01)	3–11 mmol/mol Hgb
α-Glucosidase inhibitors	Intermediate	0.3%–1% (0.003–0.01)	3–11 mmol/mol Hgb
Central-acting dopamine agonists	Low	0.3%–0.6% (0.003–0.006)	3–7 mmol/mol Hgb
Pramlintide	Low	0.4%–0.5% (0.004–0.005)	4–5 mmol/mol Hgb
Bile acid sequestrants	Low	0.4% (0.004)	4 mmol/mol Hgb

A_{1c}, hemoglobin A_{1c}; GLP-1, glucagon-like peptide-1; Hgb, hemoglobin; SGLT2, sodium-dependent glucose cotransporter-2.

nonsulfonylurea secretagogues is in reducing postmeal glucose levels. These agents have demonstrated a reduction in A_{1c} levels between 0.3% and 1% (0.003 and 0.01; 3–11 mmol/mol Hgb).[40] Because they have a rapid onset and short duration of action, they should be taken 15 to 30 minutes before a meal three times a day.

▶ *Biguanides*

Metformin is the only biguanide approved by the FDA and currently available in the United States. This agent is thought to lower BG by decreasing hepatic glucose production and increasing insulin sensitivity in both hepatic and peripheral muscle tissues; however, the exact mechanism of action remains unknown. Metformin reduces A_{1c} levels by 1.5% to 2% (0.015–0.02; 17–22 mmol/mol Hgb) and FPG levels by 60 to 80 mg/dL (3.3–4.4 mmol/L) when used as monotherapy.[40] Unlike sulfonylureas, metformin retains the ability to reduce FBG levels when they are over 300 mg/dL (16.7 mmol/L). Metformin does not affect insulin release from β-cells of the pancreas, so hypoglycemia is not a common side effect.[38]

Metformin significantly reduced all-cause mortality and risk of stroke in overweight patients with T2DM compared with intensive therapy with sulfonylurea or insulin in the UKPDS.[41] It also reduced diabetes-related death and myocardial infarction compared with a conventional therapy arm. Metformin is recommended for prevention of T2DM in patients with prediabetes, especially when the patient has a BMI greater than or equal to 35 kg/m^2, is less than 60 years old, or is a woman with a history of GDM.[34] Metformin is considered foundational therapy along with lifestyle modification for T2DM and often used in combination with other antihyperglycemics for synergistic effects.[28]

Per US labeling, metformin is contraindicated in patients with estimated glomerular filtration rates (eGFR) less than 30 mL/min/1.73 m^2.[38] It is not recommended for new start in patients whose eGFR is 30 to 45 mL/min/1.73 m^2. In those whose eGFR falls to less than 45 mL/min/1.73 m^2, a consideration of benefits and risks should be undertaken and the dose reduced to no more than 500 mg twice daily and renal monitoring every 3 months. No adjustment is required for patients with an eGFR greater than 45 mL/min/1.73 m^2, though more frequent monitoring (every 3 to 6 months versus annually) is recommended for patients with eGFR greater than 45 but less than 60 mL/min/1.73 m^2. Additionally, therapy with metformin should be withheld in patients undergoing radiographic procedures in which nephrotoxic dye is used if their eGFR is between 30 and 60 mL/min/1.73 m^2. Therapy should be withheld the day of the radiographic procedure, and renal function should be assessed 48 hours after the procedure. If renal function is normal, therapy may be resumed. Metformin should also be held 24 hours before surgery and restarted after oral intake is resumed and renal function is evaluated as normal.

Primary side effects associated with metformin include decreased appetite, nausea, and diarrhea. Side effects can be minimized through use of extended-release products and slow titration of the dose and often subside within 2 weeks.[42] Interference with vitamin B_{12} absorption has also been reported and periodic B_{12} testing is recommended especially in those patients with macrocytic anemia or peripheral neuropathy.[28] Metformin is thought to inhibit mitochondrial oxidation of lactic acid, thereby increasing the chance of lactic acidosis, a condition which rarely occurs. Patients at risk for lactic acidosis include those with renal impairment and those who are of advanced age.[38] Metformin should be withheld promptly in cases of hypoxemia, sepsis, or dehydration. Patients should avoid consumption of excessive amounts of alcohol while taking metformin, and use of the drug should be avoided in patients with liver disease.

▶ *Thiazolidinediones (TZDs)*

TZDs are known to increase insulin sensitivity by stimulating peroxisome proliferator-activated receptor gamma (PPAR-γ) which increases insulin sensitivity and decreases plasma fatty acids. As monotherapy, TZDs reduce FPG levels by around 60 to 70 mg/dL (3.3–3.9 mmol/L), and the effect on A_{1c} is an up to 1.5% (0.015; 17 mmol/mol Hgb) reduction.[40] Onset of action for TZDs is delayed for several weeks and may require 12 weeks or more before maximum effects are observed.

TZDs may produce fluid retention and edema and are, thus, contraindicated in New York Heart Association Class III and IV heart failure. Fluid retention appears to be dose related and increases when combined with insulin therapy. While rare, TZDs can worsen macular edema. Weight gain of 4 kg (8.8 lb) is common with TZDs and results from both fluid retention and fat accumulation.[40]

Increased rates of upper and lower limb fractures are known to occur with TZD therapy. Premenopausal anovulatory women may begin to ovulate on TZD therapy, and therefore, counseling regarding this should be provided to all women capable of becoming pregnant. An increased risk for bladder cancer has been noted with pioglitazone therapy, especially among men and smokers.

Safety of TZD therapy in patients with cardiovascular disease seems to differ between specific drugs. A meta-analysis reported a significantly greater risk of myocardial infarction with rosiglitazone compared with other oral agents.[43] A subsequent study found rosiglitazone use associated with a nonsignificant increase in myocardial infarction risk and nonsignificant reduction in stroke, but a trend toward increased cardiovascular risk in patients with a history of ischemic heart disease.[44] A meta-analysis of pioglitazone in patients with established cardiovascular disease demonstrated significant reduction in major adverse cardiovascular events (MACE), myocardial infarction, and stroke but did not reduce risk of all-cause mortality.[45]

▶ *α-Glucosidase Inhibitors*

Acarbose and miglitol are α-glucosidase inhibitors that compete with enzymes of the small intestines that break down complex carbohydrates. These drugs delay absorption of carbohydrates and reduce postprandial BG concentrations as much as 40 to 50 mg/dL (2.2–2.8 mmol/L); however, A_{1c} reductions range only from 0.3% to 1% (0.003–0.01; 3–11 mmol/mol Hgb).[40] High incidences of GI side effects have limited their use.[38]

▶ *Dipeptidyl Peptidase-4 Inhibitors*

DPP-4 inhibitors (or gliptins; sitagliptin, saxagliptin, linagliptin, and alogliptin) are approved as adjunct to diet and exercise to improve glycemic control in adults with T2DM. They lower BG concentrations by inhibiting DPP-4, the enzyme that degrades endogenous GLP-1, thereby increasing the amount of endogenous GLP-1. The BG-lowering effect of gliptins is primarily on postprandial levels. Typical A_{1c} reductions are 0.7% to 1% (0.007–0.01; 8–11 mmol/mol Hgb).[40] Common adverse effects include headache and nasopharyngitis. Hypoglycemia is not a common adverse effect with these agents because insulin secretion results from GLP-1 activation caused by meal-related glucose detection and not from direct pancreatic β-cell stimulation. Acute pancreatitis, including hemorrhagic and necrotizing pancreatitis, has been reported in patients taking glipitins.[38] These agents should not be given to patients with a history of pancreatitis. Cardiovascular outcomes trials (CVOTs) comparing DPP-4 inhibitors to placebo have not demonstrated cardiovascular benefits, and an increase in hospitalization for heart failure was shown with saxagliptin.[23]

▶ Sodium-Dependent Glucose Cotransporter-2 Inhibitors

SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin) are approved as adjunct to diet and exercise to improve glycemic control in adults with T2DM and may be used as monotherapy or add-on.[38] Several agents in this class have expanded FDA approvals to include cardiovascular benefits, though specific approval varies per agent. Inhibition of SGLT2 in the proximal tubules reduces reabsorption of filtered glucose and lowers the renal threshold for glucose which together cause increased urinary excretion of glucose and decreased plasma glucose concentrations. Typical A_{1c} reductions are 0.5% to 1% (0.005–0.01; 5–11 mmol/mol Hgb).[40]

Empagliflozin, added to standard of care in patients with established ASCVD, was shown to reduce the composite of cardiovascular death, all-cause mortality, and death from cardiovascular causes.[46] Canagliflozin was evaluated in two trials which enrolled patients with T2DM at high cardiovascular risk.[47] Canagliflozin reduced the risk of primary outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. An increased risk for lower-limb amputation was detected, primarily involving the toe or metatarsal in patients with a history of previous amputation or peripheral vascular disease. Dapagliflozin did not show a difference in the risk of cardiovascular death, nonfatal myocardial infarction, and stroke in patients with ASCVD or ASCVD risk factors but did lower risk of cardiovascular death or hospitalization for heart failure.[48] All three medications have shown a significant reduction in hospitalizations for heart failure, leading to development of ongoing clinical trials in patients with heart failure with and without diabetes.[23] Additionally, CVOTs for empagliflozin,[49] canagliflozin,[47] and dapagliflozin[48] evaluated the effects of these agents on renal outcomes. All were found to have a positive effect on renal outcomes in patients with T2DM at high cardiovascular risk.[47-49]

Possible adverse reactions with SGLT2 inhibitors include an increased incidence of urinary tract infections (UTIs) and genital mycotic infections due to increased glucose excretion.[38] Osmotic diuresis occurs which may result in symptomatic hypotension. Renal function should be monitored at baseline to guide initial dosing and periodically during treatment to assess suitability of continuation. Volume status including BP, hematocrit, serum potassium, serum magnesium, serum phosphate, and low-density lipoprotein (LDL) cholesterol are also recommended monitoring parameters for this drug class. Cases of euglycemic ketoacidosis have been reported with SGLT2 inhibitors. Before initiation, patients should have risk for ketoacidosis assessed (including insulin deficiency, dose decreases of insulin, caloric restriction, surgery, and infection). SGLT2 inhibitors should be held at least 3 days prior to surgery then restarted once the patient is stable to minimize risk of DKA. Should ketoacidosis occur, the SGLT2 inhibitor should be held or discontinued. Increased risk for bone fracture has been associated with SLGT2 inhibitor use as well as newly diagnosed bladder cancer with dapagliflozin. Although rare, patients may develop necrotizing fasciitis of the perineum (Fournier gangrene).

▶ Glucagon-Like Peptide 1 Receptor Agonists

Exenatide, liraglutide, dulaglutide, semaglutide, and lixisenatide are indicated for treatment of T2DM to improve glycemic control. These agents are part of the group of drugs known as incretins (Table 44–10).[38,39,50,51]

GLP-1 RAs lower BG levels by (a) producing glucose-dependent insulin secretion; (b) reducing postmeal glucagon secretion, which decreases postmeal glucose output; (c) increasing satiety which decreases food intake; and (d) regulating gastric emptying, which allows nutrients to be absorbed into the circulation more smoothly. Typical A_{1c} reductions vary between GLP-1 RAs and are also affected by baseline glucose control.[39,50,51] Exenatide immediate release and lixisenatide daily are less effective at lowering A_{1c} compared to other GLP-1 RAs: −0.5% to 1% reduction in A_{1c} (0.005–0.01; 5–11 mmol/mol Hgb) versus 1% to 1.9% (0.01–0.019; 11–20 mmol/mol Hgb) with liraglutide and weekly formulations of exenatide, dulaglutide, and semaglutide (injectable), as well as daily oral semaglutide. Exenatide immediate release has less impact on fasting blood sugar levels compared with longer acting GLP-1 RAs owing to its shorter duration of action.[40]

GLP-1 RAs typically produce moderate weight loss of around 2 to 4 kg (4.4–8.8 lb) depending on the drug chosen.[40,50,51] Exenatide and lixisenatide are eliminated renally. Exenatide is not recommended in patients with creatinine clearance (CrCl) of less than 30 mL/min (0.50 mL/s), and lixisenatide is not recommended in patients with CrCl less than 15 mL/min (0.25 mL/s).[38] No specific dose adjustments are recommended for liraglutide, semaglutide, or dulaglutide in renal impairment. The main side effects of GLP-1 RA therapy include nausea, vomiting, and diarrhea. These GI adverse effects tend to lessen over time.[38,50,51] GLP-1 RAs have been associated with cases of acute pancreatitis and should not be started in patients with a history of pancreatitis. Any patient with symptoms of acute pancreatitis, including abdominal pain, nausea, and vomiting, should have GLP-1 RA therapy discontinued until pancreatitis can be ruled out. All GLP-1 RAs except for lixisenatide contain a black-box warning about thyroid C-cell tumors.[38] These agents are contraindicated in patients with a personal or family history of medullary thyroid cancer and in those with a history of multiple endocrine tumors. Antibody formation can occur with GLP-1 RAs leading to treatment failure or increased allergic reaction side effects.

CVOTs with GLP-1 RAs have demonstrated mixed results.[23,51,52] The majority of trials compared active drug to placebo with a primary outcome of three-point MACE (first nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) over 1.3 to 5.5 years.[23,52] The number of patients with preexisting cardiovascular disease also varied across trials, with as few as 31% in the dulaglutide trial to 100% in the lixisenatide trial.[52] Although all GLP-1 RA CVOTs demonstrated noninferiority compared to placebo, liraglutide, dulaglutide, and injectable semaglutide significantly reduced risk of cardiovascular events.[23,52] Additionally, both liraglutide and semaglutide have been shown to reduce risk for new or worsening nephropathy.[52] Given these potential cardiovascular and renal outcome benefits coupled with their ability to produce weight loss and help control weight gain from insulin therapy, the GLP-1 RAs have had considerable increased utilization in recent years both as monotherapy and add-on. As such, a market for combination insulin and GLP-1 RA products has developed. There are now two basal insulin/GLP-1 RA combination products available.[38] One contains insulin glargine in combination with lixisenatide and the other contains insulin degludec in combination with liraglutide.

▶ Central-Acting Dopamine Agonist

A quick release formulation of the central-acting dopamine agonist, bromocriptine, is approved for treatment of T2DM but should be considered a last line option due to the modest impact on BG levels and A_{1c}.[22] The mechanism of action for how bromocriptine regulates glycemic control is unknown, but data indicate that bromocriptine administered in the morning improves

Table 44–10

Noninsulin Injectable Agents for Treatment of Diabetes[38,39,50,51]

Generic Name (Brand)	Type of Diabetes	Dosage Strengths[a]	Starting Dosage	Dosage Interval	Titration Interval	Maximum Dose	Time to Effect (minutes)	Comments and Cautions
Pramlintide[b] (Symlin)	T1DM	1.5 mL for 15, 30, 45, 60 mcg doses	15 mcg	Three times a day with meals	3–7 days	60 mcg	20	Take just before major meals; reduce insulin by 50% Maintenance dose 30–60 mcg
	T2DM	2.7 mL for 60, 120 mcg doses	60 mcg	Three times a day with meals	3–7 days	120 mcg	20	Side effects: Hypoglycemia, nausea, vomiting Available in SymlinPen 60 and 120
Exenatide[b] (Byetta, Bydureon, Bydureon BCISE)	T2DM	Immediate-release: 5 mcg, 10 mcg	Immediate-release: 5 mcg	Immediate-release: twice daily	Immediate-release: 1 month	Immediate-release: 10 mcg twice daily	Immediate-release: 15–30	Inject immediate-release formulation 15–20 minutes before two meals of the day with 6 hours separating the meals; prefilled disposable pen; may delay absorption of oral drugs; separate doses by 1 hour Side effects: Nausea, vomiting, diarrhea, increased hypoglycemia with sulfonylureas
		Extended-release: 2 mg	Extended-release: 2 mg	Extended-release: once weekly	Extended-release: N/A	Extended-release: 2 mg	N/A	Extended-release formulation can be administered regardless of meals
Lixisenatide[b] (Adlyxin)	T2DM	10 mcg and 20 mcg pen-injector starter kit; 20 mcg pen-injector	10 mcg	Once daily	14 days	20 mcg	N/A	If missed dose, administer within 1 hour of next meal
Liraglutide[b] (Victoza)	T2DM	18 mg/3 mL pen	0.6 mg	Once daily	1 week	1.8 mg	N/A	Can be dosed at any time of day regardless of meals; may delay absorption of oral drugs; separate doses by 1 hour Side effects: Nausea, vomiting, increased hypoglycemia with sulfonylureas
Dulaglutide[b] (Trulicity)	T2DM	0.75 mg single-dose pen; 1.5-mg single-dose pen; 3.0-mg single-dose pen; 4.5-mg single-dose pen	0.75 mg	Once weekly	4–8 weeks	4.5 mg	N/A	If missed dose occurs within 3 days of regularly scheduled dose, dose should be administered at that time. If missed dose occurs more than 3 days past scheduled dose, wait until next regularly scheduled dose to administer next dose Side effects: nausea, diarrhea, vomiting, abdominal pain, decreased appetite, dyspepsia, fatigue
Semaglutide[b] (Ozempic)	T2DM	2 mg/1.5 mL pen-injector for 0.25 or 0.5 mg/dose pen; 4 mg/3 mL pen-injector for 1 mg/dose pen	0.25 mg	Once weekly	4 weeks	1 mg	N/A	If missed dose occurs within 5 days, administer the dose as soon as possible. If > 5 days, do not administer until the next scheduled weekly dose. Side effects: nausea, vomiting, diarrhea, abdominal pain, risk of hypoglycemia, tachycardia

[a] Pramlintide supplied as 0.6 mg/mL in 5 mL vials. Exenatide immediate-release supplied as 250 mcg/mL, 1.2 mL for the 5-mcg prefilled pen, and 2.4 mL for the 10-mcg/dose prefilled pen. Exenatide extended-release supplied as prefilled pen-injector. Lixisenatide supplied in 10 and 20 mcg pen-injector starter kit and 20-mcg pen-injector for maintenance use. Liraglutide supplied in 6 mg/3 mL prefilled pen, which can be dialed to desired dose of 0.6, 1.2, or 1.8 mg. Dulaglutide supplied in 0.75-, 1.5-, 3.0-, and 4.5-mg single-dose pen. Semgalutide supplied in 2 mg/1.5 mL prefilled pen which can be dialed to desired dose of 0.25 or 5 mg in one pen or in 4 mg/3 mL prefilled pen for 1 mg dose.

[b] Generic not available in the United States.

N/A, not applicable; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

insulin sensitivity, likely a result of its effect on dopamine oscillations.[40] Main side effects include rhinitis, dizziness, asthenia, headache, sinusitis, constipation, and nausea. Contraindications include syncopal migraine and women who are nursing.[38]

▶ *Bile Acid Sequestrants*

Colesevelam is the only bile acid sequestrant currently approved as adjunctive therapy to improve glycemic control in conjunction with diet, exercise, and insulin or oral agents for treatment of T2DM, though rarely used. Drug–drug interactions are possible because of absorption and can be particularly important in patients who are taking levothyroxine, glyburide, oral contraceptives, phenytoin, warfarin, and digoxin. These medications should not be taken together, and should be separated by at least 4 hours before dosing colesevelam. Malabsorption of fat-soluble vitamins (A, D, E, and K) is also a concern.

▶ *Insulin*

Insulin is the one agent that can be used in all types of DM, has no specific maximum dose, and can be titrated to suit each individual patient's needs. **KEY CONCEPT** Insulin is the primary treatment to lower BG levels for patients with T1DM, and injected amylin can be added to decrease fluctuations in BG levels. An insulin treatment algorithm for T2DM is found in Figure 44–3.[28]

Insulin can be divided into two main classes, basal and bolus (prandial), based on length of action to mimic endogenous insulin physiology. Most formulations are available as U-100, indicating a concentration of 100 U/mL, though more concentrated insulin formulations have become available in recent years including 200 U/mL (insulin degludec and insulin lispro) and 300 U/mL (insulin glargine), which join the older 500 U/mL regular insulin traditionally available.[38,39] Insulin is typically refrigerated, though most products are stable for 28 days at room temperature.[38] Available insulins are listed in Table 44–11.[38,39,53]

The most common route of insulin administration is subcutaneous injection using a syringe or pen device. Patients should be educated to rotate injection sites to minimize lipohypertrophy, a buildup of fat that decreases or prevents proper insulin absorption. Additionally, patients should understand that absorption rate may vary among injection sites (abdomen, thigh, arm, and buttocks) because of differences in blood flow, with absorption occurring fastest in the abdomen and slowest in the buttocks.

Both insulin syringes and pens are available with shorter needles (4–6 mm) that do not require the patient to pinch up their skin before injecting. With the no pinch technique, the needle is injected straight in at a 90-degree angle until flush with the skin. These products require a 10-second count to allow time for insulin to be injected.

Bolus (Prandial) Insulins

Regular Regular insulin is unmodified crystalline insulin commonly referred to as natural or human insulin. It is a clear solution with a relatively short onset and duration of action and designed to cover insulin response to meals. On subcutaneous injection, regular insulin forms small aggregates called hexamers that undergo conversion to dimers followed by monomers before systemic absorption can occur. Patients should be counseled to inject regular insulin subcutaneously 30 minutes before consuming a meal. Regular insulin, insulin lispro (100 U/mL), insulin aspart, and insulin glulisine can be administered intravenously (IV).

Rapid-Acting Three rapid-acting injectable insulins have been approved in the United States: aspart, glulisine, and lispro (available as 100 and 200 U/mL). Substitution of one or two amino acids in regular insulin results in the unique pharmacokinetic properties characteristic of these agents. Onset of action of injectable rapid-acting insulins (typically dosed 15 minutes before or immediately prior to meals) varies from 15 to 30 minutes, with peak effects occurring 1 to 2 hours after administration. A unique formulation of niacinamide added to insulin lispro allows for a slightly faster onset of action for this specific product. An inhaled rapid-acting insulin is also available, with peak effect expected to occur around 12 to 15 minutes following a dose and duration of action of approximately 2.5 to 3 hours.

Basal Insulins

Intermediate-Duration NPH insulin is prepared by a process in which protamine is conjugated with regular insulin, rendering a product with delayed onset but extended duration of action. It is designed to cover insulin requirements in between meals and/or overnight. With the advent of the long-acting insulins, NPH insulin use has declined because of (a) an inability to accurately predict when peak effects occur, and (b) a duration of action of less than 24 hours. Additionally, protamine is a foreign protein that may increase the possibility of an allergic reaction.

NPH insulin can be mixed with regular insulin and used immediately or stored for future use. NPH insulin can be mixed with either aspart or lispro insulins, but it must be injected immediately after mixing. Whenever mixing insulin products with NPH insulin, the shorter acting insulin should be drawn into the syringe first.

When utilized in the 500 U/mL (U-500) concentration, regular insulin takes on a different pharmacokinetic/pharmacodynamic profile than when utilized in the 100 U/mL concentration.[38,53] While its onset of action remains about 30 minutes post injection, its duration of action extends to be more similar to that of NPH. Insulin regular U-500 is now available in a pen device to improve patient safety.[53] The pen device dials in 5-unit increments and takes care of dosing conversion for the patient, meaning the dose displayed in the pen window is the actual number of units being delivered. Capable of delivering a single dose of up to 300 U at one time, a single pen holds 1500 U total.

Long-Duration Glargine, detemir, and degludec are designed as once-daily-dosing basal insulins that provide a relatively constant insulin concentration over 24 hours.[38,39] Insulin glargine differs from regular insulin by three amino acids, resulting in a low solubility at physiologic pH. The clear solution is supplied at a pH of 4, which precipitates on subcutaneous administration. Detemir binds to albumin in the plasma, which gives it sustained action. Neither glargine nor detemir completely mimic physiological insulin since, when delivered at high doses, a peak occurs and, when delivered at low doses, the dose may not cover 24 hours.

Insulin glargine at a higher concentration of 300 U/mL (U-300) forms a depot with a smaller surface area which creates a more prolonged release than the 100 U/mL (U-100) formulation and a flatter pharmacokinetic/pharmacodynamic response curve. U-300 has been found to result in fewer episodes of hypoglycemia including nocturnal hypoglycemia and decreased weight gain compared with U-100 glargine. Duration of action for U-300 glargine is approximately 36 hours, about 12 hours longer than the U-100 product. Insulin glargine U-300 is available in a pen device which delivers up to 80 U in a single injection or 160 U, depending on the specific product.[38] The pen window displays actual units delivered, meaning no dosing conversion is required. Insulin should not be transferred from the pen to a syringe as incorrect dosing and subsequent adverse effects can occur.

Table 44–11

Insulin Agents for Treatment of Type 1 and Type 2 Diabetes Mellitus[38,39,53]

Generic Name (Insulin)	Brand/Rx Status	Strength	Onset	Peak (hours)	Duration (hours)	Administration Options
Ultra–rapid-acting Insulin						
Aspart with niacinamide	Fiasp/Rx	U-100	15–20 minutes	1.5–2	5–7	CSII, IV, SC; 10-mL vial; 3-mL cartridge and FlexTouch disposable pen
Recombinant human insulin regular	Afrezza/Rx	Not applicable	12–15 minutes	1	1.5–3	Inh; Technosphere insulin particles for oral inhalation; 4, 8, and 12 U as cartridges
Rapid-acting Insulin						
Lispro	Humalog/Rx	U-100, U-200	15–30 minutes	0.5–1.5	3–4	CSII, IV, SC; 3-mL and 10-mL vial, 3-mL cartridge, and KwikPen disposable pen
	Admelog/Rx	U-100				CSII, IV, SC; 3-mL and 10-mL vial; 3-mL SoloStar disposable pen
Lispro-aabc	Lyumjev/Rx	U-100, U-200	15–30 minutes	0.5-1.5	4-7	IV, SC; 10-mL vial, 3-mL cartridge and KwikPen disposable pen
Aspart	Novolog/Rx	U-100	15–30 minutes	0.5-1.5	3–5	CSII, IV, SC; 10-mL vial, 3-mL cartridge, and FlexPen disposable pen
Glulisine	Apidra/Rx	U-100	15–30 minutes	1–2	3–4	CSII, IV, SC; 10-mL vial, 3-mL SoloStar disposable pen
Short-acting Insulin						
Regular	Humulin R/OTC	U-100, U-500	30–60 minutes	2–4	5–8	CSII, IV, SC; U-100 10-mL vial; U-500 20-mL vial and 3-mL KwikPen disposable pen
	Novolin R/OTC	U-100				CSII, IV, SC; 10-mL vial, 3-mL cartridge, 3-mL *Innolet*
Intermediate-acting Insulin						
Neutral protamine Hagedorn	Humulin N/OTC	U-100	2–4 hours	4–10	10–24	SC; 10-mL vial, 3-mL cartridge
	Novolin N/OTC	U-100				SC; 10-mL vial, 3-mL cartridge, 3-mL *InnoLet*
Long-acting Insulin						
Glargine	Lantus/Rx	U-100	2–4 hours	Flat	20–24	SC; 10-mL vial, 3-mL SoloSTAR disposable pen
	Toujeo/Rx	U-300	6 hours	Flat	36	SC;1.5-mL SoloStar disposable pen
	Toujeo Max/Rx	U-300				SC; 3-mL SoloStar disposable pen
	Basaglar/Rx	U-100	2–4 hours	Flat	20–24	SC; 3-mL KwikPen disposable pen
	Semglee/Rx	U-100	1–3 hours	Flat	≥ 24	SC; 10-mLvial, 3-mL disposable pen
Detemir	Levemir/Rx	U-100	1.5–4 hours	6-14	16-20	SC; 10-mL vial, 3-mL FlexTouch disposable pen
Degludec	Tresiba/Rx	U-100, U-200	1 hour	Flat	42	SC; 3-mL disposable FlexTouch pen
Combination Insulin Products						
Neutral protamine Hagedorn and regular	Humulin 70/30/OTC	U-100	30–60 minutes	1.5–16	10–16	SC: 10-mL vial, 3-mL KwikPen disposable pen
	Novolin 70/30/OTC	U-100	30–60 minutes	2–12	10–16	SC; 10-mL vial, 3-mL FlexPen disposable pen
Neutral protamine lispro and lispro	Humalog Mix 75/25/Rx	U-100	15–30 minutes	1–6.5	15–18	SC; 10-mL vial, 3-mL KwikPen disposable pen
	Humalog Mix 50/50/Rx	U-100				SC; 10-mL vial, 3-mL KwikPen disposable pen
Neutral protamine aspart and aspart	Novolog Mix 70/30/Rx	U-100	15–30 minutes	1–4	Up to 24	SC; 10-mL vial, 3-mL cartridge, 3-mL FlexPen disposable pen
Combination Insulin GLP-1 Agonist Products						
Degludec and liraglutide	Xultophy/Rx	U-100 degludec/ 3.6 mg/mL liraglutide	N/A	N/A	N/A	SC; 3-mL pen-injector
Glargine and lixisenatide	Soliqua/Rx	U-100 glargine/ 33 mcg/mL liraglutide	N/A	N/A	N/A	SC; 3-mL pen-injector

CSII, continuous subcutaneous insulin infusion; GLP-1, glucagon like peptide; Inh, inhalation; IV, intravenous; N/A, not applicable; OTC, over-the-counter; Rx, prescription required; SC, subcutaneous.

Further search for a more physiologically perfect basal insulin led to development of degludec.[54] A modified B chain analogue which forms multihexamers when injected, insulin degludec provides a flatter pharmacokinetic/pharmacodynamic profile than detemir or glargine. Zinc molecules, present in the hexamers, slowly diffuse allowing insulin monomers to be absorbed. This ultraslow insulin release allows degludec to have a half-life of 25 hours and duration of action exceeding 42 hours. Though still recommended for daily dosing at the same time each day, degludec's long duration of action means patients taking it can miss or delay a dose as long as they keep an 8-hour interval between any two doses.

Combination Products A number of combination insulin products are available commercially.[38,39] These combination products allow some patients to manage their insulin therapy with only two injections per day, avoiding the difficulty and possible errors that can occur when manually mixing insulins. NPH is available in a combination of 70/30 (70% NPH and 30% regular insulin). Three short-acting insulin analog mixtures are also available. Humalog mix 75/25 contains 75% neutral protamine lispro suspension and 25% insulin lispro. Novolog mix 70/30 contains 70% insulin aspart protamine suspension and 30% insulin aspart. Humalog mix 50/50 contains 50% neutral protamine lispro and 50% lispro. The lispro and aspart insulin protamine suspensions were developed specifically for these mixture products and are not commercially available separately.

General Insulin Treatment Strategy

Over time, patients with T2DM may require initiation of insulin therapy to better control BG.[22,28] Basal insulin should be initiated first, generally at 10 U once daily or with a starting dose of 0.1 to 0.2 U/kg/day (see Figure 44–3). Doses should be individualized and titrated to control blood glucose. Prandial insulin may be considered when FBG is at or near goal, yet the A_{1c} remains elevated. GLP-1 RA therapy should be considered prior to prandial insulin if the patient is not already on this therapy. Adjustment of insulin doses will then depend on fasting and postprandial BG levels.

Insulin Pump Therapy Insulin pump therapy consists of a programmable infusion device that allows for basal infusion of insulin 24 hours daily (see Figure 44–1), as well as bolus administration before meals and snacks.[40] Optimal insulin dosing allows for 50% of the total daily dose of insulin to be delivered as a basal dose, with the remaining 50% divided into prandial doses. Regular or rapid-acting insulin is delivered from a reservoir either by infusion set tubing or through a small canula, though rapid-acting insulin is more commonly used. Most pump infusion sets are inserted in the abdomen, arm, or other infusion site by a small needle. Most patients prefer insertion in abdominal tissue because this site provides optimal insulin absorption. However, they must rotate sites to avoid development of scar tissue. Infusion sets should be changed every 2 to 3 days to reduce the possibility of infection.

Patients use a carbohydrate-to-insulin ratio to determine how many units of insulin are required. More specifically, an individual's ratio is calculated to determine how many units of the specific insulin being used in the pump "covers" for a certain amount of carbohydrates to be ingested at a particular meal. Generally, the carbohydrate-to-insulin ratio can be calculated by dividing 550 by the total daily dose of insulin. Once this ratio is determined, patients can eat more or fewer carbohydrates at a given meal and adjust the bolus dose accordingly.

In addition to mealtime boluses, correction doses (also known as the correction factor) based on premeal glucose readings are also used. The amount of additional insulin for the correction is based on dividing 1650 by the total daily dose of insulin. The resulting value will represent the reduction in glucose (mg/dL [multiplying the resulting value by 0.0555 will give the corresponding result in mmol/L]) produced by one unit of insulin. The correction dose would be given in addition to the bolus dose needed based on the patient's carbohydrate-to-insulin ratio and amount of carbohydrates present in the meal he or she is about to consume. These calculations are just estimates, as there are no set guidelines for determining these doses. A patient's correction factor and carbohydrate-to-insulin ratio may change over time and can be readjusted based on glycemic values.

Insulin pump therapy may be used to lower BG levels in any type of DM; however, patients must be on multiple daily insulin injections, and therefore, patients with T1DM are always candidates and those with T2DM are sometimes candidates to use these devices. Use of an insulin pump may improve BG levels, reduce wide fluctuations in BG levels, and allow individuals to have more flexibility in timing and content of meals and exercise schedules, resulting in improved quality of life.

▸ *Noninsulin Injectable Agents*

Amylin Pramlintide acetate is a synthetic analog of human amylin, which is a naturally occurring neuroendocrine peptide cosecreted with insulin by the β-cells of the pancreas in response to food.[38,39] Amylin secretion is very low or completely deficient in patients with T1DM and lower than normal in patients with T2DM who require insulin. Pramlintide slows gastric emptying without altering absorption of nutrients, suppresses glucagon secretion, and leads to reduction in food intake by increasing satiety. By slowing gastric emptying, the normal initial postmeal spike in BG is reduced.

Pramlintide is given by subcutaneous injection before meals to lower postprandial BG elevations in patients with types 1 or 2 DM. This generally results in an additional A_{1c} reduction of 0.4% to 0.5% (0.004–0.005; 4–5 mmol/mol Hgb).[38] Hypoglycemia, nausea, and vomiting are the most common side effects encountered with pramlintide therapy, although pramlintide itself does not produce hypoglycemia. To decrease risk of hypoglycemia, doses of short-acting, rapid-acting, or premixed insulins should be reduced by 30% to 50% before pramlintide is initiated. Primarily, the kidneys metabolize pramlintide, but dosage adjustments in liver or kidney impairment are not required.

Pramlintide has the potential to delay absorption of orally administered medications. When rapid absorption is needed for the efficacy of an agent, pramlintide should be administered 1 hour after or 3 hours before the drug. Pramlintide should not be used in patients receiving medications that alter GI motility.

Treatment of Concomitant Conditions

The ADA standards of medical care address many of the common comorbid conditions, as well as complications that result from progression of DM.

▸ *Cardiovascular Health*

Cardiovascular disease is the major cause of morbidity and mortality for patients with DM. Interventions targeting smoking cessation, BP control, lipid management, antiplatelet therapy, and lifestyle changes (including diet and exercise) can reduce risk of cardiovascular events and should be considered important as glycemic control in management of a patient with DM. All patients with a history of cardiovascular disease should be prescribed aspirin 75 to 162 mg/day as a secondary prevention strategy.[23] Clopidogrel is an option for patients with atherosclerosis who are allergic to aspirin. The ADA currently recommends antiplatelet therapy be considered for patients with DM and no history of heart disease if patient is 50 years of age or older and has at least one additional cardiovascular risk factor including family history of premature ASCVD, hypertension, dyslipidemia, smoking, or albuminuria.[23]

Results of a number of trials, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD),[55] Action in Diabetes and Vascular Disease (ADVANCE),[56] and Veterans Affairs Diabetes Trial (VADT)[57] taken together with long-term follow-up information from the UKPDS[58] and DCCT[59,60] trials, have been used to formulate conclusions regarding the effect of glucose lowering on cardiovascular health. Those conclusions are (1) short-term (3–5 years) intensive glycemic control does not improve the risk of macrovascular complications in patients with long-standing T2DM; and (2) a decrease in macrovascular risk from improved glycemic control may take more than a decade to be realized. Because of the results of these trials, the A_{1c} goal used for most patients with T2DM is less than 7% (0.07; 53 mmol/mol Hgb), whereas a goal of less than or equal to 6.5% (0.065; 48 mmol/mol Hgb) may be used for otherwise healthy individuals without cardiovascular disease who are thought to be early in the course of their DM and controlled with lifestyle or metformin only and who have a long life expectancy.[20,22] A more relaxed target of less than 8% (0.08; 64 mmol/mol Hgb) may be employed for those who are older, have numerous medical conditions limiting life expectancy, are at increased risk for hypoglycemia, or have had T2DM for a long period of time.[20]

The FDA mandated in 2008 that CVOTs be completed for all new medications approved for treatment of T2DM.[23] As a result, drugs in the newest classes of glucose-lowering medications have been studied specifically for their outcomes on cardiovascular health, and findings of those clinical trials are now informing the newest ADA guidelines relative to selection of these agents for patients with certain comorbid conditions. Specific recommendations include: patients with T2DM and ASCVD or known kidney disease should be considered for therapy with a SGLT2 inhibitor or GLP-1 RA with demonstrated cardiovascular benefit (ie, empagliflozin, canagliflozin, liraglutide, injectable semaglutide, or dulaglutide) as part of their glucose-lowering drug therapy;[23] and patients with T2DM and low ejection fraction heart failure may be considered preferentially for a SGLT2 inhibitor with proven benefit in this population (ie, dapagliflozin or empagliflozin though class effect possible) to reduce risk of worsening heart failure and cardiovascular death.[23]

▶ *Dyslipidemia*

The ADA guidelines recommend obtaining a lipid profile at the time of diabetes diagnosis, at least every 5 years if under age 40, and when otherwise indicated (ie, at statin initiation, 4–12 weeks after statin initiation or dose change, and annually thereafter).[23] The ADA guidelines also outline specific dyslipidemia pharmacotherapy recommendations for those with DM including, but not limited to:[23]

1. Patients with diabetes and known ASCVD are recommended to receive high-intensity statin.
2. It may be reasonable to initiate statin therapy in patients with diabetes who are only 20 to 39 years old but have other ASCVD risk factors.
3. Patients with diabetes aged 40 to 75 years and without ASCVD are recommended to receive a moderate-intensity statin. A high-intensity statin might be considered for these patients if they are between 50 and 70 years of age and have multiple ASCVD risk factors.

Refer to Chapter 13, "Dyslipidemias," for additional information.

▶ *Hypertension*

KEY CONCEPT Uncontrolled BP plays a major role in development of macrovascular events and microvascular complications, including retinopathy, nephropathy, and erectile dysfunction, in patients with DM.[23] The ADA guidelines set BP goals based on risk, recommending a goal of less than 130/80 mm Hg for those with a 10-year ASCVD risk of greater than or equal to 15% and a goal of less than 140/90 mm Hg for those with 10-year ASCVD risk less than 15%.[23] Prompt initiation and appropriate titration of antihypertensive drug therapy is recommended in patients with BP greater than or equal to 140/90 mm Hg.[23] Various first-line antihypertensive agents can be utilized in patients with diabetes including thiazide-like diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and calcium channel blockers.[23] However, when albuminuria is present, ACE inhibitors or ARBs are recommended because of their beneficial effects on renal function.[23]

Treatment of Acute Complications

▶ *Hypoglycemia*

Hypoglycemia, or low blood sugar, can be defined by the glucose alert value of less than or equal to 70 mg/dL (3.9 mmol/L).[27] Typical symptoms of hypoglycemia include shakiness, sweating, fatigue, hunger, headaches, and confusion. Causes of hypoglycemia include delayed or inadequate amounts of food intake,

Patient Encounter Part 2: Follow-Up Visit

The patient returns 1 week later with results from her fasting blood work. The provider also requests an FBG, A_{1c}, and vitals at today's visit. Results are listed below.

VS: BP 138/78 mm Hg, P 76 beats/min, RR 17 breaths/min, T 36.8°C (98.2°F)

A_{1c} (today): 7.9% (0.079; 63 mmol/mol Hgb)

FPG (today): 178 mg/dL (9.9 mmol/L)

Labs (2 days ago): Na 135 mEq/L (mmol/L); K 4.0 mEq/L (mmol/L); Cl 98 mEq/L (mmol/L); CO_2 24 mEq/L (mmol/L); blood urea nitrogen (BUN) 15 mg/dL (5.4 mmol/L); SCr 0.8 mg/dL (71 µmol/L); BG 186 mg/dL (10.3 mmol/L)
The patient is diagnosed with T2DM.

Identify the goals of treatment for this patient.

What nonpharmacologic alternatives are available for this patient for her diabetes?

What are the three general categories of pharmacologic alternatives used to lower blood glucose?

What is the most appropriate initial therapy for this patient in regard to her diabetes?

What additional interventions are recommended for this patient today?

especially carbohydrates, excessive doses of medications (eg, sulfonylureas, insulin), exercising when insulin doses are reaching peak effect, or inadequately adjusted drug therapy in patients with impaired renal or hepatic function. Patients experiencing symptoms of hypoglycemia should check their BG level, consume 15 g of carbohydrate, wait 15 minutes for symptom resolution, and retest.[61] Examples of 15 g of carbohydrate may include a small box of raisins, 4 oz (approximately 120 mL) of orange juice, 8 oz (approximately 240 mL) of skim milk, or three to four glucose tablets. In patients receiving an α-glucosidase inhibitor, hypoglycemia should be treated with glucose tablets or skim milk. For patients with hypoglycemia experiencing a loss of consciousness, a glucagon emergency kit should be administered by the intramuscular (IM) or subcutaneous route. It is important to contact emergency medical personnel in this situation. The patient should be rolled onto their side as many injected with glucagon vomit.

Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State (HHS)

DKA is a reversible but potentially life-threatening medical emergency that results from a deficiency in insulin. Without insulin, the body cannot use glucose and must obtain energy via lipolysis. This produces ketones and acidosis. Precipitating factors include infection and the omission or inadequate administration of insulin.[62] Signs and symptoms develop rapidly within 1 day or so and commonly include fruity or acetone breath, nausea, vomiting, dehydration, polydipsia, polyuria, and deep, rapid breathing.

Hallmark diagnostic criteria for DKA include hyperglycemia (greater than 250 mg/dL [13.9 mmol/L]), moderate ketonuria or ketonemia with bicarbonate less than or equal to 15 mEq/L [mmol/L], and acidosis (arterial pH less than or equal to 7.3).[62] Serum sodium is usually low due to extracellular movement of water. A corrected sodium (addition of 1.6 mEq/L [mmol/L] for every 100 mg/dL [5.6 mmol/L] of glucose above 100 mg/dL [5.6 mmol/L]) should be calculated to assess the true sodium and water deficit.[62] Serum potassium is typically elevated due to an extracellular shift brought on by insulin deficiency.[62]

DKA severity depends on magnitude of the decrease in arterial pH, serum bicarbonate levels, and mental state rather than magnitude of hyperglycemia. Treatment goals of DKA consist of reversing the underlying metabolic abnormalities, rehydrating the patient, and normalizing serum glucose. Fluid replacement with normal saline at 1 to 1.5 L/hour for the first hour is recommended to rehydrate the patient and ensure the kidneys are perfused.[62]

Potassium and other electrolytes are supplemented as indicated by laboratory assessment. Use of sodium bicarbonate in DKA is controversial and generally only recommended when the pH is less than 6.9.[62] Regular insulin at 0.1 U/kg/hour by continuous IV infusion is the preferred treatment in DKA to regain metabolic control rapidly.[62] When plasma glucose values drop below 250 mg/dL (13.9 mmol/L), dextrose 5% should be added to IV fluids.[62] During the recovery period, it is recommended to continue administering insulin and allow patients to eat as soon as possible. Dietary carbohydrates combined with insulin assist in clearance of ketones. See Table 44–12 for DKA management.[62]

HHS is a life-threatening condition similar to DKA that also arises from inadequate insulin, but HHS occurs primarily in older patients with T2DM. DKA and HHS also differ in that HHS lacks the ketonemia and acidosis associated with DKA. Key diagnostic criteria for HHS are a plasma glucose value of greater than 600 mg/dL (33.3 mmol/L), arterial pH greater than 7.3, serum bicarbonate greater than 15 mEq/L (mmol/L), and minimal ketonuria and ketonemia.[62] Similar to DKA, treatment of HHS consists of aggressive rehydration, correction of electrolyte imbalances, and continuous insulin infusion to normalize serum glucose. BG levels should be reduced gradually to minimize risk of cerebral edema.

Table 44–12

Management of Diabetic Ketoacidosis[62]

1. Confirm diagnosis (increased plasma glucose, positive serum ketones, metabolic acidosis).
2. Admit to hospital; intensive care setting may be necessary for frequent monitoring or if pH < 7 or unconscious.
3. Assess serum electrolytes (K^+, Na^+, Mg^{2+}, Cl^-, bicarbonate, phosphate), acid–base status—pH, HCO_3^-, PCO_2, β-hydroxybutyrate, and renal function (creatinine, urine output).
4. Replace fluids: 0.9% saline 1 L/hour over first 1–3 hours; subsequently, 0.45% saline at 4–14 mL/kg/hour; change to 5% dextrose with 0.45% saline when plasma glucose reaches 250 mg/dL (13.9 mmol/L).
5. Administer regular insulin: IV (0.15 U/kg bolus followed by 0.1 unit/kg/hour infusion); check glucose hourly and double insulin infusion until glucose level falls at steady hourly rate of 50–70 mg/dL (2.8–3.9 mmol/L). Alternatively, could use SC or IM routes, although dosing regimen different. If initial serum potassium is < 3.3 mEq/L (mmol/L), do not administer insulin until the potassium is corrected to > 3.3 mEq/L (mmol/L).
6. Assess patient: What precipitated the episode (eg, nonadherence, infection, trauma, infarction, cocaine)? Initiate appropriate workup for precipitating event (cultures, chest X-ray, ECG).
7. Measure chemistry (especially K^+, bicarbonate, phosphate, and anion gap) every 2–4 hours until stable.
8. Replace K^+: If K^+ is < 3.3 mEq/L (mmol/L), hold insulin and give 40 mEq (mmol) of K^+ per liter of IV fluid. If K^+ is > 5 mEq/L (mmol/L), do not give K^+ but check level every 2 hours. When K^+ > 3.3 mEq/L (mmol/L) but < 5 mEq/L (mmol/L), ECG normal, urine flow and normal creatinine documented, administer 20–30 mEq/L (mmol/L) of IV fluid to maintain K^+ at 4–5 mEq/L (mmol/L).
9. Continue the previous step until patient is stable, glucose goal is 150–250 mg/dL (8.3–13.9 mmol/L), and acidosis is resolved. Insulin infusion may be decreased to 0.05–0.1 U/kg/hour.
10. Administer intermediate- or long-acting insulin as soon as patient is eating. Allow for overlap in insulin infusion and SC insulin injection.

Cl, chloride; ECG, electrocardiogram; HCO_3, serum bicarbonate; IM, intramuscular; IV, intravenous; K, potassium; Mg, magnesium; Na, sodium; PCO_2, partial pressure of carbon dioxide in the arterial blood; SC, subcutaneous.

Treatment of Long-Term Complications

Retinopathy

Diabetic retinopathy occurs when the microvasculature that supplies blood to the retina becomes damaged. This damage permits leakage of blood components through the vessel walls. The ADA recommends that patients with T2DM receive a dilated eye examination at the time of diagnosis by an ophthalmologist or optometrist.[24] Examinations should begin within 5 years of diagnosis of T1DM.[24] Once one or more normal examinations occur, dilated eye examination is recommended to be repeated at least every 2 years.[24] In patients with any level of documented retinopathy, an annual dilated eye examination is recommended.[24] Glucose and BP control are the best strategies for decreasing risk and slowing progression of retinopathy.

▶ *Neuropathy*

KEY CONCEPT Peripheral neuropathy is a possible complication of DM. The most common types of peripheral neuropathy include chronic sensorimotor distal peripheral neuropathy, which can cause pain, tingling, and numbness in the feet and hands, and autonomic neuropathy, which can lead to hypotension, gastroparesis, sexual dysfunction, and autonomic failure in response to hypoglycemia. The ADA recommends use of pregabalin, duloxetine, or gabapentin as first-line pharmacologic treatment for neuropathic pain.[24] Optimization of glucose control is key to prevention and slowing progression of neuropathy.

▶ *Microalbuminuria and Nephropathy*

DM is a leading contributor to end-stage renal disease. Early evidence of nephropathy is presence of albumin in the urine. Therefore, as the disease progresses, larger amounts of protein spill into the urine. The ADA recommends urine protein tests annually in T2DM patients.[24] For patients with T1DM, annual urine protein testing should begin 5 years after diagnosis of diabetes.[24] The most common form of screening for protein in the urine is a random collection for measurement of the urine albumin-to-creatinine ratio. The desirable value is less than 30 mcg of albumin per milligram of creatinine (3.4 mg/mmol creatinine).[24] There is high variability between measurements of urinary albumin excretion. As such, the ADA recommends that two out of three albumin-to-creatinine ratios, collected over a 3- to 6-month period, be abnormal before considering the patient to have high (traditionally referred to as microalbuminuria and defined as between 30 and less than 299 mcg of albumin per milligram of creatinine [3.4–33.8 mg/mmol creatinine]) or very high (defined as greater than or equal to 300 mcg of albumin per milligram of creatinine [34 mg/mmol creatinine]) albuminuria.[24]

Glycemic and BP control are primary measures for prevention of progression of nephropathy. Patients with T2DM and kidney disease related to DM, whose estimated glomerular filtration rate remains greater than or equal to 30 mL/min/1.73 m^2, and whose urinary albumin-to-creatinine ratio is greater than 30 mcg of albumin per milligram of creatinine (3.4 mg/mmol creatinine), should be considered for therapy with a SGLT2 inhibitor to reduce risk for kidney disease progression, cardiac events, or both.[24] Patients with CKD at increased risk for cardiac events may be considered for therapy with a GLP-1 RA to reduce risk of subsequent cardiac events, progression of albuminuria, or both.[24] Either an ACE inhibitor or ARB is recommended for nonpregnant patients with diabetes and hypertension who have modest or high urinary albumin-to-creatinine ratio and/or an eGFR rate less than 60 mL/min/1.73 m^2.[24] Treatment of advanced nephropathy includes dialysis and kidney transplantation and patients with an eGFR less than 30 mL/min/1.73 m^2 should be referred to a nephrologist.[24]

▶ *Foot Ulcers*

KEY CONCEPT Lower extremity amputations are one of the most feared and disabling sequelae of long-term uncontrolled DM. A foot ulcer is an open sore that develops and penetrates to the subcutaneous tissues. Complications of the feet develop primarily as a result of peripheral arterial disease (PAD), neuropathies, and foot deformations.

Patient Encounter Part 3: Follow-Up

The patient returns in 3 months for a follow-up visit. She brings her BG readings from the past week for review in addition to more fasting blood work. BG readings are in units of mg/dL (or mmol/L). Her most recent medication list is below. There are no changes to her health record from previous visits.

Allergies: Amoxicillin

Meds: Hydrochlorothiazide 25 mg daily; ibuprofen 400 mg PRN headache; metformin 1000 mg by mouth twice daily

VS: BP 150/92 mm Hg, P 82 beats/min, RR 16 breaths/min, T 36.5°C (97.7°F)

Labs: Total cholesterol 235 mg/dL (6.08 mmol/L); HDL cholesterol 39 mg/dL (1.01 mmol/L); LDL cholesterol 158 mg/dL (4.09 mmol/L); triglycerides 191 mg/dL (2.16 mmol/L); aspartate aminotransferase (AST) 24 U/L (0.40 μkat/L); alanine aminotransferase (ALT) 35 U/L (0.58 μkat/L); A_{1c} 7.5% (0.075; 58 mmol/mol Hgb)

Day	Fasting	2-hour Postprandial
Monday	129 (7.2)	178 (9.9)
Tuesday	122 (6.8)	195 (10.8)
Wednesday	118 (6.5)	182 (10.1)
Thursday	101 (5.6)	164 (9.1)
Friday	112 (6.2)	221 (12.3)
Saturday	132 (7.3)	284 (15.8)
Sunday	136 (7.5)	262 (14.5)

Are this patient's blood glucose levels within target? What pattern seems to be established?

Which classes of antidiabetic drugs act in a manner that would specifically correct the undesirable glucose pattern?

What if the patient had a history of ASCVD or heart failure? Which antidiabetic drugs would be preferred and why?

Based on the information available from this and previous encounters, develop a care plan for this patient including (a) identification and assessment of all drug-related needs and/or problems, (b) a detailed therapeutic plan to address each need and problem, and (c) monitoring parameters to assess safety and efficacy.

PAD causes ischemia to the lower limbs depriving the tissues of oxygen and nutrients and impairing the immune system from functioning adequately. Symptoms of PAD include intermittent claudication, cold feet, pain at rest, and loss of hair on the feet and toes. Smoking cessation is the most important treatment for PAD. Exercising by walking to the point of pain and then resting until pain subsides and resuming can be a vital therapy to maintain or improve the symptoms of PAD. Pharmacologic intervention with antiplatelet therapy (aspirin 160–325 mg/day or clopidogrel 75 mg/day) is indicated in PAD.[63] For those remaining symptomatic, cilostazol 100 mg twice daily may be useful to improve blood flow and reduce symptoms of PAD.[63]

Neuropathies play a large part in development of foot ulcers. To prevent complications, the ADA recommends daily visual examination of the feet and a comprehensive foot evaluation

Table 44–13

Macrovascular and Microvascular Complications Signs and Symptoms

	Complication	Signs and Symptoms
Macrovascular	Coronary heart disease	Stable or unstable angina pectoris, myocardial infarction, or dysrhythmias; however, many patients have unrecognizable symptoms.
	PAD	Exertional leg pain that can progress to pain at rest and ischemic ulcers. Most cases are asymptomatic.
	Cerebrovascular disease/Stroke	Sudden onset of a focal neurologic deficit such as facial droop, hemiparesis, or isolated weakness of an arm or leg. Dizziness, slurred speech, gait difficulties, and visual loss may also occur.
Microvascular	Retinopathy	Minimal until advanced disease ensues with loss or blurring of vision.
	Nephropathy	Hypertension, which often coincides with the development of microalbuminuria (persistent proteinuria).
	Neuropathy	Numbness, tingling, burning, muscle pain/cramps/weakness that often gets worse at night.
	Foot care (neuropathy and/or PAD)	Calluses and corns, tinea pedis, hammertoes, bunions, cracking of skin of the feet and heels.

PAD, peripheral arterial disease.

each year.[24] Sensory testing with a 10-gauge monofilament can detect neuropathy. Ulcer treatment consists of glycemic control, preventing infection, debriding dead tissues, applying dressings, treating edema, and limiting ambulation. Individuals with diabetes should wear properly fitted, cushioned footwear and padded socks. Table 44–13 provides a list of microvascular and macrovascular complications as well as their signs and symptoms.

Special Situations

▶ *Hospitalized Care*

Current recommendations call for critically ill patients to be started on IV insulin therapy at a threshold of 180 mg/dL (10.0 mmol/L).[27] A goal range of 140 to 180 mg/dL (7.8–10.0 mmol/L) is recommended for the majority of patients.[27] More stringent goals may be considered for selected critically ill postsurgical patients, but only if hypoglycemia can be avoided.[27] Scheduled subcutaneous insulin regimens with basal, bolus, and correction components are recommended for patients who are not critically ill.[27] Patients who required insulin during hospitalization but had previously not used insulin will need education/training to successfully transition home.

Patient Encounter Part 4: Insulin Therapy

The patient returns to the office for her quarterly checkup. It has been 8 years since she was first diagnosed with diabetes—she is now 50 years old. Her updated information is below. Her past medical and family histories are unchanged with the exception that her father passed away after a stroke 2 years ago. She states that she has been adherent to medications and lifestyle changes with the exception of physical activity. She has developed osteoarthritis in her knees and has more difficulty walking.

SH: Prior history of smoking one-half pack per day for 10 years, but quit 18 years ago; denies alcohol or illicit drug use

Allergies: Amoxicillin

Meds: Losartan-hydrochlorothiazide 100-25 mg by mouth once daily; atorvastatin 40 mg by mouth once daily; metformin 1000 mg by mouth twice daily; semaglutide 1 mg SC weekly; empagliflozin 25 mg daily; ibuprofen 400 mg PRN headache; multivitamin by mouth once daily

Meal History: Has been consuming approximately 30 to 45 g of carbohydrates per meal three times a day; saturated fat is limited to 12 g/day, and sodium is 2000 mg/day

Physical Activity: Was walking 4 or 5 days per week for 30 minutes at moderate intensity but has not done so recently due to arthritis

VS: BP 126/78 mm Hg, P 78 beats/min, RR 18 breaths/min, T 36.9°C (98.4°F), Ht 5′3″ (160 cm), Wt 162 lb (74 kg)

Labs: Na 139 mEq/L (mmol/L); K 4.8 mEq/L (mmol/L); Cl 103 mEq/L (mmol/L); CO_2 24 mEq/L (mmol/L); BUN 20 mg/dL (7.1 mmol/L); SCr 1.2 mg/dL (106 μmol/L); FPG 202 mg/dL (11.2 mmol/L); A1c 9.2% (0.092; 77 mmol/mol Hgb); AST 28 U/L (0.47 μkat/L); ALT 31 U/L (0.52 μkat/L)

Fasting lipid profile:

- Total cholesterol: 202 mg/dL (5.22 mmol/L)
- LDL cholesterol: 108 mg/dL (2.79 mmol/L)
- HDL cholesterol: 43 mg/dL (1.11 mmol/L)
- Triglycerides: 205 mg/dL (2.32 mmol/L)

What additional pharmacologic options are available for this patient to lower her blood glucose to goal?

Which insulin and starting dose would be most appropriate for this patient?

When should prandial insulin be considered?

What additional medications, screenings, labs, and/or referrals are recommended for the patient at this point?

What is an important lifestyle modification this patient still needs to make?

▶ *Sick Days*

Patients should monitor their BG levels more frequently during sick days because it is common for illness to increase

Patient Care Process

Collect Information:

- Review medical history.
- Perform medication history of prescription, over-the-counter, and herbal product use.
- Collect laboratory data including chemistry panel, A_{1c}, lipid panel, and albumin-to-creatinine ratio.
- Measure BP.
- Examine patient for development or progression of DM complications.
- Record SMBG, including FPG and postprandial levels.
- Interview patient to gather information related to quality-of-life measures such as physical, psychological, and social functioning and well-being.

Assess the Information:

- SMBG for glycemic control, including FPG and postprandial levels (see Table 44–6).
  - Are BG values too high or low?
  - Are there specific times of day or specific days not within glucose goals?
  - Is hypoglycemia occurring?
- Review laboratory data for attainment of goals (see Table 44–6). What goals are not being met?
- Are there any medication problems, including presence of adverse drug reactions, drug allergies, and drug interactions?
  - Is the patient taking medications that may affect glucose control?
- If patient is already receiving treatment for DM, has he/she been adherent to recommended lifestyle modifications and drug therapies? Is the patient having difficulty affording therapies?
- Assess patient for quality-of-life measures such as physical, psychological, and social functioning and well-being.

Develop a Care Plan:

- Recommend appropriate therapy and develop a plan to assess effectiveness (see Tables 44–7, 44–10, and 44–11, and Figures 44–2 and 44–3).

Implement the Care Plan:

- Stress adherence to prescribed lifestyle and medication regimen.
  - Ensure patient has prescription coverage and/or is able to afford prescribed regimen and self-care.
- Provide education on diabetes, lifestyle modifications, appropriate monitoring, and drug therapy:
  - Causes of DM complications and how to prevent them.
  - How diet and exercise can affect diabetes.
  - How to perform SMBG and what to do with the results.
  - When to take medications and what to expect, including adverse effects.
  - What warning sign(s) should be reported to the provider.
- What tests or referrals to other health-care team members are needed?

Follow-up: Monitor and Evaluate:

- Set follow-up for SMBG and tolerability/presence of adverse effects based on therapy chosen.
- Follow-up A_{1c} every 3 months until patient reaches goal, then every 6 months. See Table 44–6 for other monitoring parameters and frequency.
- Monitor for macrovascular and microvascular signs and symptoms (Table 44–13).

BG values.[64] Patients should check their glucose and urine for ketones every 4 hours when sick and when their BG levels are greater than 240 mg/dL (13.3 mmol/L).[65] Patients should continue to take their medications while sick.[66] T1DM patients may require additional insulin coverage, and some with T2DM who are currently on oral medication regimens may require insulin during an acute illness. Patients should be advised to maintain normal caloric and carbohydrate intake while ill as well as to drink plenty of noncaloric beverages to avoid dehydration.[64] When having difficulty eating a normal diet, patients may be advised to use nondiet beverages, sports drinks, broths, crackers, soups, and nondiet gelatins to provide normal caloric and carbohydrate intake and avoid hypoglycemia. With proper management, patients can decrease their chance of illness-induced hospitalization, particularly DKA and HHS.

OUTCOME EVALUATION

- **KEY CONCEPT** The success of therapy for DM is measured by the ability of the patient to manage disease appropriately between health-care provider visits.
- Appropriate therapy necessitates adequate patient education about the disease, development of a meal plan to which patients can comply, and integration of a regular exercise program.
- Patient care plans should include a number of daily evaluations to be performed by the patient, such as examining feet for any sores, cuts, or abrasions; checking skin for dryness to prevent cracking and chafing; and monitoring BG values as directed. Weekly appraisals of weight and BP are also advised.
- Until A_{1c} levels are at goal, quarterly visits with the patient's primary health-care provider are recommended. Table 44–6 summarizes specific ADA goals for therapy. The practitioner should review SMBG data and a current A_{1c} level for progress and address any therapeutic or educational issues.
- At a minimum, yearly laboratory evaluation of serum lipids, urinary albumin-to-creatinine ratio, and SCr should be performed.
- Appropriate monitoring and treatment for DM complications should occur (Table 44–13).

Abbreviations Introduced in This Chapter

A_{1c}	Hemoglobin A_{1c}
AACE	American Association of Clinical Endocrinologists
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	Angiotensin-converting enzyme
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease
ALT	Alanine aminotransferase
ARB	Angiotensin II receptor blocker
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BG	Blood glucose
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CKD	Chronic kidney disease
Cl	Chloride
CrCl	Creatinine clearance
CSII	Continuous subcutaneous insulin infusion
CVOTs	Cardiovascular outcomes trials
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase-4
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ER	Extended release
FBG	Fasting blood glucose
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GDM	Gestational diabetes mellitus
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide-1
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
HCO_3	Serum bicarbonate
HDL	High-density lipoprotein
HFrEF	Heart failure with reduced ejection fraction
Hgb	Hemoglobin
HHS	Hyperosmolar hyperglycemic state
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IM	Intramuscular
ISF	Interstitial fluid
IV	Intravenous
K	Potassium
LADA	Latent autoimmune diabetes in adults
LDL	Low-density lipoprotein
MACE	Major adverse cardiovascular events
Mg	Magnesium
MNT	Medical nutrition therapy
MODY	Maturity onset diabetes in the young
Na	Sodium
NGSP	National Glycohemoglobin Standardization Program
NPH	Neutral protamine Hagedorn
OGTT	Oral glucose tolerance test
OTC	Over-the-counter
PAD	Peripheral arterial disease
PCO_2	partial pressure of carbon dioxide
PPAR-γ	Peroxisome proliferator-activated receptor gamma
PPG	Postprandial glucose
SC	Subcutaneous
SCr	Serum creatinine
SGLT2	Sodium-dependent glucose cotransporter-2
SMBG	Self-monitoring of blood glucose
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TLC	Therapeutic lifestyle change
TZD	Thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study
ULN	Upper limit of normal
UTI	Urinary tract infection
VADT	Veterans Affairs Diabetes Trial
WHO	World Health Organization

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45

Thyroid Disorders

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Discuss the prevalence of common thyroid disorders, including mild and overt hypothyroidism and hyperthyroidism.
2. Explain the major components of the hypothalamic–pituitary–thyroid axis and interaction among these components.
3. Discuss the relationship between serum thyroid-stimulating hormone (TSH) levels and primary thyroid disease, and advantages for the use of TSH levels over other tests such as serum T_4 (thyroxine) and T_3 (triiodothyronine) levels.
4. Identify typical signs and symptoms of hypothyroidism and consequences of suboptimal treatment.
5. Describe clinical use of levothyroxine (LT_4) in the treatment of hypothyroidism.
6. Discuss issues regarding LT_4 product bioequivalence and reasons for maintaining patients on the same product.
7. Describe the management of hypothyroidism and hyperthyroidism in special populations, including pregnant women.
8. Identify typical signs and symptoms of Graves disease and consequences of inadequate treatment.
9. Discuss the pharmacotherapy of Graves disease, including advantages and disadvantages of antithyroid drugs versus radioactive iodine, adverse effects, and patient monitoring.
10. Describe potential effects of selected drugs including amiodarone, lithium, interferon-α, tyrosine kinase inhibitors (TKIs), and immune checkpoint inhibitors on thyroid function.

INTRODUCTION

Thyroid disorders are common, with more than 2 billion people or 38% of the world's population having iodine deficiency, resulting in 74 million people with goiter. Although overt iodine deficiency is not a significant problem in developed countries, a number of common thyroid conditions exist. The most common are hypothyroidism and hyperthyroidism, which often require long-term pharmacotherapy. Undetected or improperly treated thyroid disease can result in long-term adverse sequelae, including increased mortality. It is important that clinicians are aware of the prevalence of thyroid disorders, methods of identifying thyroid disorders, and appropriate therapy. This chapter focuses on the most common pharmacologically treated thyroid disorders.

EPIDEMIOLOGY

In iodine sufficient countries such as the United States, United Kingdom, and other Western European countries, overall prevalence of hypothyroidism ranges from 1% to 2%. More specifically, in the United States, overall prevalence of overt hypothyroidism ranges from 0.3% to 3.7% in various studies, depending on how hypothyroidism is defined and patient population studied. Prevalence increases with age, rising to 7% in people between 85 and 89 years.[1] Compared with the total population, people aged 50 to 79 years have an almost twofold higher prevalence, and those aged 80 years and older have a fivefold higher prevalence. Prevalence of hypothyroidism is similar in White and Hispanic patients but lower in those of African or Afro-Caribbean descent. Pregnant women have a higher prevalence of hypothyroidism than nonpregnant women across all races and ethnicities.

Prevalence of overt hyperthyroidism ranges from 0.2% to 1.3% in iodine-sufficient parts of the world. In the United States, overt hyperthyroidism was detected in 0.5% of the general population, while 0.7% had subclinical hyperthyroidism. The Colorado Thyroid Health Survey assessed thyroid function in 25,862 subjects attending a health fair.[2] Overall prevalence of an abnormal thyroid-stimulating hormone (TSH; thyrotropin) level was 11.7% of the study population, with 9.4% hypothyroid (9% subclinical) and 2.2% hyperthyroid (2.1% subclinical). Of the 916 subjects taking thyroid medication, 60% were euthyroid (had normal thyroid function or hormone activity), with an equal distribution between subclinical hypothyroidism and hyperthyroidism. These findings imply that many patients who are receiving thyroid medications are not being managed successfully.

PATHOPHYSIOLOGY

The thyroid gland is the largest endocrine gland in the body, residing in the neck anterior to the trachea between the cricoid cartilage and suprasternal notch. The thyroid gland produces two biologically active hormones, thyroxine (T_4) and triiodothyronine (T_3).

Thyroid hormones are essential for proper fetal growth and development, particularly of the central nervous system (CNS). After delivery, the primary role of thyroid hormone is in regulation of energy metabolism. Thyroid hormones can affect the function of virtually every organ in the body. The parafollicular C cells of the thyroid gland produce calcitonin.

T_4 and T_3 are produced by the organification of iodine in the thyroid gland. Iodine is actively transported into the thyroid follicular cells. This inorganic iodine is oxidized by thyroid peroxidase and covalently bound to tyrosine residues of thyroglobulin. These iodinated tyrosine residues, monoiodotyrosine and diiodotyrosine, couple to form T_4 and T_3. About 80% of thyroid hormone is synthesized as T_4 and stored in the thyroid bound to thyroglobulin. Thyroid hormones are released from the gland when needed, primarily under the influence of TSH, which is also known as thyrotropin, from the anterior pituitary. T_4 and T_3 are transported in the blood by three proteins, 70% bound to thyroid-binding globulin (TBG), 15% to transthyretin (thyroid-binding prealbumin), and 15% to albumin. T_4 is 99.97% protein bound and T_3 is 99.7% protein bound, with only the unbound or free fractions physiologically active. The high degree of protein binding results in a long half-life of these hormones: approximately 7 to 10 days for T_4 and 24 hours for T_3.

Most of the physiologic activity of thyroid hormones is from the actions of T_3. T_4 can be thought of primarily as a prohormone. About 80% of needed T_3 is derived from conversion of T_4 to T_3 in peripheral tissue under the influence of tissue deiodinases. These deiodinases allow end organs to produce the amount of T_3 needed to control local metabolic functions. These enzymes also catabolize T_3 and T_4 to biologically inactive metabolites.

KEY CONCEPT Production and release of thyroid hormones are regulated by the hypothalamic–pituitary–thyroid axis (Figure 45–1). Hypothalamic thyrotropin-releasing hormone (TRH) stimulates the release of TSH when there are physiologically inadequate levels of thyroid hormones. TSH promotes production and release of thyroid hormones. As circulating thyroid hormone levels rise to needed levels, negative feedback results in the decreased release of TSH and TRH. Release of TRH is also inhibited by somatostatin and its analogs, and the release of TSH can also be inhibited by dopamine, dopamine agonists, and high levels of glucocorticoids.

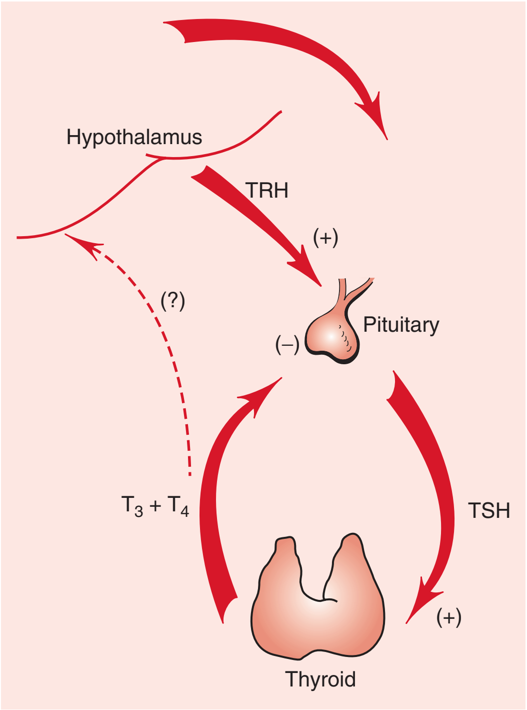

FIGURE 45–1. Hypothalamic–pituitary–thyroid axis. Thyrotropin-releasing hormone (TRH) is synthesized in the neurons within the paraventricular nucleus of the hypothalamus. TRH is released into the hypothalamic–pituitary portal circulation and carried to the pituitary, where it activates the pituitary to synthesize and release thyrotropin (TSH, or thyroid stimulating hormone). TSH activates the thyroid to stimulate the synthesis and secretion of thyroxine (T_4) and triiodothyronine (T_3). T_4 and T_3 inhibit TSH secretion, closing the feedback loop. Negative feedback from T_4 and T_3 to hypothalamic TRH is less certain, hence the question mark.

SPECTRUM OF THYROID DISEASE

There are two general modes of presentation for thyroid disorders: changes in size or shape of the gland and changes in secretion of hormone from the gland. In some cases, structural changes can result in changes in hormone secretion. Thyroid nodules and goiters in euthyroid patients are common problems. Patients with a goiter who are biochemically euthyroid do not often require specific pharmacotherapy, unless the goiter is caused by iodine deficiency. In developing countries, iodized salt is the primary therapy in treating goiter. Thyroid nodules, seen in 4% to 7% of adults, may be malignant, benign, and/or may autonomously secrete thyroid hormones. A discussion of thyroid nodules is beyond the scope of this chapter; however, thyroid cancer is discussed briefly in the context of levothyroxine (LT_4) suppressive therapy. Refer to other resources for a more extensive review of thyroid cancer management.

Changes in hormone secretion, often due to an underlying inflammatory disorder (thyroiditis), can result in hormone deficiency or excess. Although patients with overt hypothyroidism and hyperthyroidism may have dramatic signs and symptoms, most patients have subtle signs and symptoms that progress slowly over time. Availability of sensitive and specific biomarkers for the diagnosis of thyroid hormone disorders has facilitated screening and early case-finding and diagnosis, including in those with mild or subclinical thyroid disorders. Screening of newborns for congenital hypothyroidism has dramatically reduced incidence of permanent thyroid-related cognitive and developmental impairment and neonatal hypothyroidism in the United States. However, congenital hypothyroidism due to iodine deficiency remains a significant worldwide public health problem.

PATIENT ASSESSMENT AND MONITORING

Assessment of patients for thyroid disorders entails a history and physical examination. In many patients with mild or subclinical thyroid disease, there may be an absence of specific signs and symptoms, and physical examination findings may be normal. Various diagnostic tests can be used, including levels of serum thyroid hormone(s), TSH, thyroid antibody levels, and imaging techniques (Table 45–1). Laboratory assessment of patients with suspected thyroid disorders must be based on the continuum of disease from subclinical to mild to overt (Figure 45–2).

TSH Levels

KEY CONCEPT In most patients with thyroid hormone disorders, measurement of serum TSH level is adequate for initial screening and diagnosis of hypothyroidism and hyperthyroidism. Serum free thyroxine (FT_4) and triiodothyronine (FT_3) levels may be helpful

Table 45–1

Selected Thyroid Tests for Adults

Test	Reference Range	Comments
TSH	0.5–4.5 mIU/L (μIU/mL)	Gold standard; may be lowered by dopamine, dopamine agonists, glucocorticoids, octreotide, recovery from severe nonthyroidal illness
FT_4	0.7–1.9 ng/dL (9.0–24.5 pmol/L)	May be normal in mild thyroid disease
Anti-TPOAb, Anti-TGAb	Variable[a]	Present in autoimmune hypothyroidism; predicts more rapid progression from subclinical to overt hypothyroidism
TSI (TSHR-SAb)	< 1.3 (< 130%)	Confirms Graves disease

[a] Anti-TPOAb reference ranges are highly variable from one laboratory to another depending on the method used. Results greater than the upper cutoff are considered abnormal and are consistent with increased risk for autoimmune thyroid disease.

Anti-TGAb, antithyroglobulin antibody; Anti-TPOAb, antithyroid peroxidase antibody; FT_4, free T_4 (thyroxine); TSH, thyroid-stimulating hormone; TSHR-SAb, TSH receptor-stimulating antibodies; TSI, thyroid-stimulating immunoglobulin.

in distinguishing mild (subclinical) thyroid disease from overt disease. TSH for most patients being treated for thyroid disorders should be the mean normal value of 1.5 milli international units/L (mIU/L) or 1.5 micro international units/mL (μIU/mL) (target range, 0.5–4.5 mIU/L or μIU/mL; clinical laboratories use either unit of measurement, usually expressed as mIU/L or μIU/mL), although patients must be individually titrated based on resolution of signs and symptoms as well as biochemical tests. Target TSH may be different in the elderly and in patients being treated with LT_4 for thyroid cancer.

TSH is a highly sensitive biomarker of the thyroid axis. A twofold change in FT_4 levels will result in a 100-fold change in TSH levels. This biologic magnification by TSH allows it to be used in early diagnosis as well as in closely titrating therapy in hypothyroidism and hyperthyroidism. In patients with primary hypothyroidism or hyperthyroidism resulting from gland dysfunction, there is an inverse relationship between TSH level and thyroid function. High TSH signifies hypothyroidism (or iatrogenic underreplacement) and low TSH signifies hyperthyroidism (or iatrogenic overreplacement).

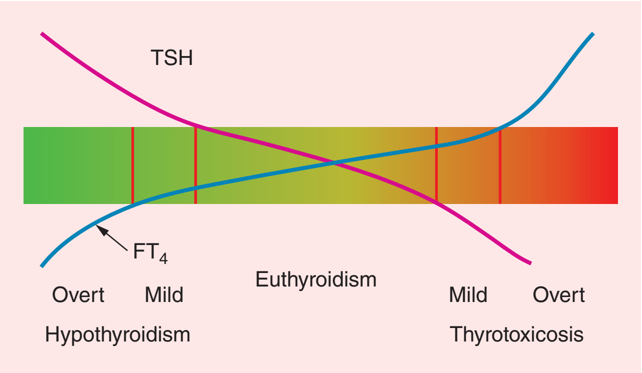

FIGURE 45–2. The continuum of thyroid disorders. (FT_4, free T_4 [thyroxine]; TSH, thyroid-stimulating hormone).

There is controversy regarding the normal or laboratory reference ranges for TSH.[3] The National Health and Nutrition Examination Survey (NHANES) showed the mean TSH level in a normal population was 1.46 mIU/L (μIU/mL), but the values were not normally distributed. Although most laboratories quote the upper limit of normal for TSH between 4 and 5 mIU/L (μIU/mL), 95% of subjects had a TSH level between 0.5 and 2.5 mIU/L (μIU/mL). The population of subjects whose TSH level was 2.5 to 4.5 mIU/L (μIU/mL) may have had mild hypothyroidism, or the nonnormal distribution may reflect different normal ranges in a heterogeneous (age, sex, and race) population. The mean normal TSH appears to be higher in the elderly with no clinical evidence of hypothyroidism,[3] and normal TSH ranges are sex and ethnicity specific.[1] Target TSH for most patients being treated for thyroid disorders is not the same as the reference range. Ideally, TSH should be the aforementioned mean normal value of 1.5 mIU/L (μIU/mL; target range, 0.5–4.5 mIU/L [μIU/mL]).[3] The upper limit of the target range may be higher in the elderly. Therapy may be titrated within the target TSH range to maximally improve patient signs and symptoms without causing adverse effects of overtreatment or undertreatment.

Serum T_4 and T_3 Levels

Serum T_4 and T_3 levels are used commonly to assess thyroid function. Older screening tests of thyroid function measure total serum T_4 or T_3 levels. Because of the high degree of protein binding of these hormones, the free fraction can be altered by changes in the levels of binding proteins or degree of protein binding. Since a number of factors can alter protein binding, these older assays are very insensitive and should no longer be used. FT_4 and FT_3 assays are readily available and more sensitive in identifying thyroid dysfunction than older total assays.[3] However, patients with mild hypothyroidism or hyperthyroidism have normal FT_4 levels despite abnormal TSH levels.

Other Diagnostic Tests

Global tests of thyroid gland function can be performed to assess the rate of hormone synthesis. Radioactive iodine uptake (RAIU) is elevated in those with hyperthyroidism and can aid in identifying thyrotoxicosis due to nonthyroid gland sources. Radionuclide thyroid scans are used in the evaluation of thyroid nodules. Because many thyroid disorders are autoimmune, measurement of various serum antithyroid antibodies can be performed. Antithyroid peroxidase antibodies (anti-TPOAb) and antithyroglobulin antibodies (anti-TGAb) are present in many patients with hypothyroidism. Most patients with Graves disease have TSH receptor-stimulating antibodies (TSHR-SAb) as well as elevated anti-TPOAb and antimicrosomal antibodies.

HYPOTHYROIDISM

Hypothyroidism is the most common clinical disorder of thyroid function and results from inadequate secretion of thyroid hormones from the thyroid gland. The vast majority of hypothyroid patients have primary gland failure, but occasional patients have pituitary or hypothalamic failure, resulting in secondary hypothyroidism. Most studies define primary hypothyroidism based on a serum TSH level above the upper limit of the laboratory reference range. In adults, 1.4% of women and 0.1% of men are biochemically hypothyroid. However, incidence is highly age dependent. In the Colorado Thyroid Health Study, by age 64 years, 12% of women and 5% of men were hypothyroid, and in the over 74 years age group, incidence in men approached that of women.[2] Most epidemiologic studies of hypothyroidism in the elderly show a prevalence of 6% to 12%.[3] There is a strong correlation between presence of anti-TPOAb or anti-TGAb and the risk of developing hypothyroidism. In patients with subclinical hypothyroidism, the clinician should be aware conditions other than hypothyroidism can cause mild elevations in TSH such as significant obesity (body mass index [BMI] > 40). Elderly patients may have an increase in TSH with aging that may not reflect a pathologic problem.[4,5] Many patients with a mild increase in TSH will revert to having normal TSH over the next 1 to 2 years, while 2% to 6% per year will progress to overt hypothyroidism, with risk of progression higher in women, those with higher TSH levels, those with higher levels of anti-TPOAbs, and those with low-normal FT_4 levels.[5] Other risk factors for development of hypothyroidism include the postpartum state, family history of autoimmune thyroid disorders, a previous history of head and neck or thyroid surgery, head and neck irradiation, other autoimmune endocrine disorders such as type 1 diabetes and Addison disease, other nonendocrine autoimmune diseases such as celiac disease and pernicious anemia, history of treatment for hyperthyroidism, treatment with certain medications including amiodarone or lithium, and an iodine-deficient diet.[3,6]

Screening

Because prevalence of hypothyroidism is high in certain populations, screening may be useful. Screening for hypothyroidism in women older than age 35 years may be cost-effective, though some organizations recommend screening of adults after age 50 or 60 years.[7] Others advocate a case-finding approach, defined as performing a TSH determination in patients based on risk factors or the presence of signs and symptoms.[3] However, there are no studies that demonstrate a positive impact of screening for thyroid disease on morbidity and mortality.[8]

Causes

The most common causes of hypothyroidism are listed in Table 45–2.[3-6,9-12] Up to 90% of patients with autoimmune thyroiditis (Hashimoto disease) have circulating anti-TPOAbs. The autoimmune inflammatory response results in a lymphocytic infiltration of the thyroid gland and its eventual destruction.

Table 45–2

Common Causes of Hypothyroidism[3-6,9-12]

Primary Hypothyroidism
Chronic autoimmune thyroiditis (Hashimoto disease)
Iatrogenic (irradiation, surgery)
Drugs (amiodarone, radiocontrast media, lithium, interferon-α, tyrosine kinase inhibitors, immune checkpoint inhibitors)
Transient thyroiditis (including viral and postpartum)
Iodine deficiency and excess
Thyroid gland infiltration (infectious, malignant, autoimmune, inflammatory)

Secondary Hypothyroidism
Pituitary disease
Hypothalamic disease

Iatrogenic hypothyroidism can occur after thyroid irradiation or surgery and excessive doses of antithyroid drugs. Several drugs can cause hypothyroidism including iodine-containing drugs (such as amiodarone and iodinated radiocontrast media), lithium, interferon-α, multikinase and tyrosine kinase inhibitors (TKIs, such as imatinib, sunitinib, and sorafenib), immune checkpoint inhibitors (ICPIs, such as ipilimumab, nivolumab, atezolizumab, avelumab, and durvalumab), *p*-aminosalicylic acid, ethionamide, sulfonylureas, tetracyclines, thalidomide, valproic acid and other antiepileptic drugs, and aminoglutethimide.[3,9,12,13] Iodine deficiency is a common worldwide cause of hypothyroidism, including congenital hypothyroidism in newborns. Patients with hypothalamic or pituitary disease often have other signs of pituitary disease, such as hypogonadism, and their TSH levels are low.

Signs and Symptoms

Hypothyroidism can affect virtually any tissue or organ in the body. The most common symptoms, such as fatigue, lethargy, sleepiness, cold intolerance, and dry skin, are nonspecific and can be seen with many other disorders. The classic overt signs, such as myxedema and delayed deep tendon reflexes, are seen uncommonly now because more patients are screened or seek medical attention earlier. Patients with mild (also known as subclinical) hypothyroidism or elderly patients may have subtle symptoms or may progress so slowly they are not noticed easily by the patient or family. The lack of overt or specific signs and symptoms emphasizes the importance of using serum TSH level to identify patients with hypothyroidism.

Clinical Presentation and Diagnosis of Hypothyroidism[3-6,9-11]

Symptoms

Fatigue
Lethargy
Sleepiness
Mental impairment
Depression
Weight gain
Menstrual disturbances
Paresthesia
Cold intolerance
Change in voice
Dry skin
Decreased perspiration
Decreased appetite
Constipation
Arthralgia, myalgia
Infertility

Signs

Slow movements
Goiter
Slow speech
Hoarseness
Bradycardia
Anemia
Dry skin
Weight gain (slight to moderate)
Nonpitting edema (myxedema)
Hyporeflexia
Delayed relaxation of reflexes

Screening/Diagnosis

- TSH level of 4.5 to 10 mIU/L (μIU/mL) may constitute mild or subclinical hypothyroidism.
- TSH level greater than 10 mIU/L (μIU/mL) signifies overt hypothyroidism.
- FT_4 level will be normal (0.7–1.9 ng/dL or 9.0–24.5 pmol/L) in mild or subclinical hypothyroidism and low (< 0.7 ng/dL or 9.0 pmol/L) in patients with obvious signs and/or symptoms.

Mild (Subclinical) Hypothyroidism

Mild or subclinical hypothyroidism is present when a patient has a TSH above the upper limit of the laboratory reference range but usually below 10 mIU/L (μIU/mL), normal FT_4, and no overt hypothyroid signs and symptoms.[4,5,9-11] Many of these patients have autoimmune thyroiditis and anti-TPOAbs, and some will progress to overt hypothyroidism. Although patients may not express typical symptoms of hypothyroidism, many patients do have mild, nonspecific symptoms (eg, fatigue, cold intolerance, and constipation). Studies have shown subclinical hypothyroidism to be a risk factor for cardiovascular mortality and to be associated with decreased myocardial contractility, decreased exercise tolerance, elevated low-density lipoprotein (LDL) cholesterol, and neuropsychiatric symptoms.[4-6,10,11,14-16]

Sequelae of Hypothyroidism

Hypothyroidism is a chronic disease that may result in significant long-term sequelae. Hypercholesterolemia is associated with hypothyroidism, increasing long-term risk of cardiovascular disease and cardiovascular mortality. Between 4% and 14% of patients with hypercholesterolemia are found to be hypothyroid. The Colorado Thyroid Health Study showed a direct correlation between degree of TSH elevation and rise in serum cholesterol.[2] Hypothyroidism also may result in increased systemic vascular resistance, decreased cardiac output, and increased diastolic blood pressure. Hypothyroidism can cause significant neuropsychiatric problems, including a dementia-like state in the elderly that is reversible with LT_4 therapy. Maternal hypothyroidism can have dire consequences for developing fetuses. Fetuses are almost completely dependent on maternal thyroid hormones during the first trimester, a time crucial for development of the CNS. Inadequately treated maternal hypothyroidism results in increased risk of miscarriage and developmental impairment in the child.[3]

Myxedema coma is seen in advanced hypothyroidism. These patients develop CNS depression, respiratory depression, cardiovascular instability, and fluid and electrolyte disturbances. Myxedema coma often is triggered by an underlying acute medical condition such as infection, stroke, trauma, or administration of CNS depressant drugs.

Treatment

▶ *Desired Outcomes*

KEY CONCEPT There are three major goals in the treatment of hypothyroidism: replace the missing hormones, relieve signs and symptoms, and achieve a stable biochemical euthyroid state. Although these goals should not be difficult to achieve, 20% to 40% of treated patients are not receiving optimal pharmacotherapy.

▶ *Thyroid Hormone Products*

A number of thyroid hormone products are marketed in the United States (Table 45–3). These products include synthetic LT_4 and T_3, combinations of synthetic LT_4 and T_3, and animal-derived products. KEY CONCEPT Despite the availability of a wide array of thyroid hormone products, synthetic LT_4 is the treatment of choice for almost all patients with hypothyroidism.[3,6,10,14,17-19] LT_4 mimics the normal physiology of the thyroid gland, which secretes mostly T_4 as a prohormone. Peripheral tissues convert T_4 to T_3 as needed based on metabolic demands. If T_3 is used to treat hypothyroidism, the peripheral tissues lose their ability to control local metabolic rates. LT_4 also has distinct pharmacokinetic advantages over T_3. With a 7- to 10-day half-life, LT_4 provides a very smooth dose-response curve with little peak and trough effect. In a small number of patients who have impairment of conversion of T_4 to T_3, addition of T_3 may be warranted. T_3, with a 24-hour half-life, provides a significant peak and trough effect, and many patients have symptoms of thyrotoxicosis after each dose is administered. The use of compounded T_3 or other thyroid hormone products not approved by the Food and Drug Administration (FDA) or dietary supplements marketed for "thyroid health" should be strongly discouraged.[17] For patients who have difficulty adhering to a once-daily regimen, a once-weekly LT_4 regimen is safe and effective.[3,17]

Table 45–3

Thyroid Preparations

Drug (Brand Name)	Content	Relative Dose	Comments
Levothyroxine, (Synthroid, Levoxyl, Unithroid), other brands, and generics	Synthetic LT_4; 25-, 50-, 75-, 88-, 100-, 112-, 125-, 137-, 150-, 175-, 200-, and 300-mcg tablets; 13-, 25-, 50-, 75-, 100-, 125-, 150-mcg softgel capsules; 100-, 200-, and 500-mcg vial for injection	60 mcg	Gold standard for treating hypothyroidism; products not therapeutically equivalent; full replacement dose, 1–1.6 mcg/kg/day; when switching from animal product, lower calculated daily dose by 25–50 mcg; IV form rarely needed
Liothyronine (Cytomel)	Synthetic T_3; 5-, 25-, and 50-mcg tablets	15 mcg	Rarely needed in treatment of hypothyroidism; rapid absorption and pharmacologic effect; increased toxicity versus LT_4; no outcome benefit to combining with LT_4
Thyroid (desiccated) USP (Armour, others)	Desiccated pork thyroid glands; contains T_3 and T_4; 15-, 16.25-, 30-, 32.5-, 48.75-, 60-, 65-, 90-, 97.5-, 120-, 130-, 162.5-, 180-, 195-, 240-, 260-, 300-, and 325-mg tablets	65 mg	Nonphysiologic T_4:T_3 ratio; T_3 content may cause toxicity; no advantage over LT_4 monotherapy; no role in modern therapy
Liotrix (Thyrolar)	Synthetic T_4, T_3 in fixed 4:1 ratio; ¼-, ½-, 1-, 2-, 3-strength tablets	12.5/50 mcg T_3:T_4 (1 strength)	Nonphysiologic T_4:T_3 ratio; T_3 content may cause toxicity; no role in modern therapy; *withdrawn in United States by manufacturer in 2018*

IV, intravenous; LT_4, levothyroxine; T_3, triiodothyronine; T_4, thyroxine.

Animal-derived products such as desiccated thyroid are obtained from pig or cow thyroid and have various degrees of purity. These products contain both LT_4 and T_3, but the ratio of T_3 is much higher (T_4:T_3 = 4:1) than what would be found in the human thyroid gland (T_4:T_3 = 14:1). Although some patients want to use desiccated thyroid extract because it is "natural," the products are in no way natural for humans. With strong evidence supporting the safety and efficacy of LT_4 in the treatment of hypothyroidism, there is no rationale for use of these animal-derived products, and no evidence that desiccated thyroid extract has any benefits over synthetic LT_4.[18,19] Patients who are treated with these agents should be strongly encouraged to switch to synthetic LT_4. Additionally, patients should be encouraged to not purchase thyroid hormone- or iodine-containing products from health food stores or Internet sites.

Several studies have been published that evaluate the use of LT_4 and T_3 combinations in ratios that mimic human physiology. A large number of clinical trials and meta-analyses of studies comparing LT_4 and T_3 combinations with LT_4 monotherapy show no outcome benefit with combination therapy.[17,20] Except in rare circumstances (eg, patients with impaired T_4-to-T_3 conversion as evidenced by adequate LT_4 dose, continued symptoms, and low FT_3 level), there is no evidence to support the use of LT_4 and T_3 combinations over LT_4 monotherapy.

▶ *Bioequivalence and LT_4 Product Selection*

LT_4 products have a long history of bioavailability problems.[3,17-19] Over the years, LT_4 bioavailability has increased, so maintenance doses today are significantly lower than those seen before the early 1980s. Currently, average bioavailability of LT_4 tablet products is about 70% to 80%. Because of long-standing concerns about LT_4 bioequivalence and because LT_4 products had never undergone formal approval by the FDA under the 1938 Food, Drug, and Cosmetics Act, the FDA mandated that all manufacturers of LT_4 products submit an abbreviated new drug application (ANDA) to keep their products on the US market after 2001.[15,17-19] Products approved under this process would have to comply with FDA manufacturing and bioequivalence standards. This action has resulted in many changes in the US LT_4 market, as well as renewed interest in LT_4 bioequivalence. Since 2001, a variety of brand and generic products have been approved by the FDA. Some marketed products carry AB ratings (bioequivalence) to certain other products, using a complex AB1, AB2, AB3, and AB4 system.[21,22]

For many years, there have been concerns regarding the FDA bioequivalence methodology for LT_4 products. FDA bioequivalence standards allow a −20% to +25% variance in single-dose pharmacokinetic parameters between the test and reference products. Many people believe this degree of allowed variance is not appropriate for a narrow-therapeutic-index (NTI) drug such as LT_4. Furthermore, there are unique challenges to performing bioequivalence studies with an endogenous hormone such as LT_4. Because these single-dose pharmacokinetic studies are done in healthy volunteers, the pharmacokinetic data are a combination of endogenous and exogenous LT_4. About 70% of the area under the curve (AUC) in these studies consists of the subjects' endogenous T_4. A study showed the standard FDA bioequivalence methodology would rate 600-, 450-, and 400-mcg LT_4 doses as bioequivalent, and that mathematically removing the subjects' endogenous T_4 level (baseline correction) improves sensitivity of the analysis.[22] Based on these data, since 2003, the FDA has required that LT_4 bioequivalence data undergo baseline correction. Although this method has improved the ability to identify large differences in LT_4 bioequivalence, small but clinically significant differences will not be identified. In 2008, the FDA adopted stricter criteria for LT_4 tablet shelf-life potency (95%–105% of stated potency versus standard 90%–110%), which may reduce the intrapatient variability seen during long-term LT_4 therapy.

More important than bioequivalence is the therapeutic equivalence of LT_4 products. Will patients have the same outcomes if bioequivalent products are used? Studies show that switching among various LT_4 products in stable hypothyroid patients results in abnormal TSH levels in about half the patients, providing strong evidence that products deemed bioequivalent by the US FDA may not be therapeutically equivalent.[19,22]

Evidence does exist that small differences in LT_4 dose can result in large changes in TSH. In one study, when daily dose was reduced by 25 mcg, 78% had an elevated TSH level.[23] When daily dose was increased by 25 mcg, 55% had a low TSH level. Clearly, differences in LT_4 dose or bioavailability within the FDA-allowed variance for bioequivalent products can cause significant changes in TSH.

KEY CONCEPT There is no evidence that one LT_4 product is better than another. However, given the evidence that these products do have differences in bioavailability, patients should be maintained on the same LT_4 product. Given the generic substitution regulations of most states, this is best accomplished by prescribing a brand-name product or otherwise ensuring the product remains constant and not allowing substitution.[17-19] Although practitioners are pressured by insurance companies and employers to substitute LT_4 products as a cost-saving measure, such switching is not in the best interest of the patient and should not be allowed. If patients are switched to a different product, the prescriber should be notified, and a TSH determination should be done in 6 to 8 weeks to allow dose retitration. Changes in LT_4 dose significantly increase the cost of care.[24]

▶ *Therapeutic Use of LT_4*

LT_4 replacement is indicated for patients with overt hypothyroidism.[3,5,8-11,14,16-19] However, the need for treatment is controversial in patients with mild or subclinical disease. There are no prospective clinical trials showing an outcome benefit with treating these patients. A systematic review of 21 trials in nonpregnant adults with subclinical hypothyroidism showed that the use of thyroid hormone therapy was not associated with improvements in general quality of life or thyroid-related symptoms.[25] In patients without symptoms, who are children or have an underlying heart disease, high cardiovascular risk, diabetes, elevated serum cholesterol, goiter, positive anti-TPOAb, progressive rise in TSH, depression or bipolar disorder, and/or are infertile or pregnant, LT_4 replacement may be considered.[3,10,11,14,17] Patients with mild or subclinical hypothyroidism do not need to be started on the full LT_4 replacement dose because they still have some endogenous hormone production.[26] Start these patients on 12.5 to 50 mcg/day and titrate every 6 to 8 weeks to target TSH level. Over time, it is likely the LT_4 dose will need to be increased slowly as the patient's thyroid gland loses residual function.

In patients younger than age 65 years with overt hypothyroidism and moderate-to-severe signs and symptoms, the average LT_4 replacement dose is 1.6 to 1.8 mcg/kg/day (use ideal body weight in obese patients[17,18]). Patients with mild, overt signs and symptoms may be started on a lower than full replacement dose. There is wide interpatient variability in the optimal replacement dose, so individual dose titration is necessary.

The full replacement dose in patients older than age 75 years is lower, about 1 mcg/kg/day.[3,17] In the elderly, starting dose should be 12.5 to 25 mcg/day, and dose should then be titrated to the target TSH value. In patients with ischemic heart disease, start with 12.5 to 25 mcg/day and slowly titrate. If the patient develops angina or other forms of myocardial ischemia, lower the dose and titrate more slowly. At the start of therapy, and with each change in dose, recheck the TSH in 6- to 8-week intervals. If the TSH is not in the target range (0.5–2.5 mIU/L [μIU/mL]), change the dose by 10% to 20% and then recheck TSH 6 to 8 weeks later. As the dose is titrated, assess the patient's symptoms. Many patients will improve quickly, and younger patients will feel best if TSH is titrated to low-normal to middle-normal levels (0.5–1.5 mIU/L [μIU/mL]).

▶ *Risks of Overtreatment and Undertreatment*

Patients receiving LT_4 therapy who are not maintained in an euthyroid state are at risk for long-term adverse sequelae.[18] In general, overtreatment and a suppressed TSH are more common than undertreatment with an elevated TSH. Patients with long-term overtreatment are at higher risk for atrial fibrillation and other cardiovascular morbidities; anxiety, depression, or mental status changes; and osteoporosis. Elderly patients being treated with LT_4 may have a dose-related risk of fractures even if TSH is not suppressed below normal values. Although studies have not defined a specific TSH target range for the elderly, these patients should receive close monitoring and dose adjustments to prevent over- and undertreatment. Patients who are undertreated are at higher risk for hypercholesterolemia and other cardiovascular problems, depression and/or other mental status changes, and obstetric complications.

Patient Encounter 1, Part 1

A 36-year-old female comes to the clinic complaining of fatigue and feeling a little "slow" for the past 3 months. She thought it was because she is working too hard and her kids are stressing her out, but the symptoms have not improved despite her taking some vitamins with iron and an energy drink. She noticed a 2-kg (4.4 lb) weight gain over the past few months. Her friend gave her a ginseng product to give her energy, but she is not sure it helps. Her current medications include the vitamin and herbal product mentioned above, hormonal contraceptive, calcium and vitamin D, occasional acetaminophen for headache, and MiraLAX for occasional constipation.

PE:

Wt 67 kg (147 lb); Ht 5 ft 5 in. (165 cm); BMI 24.6 kg/m^2

VS: BP 124/76 mm Hg, P 68, RR 12 breaths/min

Skin, HEENT, thyroid, pulmonary, and cardiovascular examinations are normal.

Labs

Serum Cholesterol: 205 mg/dL (5.30 mmol/L); LDL cholesterol 96 mg/dL (2.48 mmol/L)

TSH: 6.8 mIU/L (μIU/mL; reference range, 0.5–4.5 mIU/L [μIU/mL])

FT_4: 0.96 ng/dL (12.4 pmol/L; reference range, 0.7–1.9 ng/dL, or 9.0–24.5 pmol/L)

Should the patient receive LT_4 therapy? Why or why not?

If you think treatment is indicated, what initial dose of LT_4 would you choose?

If you think treatment is not indicated, how would you monitor the patient?

What would you tell the patient regarding the significance of her symptoms, elevated TSH level, and risk versus benefits of LT_4 therapy?

▶ *Alterations in LT_4 Dose Requirements*

A number of factors can alter LT_4 dose requirements (Table 45–4), including time of administration and drug–drug and drug–food interactions.[3,8,17-19] LT_4 has the greatest and most consistent bioavailability when taken in the evening on an empty stomach.[17,22,27] The most common cause of increased dose requirement is coadministration of LT_4 with calcium or iron supplements (including prenatal vitamins) or concomitant use of proton pump inhibitors. In patients who have impaired absorption of standard LT_4 dosage forms, the use of a liquid or gelcap formulation may improve absorption.[28] Counsel patients that they should take the LT_4 dose at least 2 hours before or 6 hours after the calcium or iron dose. The most common reason for decreased dose requirement is aging.

▶ *Patient Monitoring*

Patients on stable LT_4 therapy do not need frequent monitoring. In most patients, measuring TSH every 6 to 12 months along with an assessment of clinical status is adequate (Table 45–5). If the patient's clinical status changes (eg, pregnancy), more frequent monitoring may be necessary. LT_4 prescriptions should be written as microgram doses to avoid potential errors when written as milligram doses.

Patient education is an important component of care. Treatment adherence rate (at least 80% of doses taken) in hypothyroid patients is 68%, slightly less than adherence rates seen in patients with hypertension.[29] Educate patients about the benefits of proper therapy, importance of adherence, consistency in time and method of administration, and importance of receiving a consistent LT_4 product. Some patients take excessive amounts of LT_4 in an effort to "feel better" or as a weight loss treatment. Explain to patients that excessive amounts of LT_4 will not improve symptoms more than therapeutic doses, can cause serious problems, and is not an effective nor safe treatment for obesity.

▶ *Special Populations and Conditions*

Hypothyroidism and Pregnancy Hypothyroidism during pregnancy has a variety of maternal and fetal adverse effects.[3,30,31] During pregnancy, β-human chorionic gonadotropin (β-hCG) acts as a TSH receptor agonist, increasing the amount of thyroid hormone available for fetal growth and development.

Maternal hypothyroidism results in an increased rate of miscarriage and decreased intellectual capacity of the child. Endocrinologists recommend a TSH measurement as soon as pregnancy is confirmed. Most hypothyroid women who become pregnant will quickly need an increased dose of LT_4, typically 20% to 30% or two tablets per week above the prepregnancy dose.[30] The increased dose should be maintained throughout the pregnancy, with monthly TSH monitoring to keep TSH in the middle- to low-normal range. After delivery, LT_4 dose usually can be reduced to prepregnancy levels, although patients with preexisting autoimmune thyroiditis may have increased postpartum

Table 45–4

Factors That Alter LT_4 Dose Requirements[3,17-19]

Increased Dose Requirement	Decreased Dose Requirement
Nonadherence	Aging
Decreased LT_4 Absorption	Post-menopause
Malabsorption syndromes	Delivery of pregnancy
Helicobacter pylori infection	Withdrawal of interacting substance
Drugs or Diet	Weight loss
Bile acid binders	
Caffeine	
Calcium	
Charcoal	
Chromium picolinate	
Ciprofloxacin	
Fiber	
Grapefruit juice	
H_2-blockers	
Iron	
Malabsorption syndromes	
Oral bisphosphonates	
Orlistat	
Phosphate binders (sevelamer, aluminum)	
Proton pump inhibitors	
Sodium polystyrene sulfonate	
Soy	
Sucralfate	
Tube feeding	
Increased TBG	
Cirrhosis	
Estrogen therapy	
Hereditary	
Pregnancy	
Tamoxifen, raloxifene therapy	
Increased Clearance	
Carbamazepine	
Growth hormone	
Nevirapine	
Oxcarbazepine	
Phenobarbital	
Phenytoin	
Primidone	
Quetiapine	
Rifampin	
Sertraline	
Stavudine	
Tyrosine kinase inhibitors	
Valproic acid	
Impaired Deiodination	
Amiodarone	
Mechanism Unknown	
Critical illness	

LT_4, levothyroxine; TBG, thyroxine-binding globulin.

Table 45–5

Monitoring Levothyroxine (LT_4) Therapy

- Serum TSH
  - Every 6–12 months or if change in clinical status
  - 6–8 weeks after any dose or product change
  - As soon as possible in pregnancy; then monthly
- Same product prescribed and dispensed with every refill
- Watch for mg/mcg dosing errors
- Assess patient's understanding of disease, therapy, and need for adherence and tight control
- Assess for signs and symptoms of over- and undertreatment
- Identify potential interactions between LT_4 and foods and/or drugs
- In persons with diabetes, monitor for changes in glycemic control as thyroid function changes

TSH, thyroid-stimulating hormone.

dose requirements. Because prenatal vitamins contain significant amounts of calcium and iron, remind patients to take the LT_4 dose at least 2 hours before or 6 hours after the vitamin.

Children Congenital hypothyroidism is uncommon in the United States, and all newborns there undergo screening with a TSH level. As soon as the hypothyroid state is identified, the newborn should receive the full LT_4 replacement dose. The replacement dose of LT_4 in children is age dependent. In newborns, the usual dose is 10 to 15 mcg/kg/day. LT_4 tablets may be crushed and mixed with breast milk or formula, but it is best to administer LT_4 to infants and children on an empty stomach.[32] Serum TSH in the mid-to-lower half and FT_4 levels in the mid-to-upper half of the pediatric reference ranges are used for dose titration. By 6 months of age, the required dose is reduced to 6 to 8 mcg/kg/day; from ages 1 to 5 years, 5 to 6 mcg/kg/day; and from ages 6 to 12 years, 4 to 5 mcg/kg/day. After age 12 years, adult doses can be given. In children with subclinical hypothyroidism, treatment can be considered when serum TSH is over 10 mIU/L (μIU/mL).

Myxedema Coma Myxedema coma is a life-threatening condition owing to severe, long-standing hypothyroidism and has a mortality rate of 60% to 70%. These patients are given 200 to 400 mcg LT_4 intravenously (IV) initially, using caution in patients with underlying cardiac disease. Although administration of T_3 would provide a more rapid onset of action, there is no evidence T_3 improves outcomes in patients with myxedema coma.

Patient Encounter 1, Part 2

Twelve months later, the patient comes back to you for a routine follow-up stating that she has felt progressively worse since her last visit, especially over the past few months. Her best friend passed away from breast cancer 6 months ago, but she does not think she is depressed. She feels more fatigued and has gained 2 kg (4.4 lb) since her last visit. She has noticed that her skin is always dry, she has more frequent constipation, and her periods have become heavier. After her friend died, she elected to "go natural," and started taking more supplements purchased at a health food store. Her most recent TSH determination, obtained 2 days ago, was 14.2 mIU/L (μIU/mL; reference range, 0.5–4.5 mIU/L [μIU/mL]) and FT_4 0.61 ng/dL (7.9 pmol/L; reference range, 0.7–1.9 ng/dL, or 9.0–24.5 pmol/L)

Why is LT_4 therapy indicated now?

What would you recommend regarding her LT_4 dose and monitoring?

What instructions would you give the patient regarding her LT_4 therapy?

Patient Care Process: Hypothyroidism

Collect Information:

- Perform a medication history or medication reconciliation for the use of all medications and supplements. Identify adverse drug events, allergies, and hypersensitivities.
- Review the medical history and physical assessment findings.
- Speak with the patient and other caregivers as appropriate to identify the issues that affect medication access and other aspects of care.

Assess the Information:

- Evaluate for signs and symptoms of hypothyroidism (see Clinical Presentation and Diagnosis of Hypothyroidism). As signs and symptoms of hypothyroidism are nonspecific, clinicians should have a high index of suspicion in higher risk patients including women and the elderly.
- Use serum TSH to identify patients with hypothyroidism (see Clinical Presentation and Diagnosis of Hypothyroidism), and check TSH in pregnant women as soon as pregnancy is determined.
- If the patient has been or is already receiving pharmacotherapy to treat thyroid disease, assess efficacy, safety, LT$_4$ product received (eg, any recent changes in product), and patient adherence. Are there any significant drug interactions?
- If patient is not at desired TSH level and not on therapy, determine if pharmacotherapy is indicated.

Develop a Care Plan:

- Provide synthetic LT$_4$ replacement to patients with overt hypothyroidism.
- Consider replacement therapy in patients with TSH level of greater than 4.5 but less than 10 mIU/L (μIU/mL) who have nonspecific or subtle symptoms (eg, mild fatigue, lethargy), an elevated cholesterol level, underlying heart disease, or positive anti-TPOAbs.
- Patients with mild hypothyroidism may be started at 12.5 to 25 mcg/day of LT$_4$.
- Patients with overt hypothyroidism who are older than 12 and younger than 65 years and do not have cardiac disease may receive the calculated full replacement LT$_4$ dose of 1.6 mcg/kg/day (based on ideal body weight if obese).
- Elderly patients or those with cardiac disease should be started at a lower LT$_4$ dose (eg, 12.5–25 mcg/day).
- Provide a brand-name LT$_4$ product, and do not allow product switches. If the product is switched, check TSH in 6 weeks and retitrate the dose.
- Provide LT$_4$ prescriptions as microgram, not milligram, doses to avoid errors.
- Make sure patients understand importance of adherence and risks of overuse and underuse of LT$_4$.
- In pregnant patients, expect to increase LT$_4$ dose early in the first trimester. Maintain TSH in low- to middle-normal range. After delivery, reduce LT$_4$ dose to prepregnancy level, if appropriate.

Implement the Care Plan:

- Educate the patient about any changes in therapy and how to manage and report adverse effects.
- Review proper medication administration with the patient, including issues related to food and concomitant medications.
- Discuss the importance of adherence and risks of over- and undertreatment.
- Determine if the patient has insurance coverage for prescription medications.

Follow-up: Monitor and Evaluate:

- Measure serum TSH 6 to 8 weeks after starting LT$_4$ or after any dose change. If TSH level is not in target range, alter dose by 10% to 20% increments. Target TSH for patients on LT$_4$ replacement therapy for hypothyroidism is 0.5 to 2.5 mIU/L (μIU/mL). Younger patients often feel best at a TSH level in the low- to middle-normal range (ie, 0.5–1.5 mIU/L [μIU/mL]).
- Check TSH every 6 to 12 months in stable patients receiving LT$_4$ replacement.
- Monitor for drug interactions, such as LT$_4$ absorption problems caused by calcium and iron.
- At each visit, assess for signs and symptoms of over- and undertreatment.
- In pregnant patients, check TSH monthly.

Historically, glucocorticoids, such as hydrocortisone 50 to 100 mg every 6 hours, are administered owing to concern about simultaneous adrenal insufficiency. Although there is no strong evidence for an outcome benefit, the use of glucocorticoids is reasonable because such treatment may be lifesaving, and risks of a short course of corticosteroids at this dose are low. As patients improve, LT$_4$ dose can be given orally in a typical full replacement dose. Reduce the full replacement dose by 75% if continued IV therapy is needed.[17]

HYPERTHYROIDISM AND THYROTOXICOSIS

Hyperthyroidism, a subset of thyrotoxicosis, is much less common than hypothyroidism. Refer to the Epidemiology section.

Causes of Thyrotoxicosis and Hyperthyroidism

Thyrotoxicosis is any syndrome resulting from excess thyroid hormone. Hyperthyroidism is related to excess thyroid hormone production and secretion by the thyroid gland. Common causes of thyrotoxicosis are shown in Table 45–6.[33-35] **KEY CONCEPT** Graves disease is the most common cause of hyperthyroidism. Hyperthyroidism in the elderly is more likely caused by toxic thyroid nodules or multinodular goiter than by Graves disease. Excessive intake of thyroid hormone may be caused by overtreatment with prescribed therapy or as self-treatment for obesity, as thyroid hormones can be obtained easily without a prescription from health food stores or Internet sources. Ingestion of high doses of biotin may cause falsely elevated FT$_4$ levels and a false-positive

Table 45–6

Causes of Thyrotoxicosis[33-35]

Primary Hyperthyroidism
Graves disease
Toxic multinodular goiter
Toxic adenoma
Thyroid cancer
Struma ovarii
Iodine excess (including radiocontrast, amiodarone)

Thyrotoxicosis Without Hyperthyroidism
Subacute thyroiditis
Silent (painless) thyroiditis
Postpartum thyroiditis
Excess thyroid hormone intake (thyrotoxicosis factitia)
Drug-induced (amiodarone, iodine, lithium, interferons, tyrosine kinase inhibitors, immune checkpoint inhibitors)

Secondary Hyperthyroidism
TSH-secreting pituitary tumors
Trophoblastic (hCG-secreting) tumors
Gestational thyrotoxicosis

hCG, human chorionic gonadotropin; TSH, thyroid-stimulating hormone.

TSHR-SAb assay with subsequent misdiagnosis of Graves disease.[33,35]

Clinical Manifestations of Thyrotoxicosis

Many of the signs and symptoms seem to be related to autonomic hyperactivity. Clinical manifestations of hyperthyroidism may be subtle and slowly progressive. Screening of patients for thyroid disease may identify patients with subclinical or mild thyrotoxicosis. Patients may seek medical attention only after a long period of thyrotoxicosis or owing to an acute complication such as atrial fibrillation. Clinical manifestations of thyrotoxicosis in the elderly may be blunted or atypical. These patients may present only with atrial fibrillation, depression, or altered mental status or cognition.

Mild (Subclinical) Hyperthyroidism

Mild (subclinical) hyperthyroidism is defined as a low TSH level with a normal FT_4 level.[33-36] Although there may be few or no symptoms in these patients, there are several areas of concern. Some patients progress to overt thyrotoxicosis, especially when TSH is fully suppressed.[36] Patients with subclinical hyperthyroidism have been shown to experience long-term cardiovascular and bone sequelae.[33,36,37] Mild hyperthyroidism appears to increase cardiovascular morbidity and mortality.[36] Prolonged subclinical thyrotoxicosis speeds the loss of bone mineral density and increases fracture rates in postmenopausal women.[33,36,37] Associations have been reported between subclinical hyperthyroidism and cognitive impairment or dementia.[36] Treatment of patients with mild hyperthyroidism is controversial but should be considered in patients with TSH levels less than 0.1 mIU/L (μIU/mL), Graves disease, postmenopausal women, and patients with underlying cardiovascular disease.[33,36,38] Patients who do not have fully suppressed (below the lower limit of detection) TSH or other risk factors for hyperthyroid complications (eg, osteoporosis, atrial fibrillation, and heart failure) may undergo observation, with TSH testing every 6 months to identify progression of the hyperthyroid state.

Graves Disease

Graves disease is an autoimmune syndrome that includes hyperthyroidism, diffuse thyroid enlargement, exophthalmos (abnormal protrusion of the eyeball) and other eye findings, and skin findings.[33-35] Prevalence of Graves disease in the United States is approximately 0.4% in women and 0.1% in men. Peak age of incidence is 20 to 49 years, with a second peak after 80 years of age. Hyperthyroidism results from the production of TSHR-SAbs in at least 80% of patients with clinical Graves disease. These antibodies have TSH agonist activity, thereby stimulating hormone synthesis and release. These antibodies cross-react with orbital and fibroblastic tissue, resulting in ophthalmopathy and dermopathy. Although the underlying cause of Graves disease is not known, heredity seems to play a role. Subclinical Graves disease may become acutely overt in the presence of iodine excess, infection, stress, parturition, smoking, and lithium and immune modulating therapy.

Clinical Presentation and Diagnosis of Hyperthyroidism[33-35]

Symptoms

- Nervousness
- Fatigue
- Weakness
- Increased perspiration
- Heat intolerance
- Tremor
- Hyperactivity, irritability
- Palpitations
- Appetite change (usually increased)
- Weight change (usually weight loss)
- Menstrual disturbances (often oligomenorrhea)
- Frequent bowel movements or diarrhea

Signs

- Hyperactivity
- Tachycardia
- Atrial fibrillation (especially in elderly adults)
- Hyperreflexia
- Warm, moist skin
- Ophthalmopathy, dermopathy (Graves disease)
- Goiter
- Muscle weakness

Screening/Diagnosis

- Low TSH level (< 0.5 mIU/L [μIU/mL]) signifies thyrotoxicosis.
- FT_4 is elevated in overt hyperthyroidism but may be normal in mild hyperthyroidism.
- Increased radioiodine uptake in the thyroid indicates increased hormone production by the thyroid gland.
- Almost all patients with Graves disease will have positive TSHR-SAbs and positive anti-TPOAbs.

Several features of Graves disease are distinct from other forms of thyrotoxicosis. Clinically apparent ophthalmopathic changes are seen in 20% to 40% of patients and include exophthalmos, proptosis, chemosis, conjunctival injection, and periorbital edema.[33,34,39] Eyelid retraction causes a typical staring or startled appearance (Figure 45–3). Patients may complain of vague eye discomfort and excess tearing. In severe cases, the eyelids are unable to close completely, resulting in corneal damage. In very severe cases, the optic nerve can be compressed, resulting in permanent vision loss. All patients with suspected or known Graves disease must be evaluated and monitored by an ophthalmologist. Treatment of the underlying hyperthyroid state often, but not always, improves the ophthalmopathy. Teprotumumab is a relatively new agent that blocks the insulin-like growth factor I receptor (IGF-IR) and has shown better outcomes in treating thyroid eye disease versus placebo.[40]

Dermopathy occurs in 5% to 10% of patients with Graves disease and usually is associated with severe ophthalmopathy. Skin findings include hyperpigmented, nonpitting induration of the skin, typically over the pretibial area (pretibial myxedema), dorsa of the feet, and shoulder areas. Clubbing of the digits (thyroid acropachy) is associated with long-standing thyrotoxicosis.

Treatment

▶ *Desired Outcomes*

Treatment of thyrotoxicosis caused by hyperthyroidism is similar regardless of the underlying cause.[33-35] **KEY CONCEPT** Goals of treating hyperthyroidism are to relieve signs and symptoms, reduce thyroid hormone production to normal levels and achieve biochemical euthyroidism, and prevent long-term adverse sequelae.

▶ *β-Blockers*

Because many manifestations of hyperthyroidism appear to be mediated by the β-adrenergic system, β-adrenergic blockers are used to rapidly relieve palpitations, tremor, anxiety, and heat intolerance. Because β-blockers do not reduce the synthesis of thyroid hormones, they are used only until more specific antithyroid therapy is effective. Because nonselective agents can impair the conversion of T_4 to T_3, propranolol and nadolol are preferred. An initial propranolol dose of 10 to 40 mg four times daily should be titrated to relieve signs (target resting heart rate less than 90 beats/min) and symptoms. β-Blockers should not be used in patients with decompensated heart failure or asthma. A more β-1 specific blocker (eg, metoprolol, atenolol) may be used when a relative contraindication to a β-blocker exists; however, when an absolute contraindication to β-blockers exists, clonidine, verapamil, or diltiazem may be used for heart rate control.

▶ *Methods to Reduce Thyroid Hormone Synthesis*

Excess production of thyroid hormone can be reduced in four ways: iodides, antithyroid drugs, radioactive iodine, and surgery.

Iodide Large doses of iodide inhibit the synthesis and release of thyroid hormones. Serum T_4 levels may be reduced within 24 hours, and the effects may last for 2 to 3 weeks. Iodides are most commonly used in Graves disease patients before surgery and to quickly reduce hormone release in patients with thyroid storm. Potassium iodide is administered either as a saturated solution (SSKI) that contains 38-mg iodide per drop or as Lugol solution, which contains 6.3-mg iodide per drop. In thyroid storm, the typical starting dose of SSKI is five drops every 6 to 8 hours. Iodide therapy should start 7 to 14 days before surgery. Iodide should

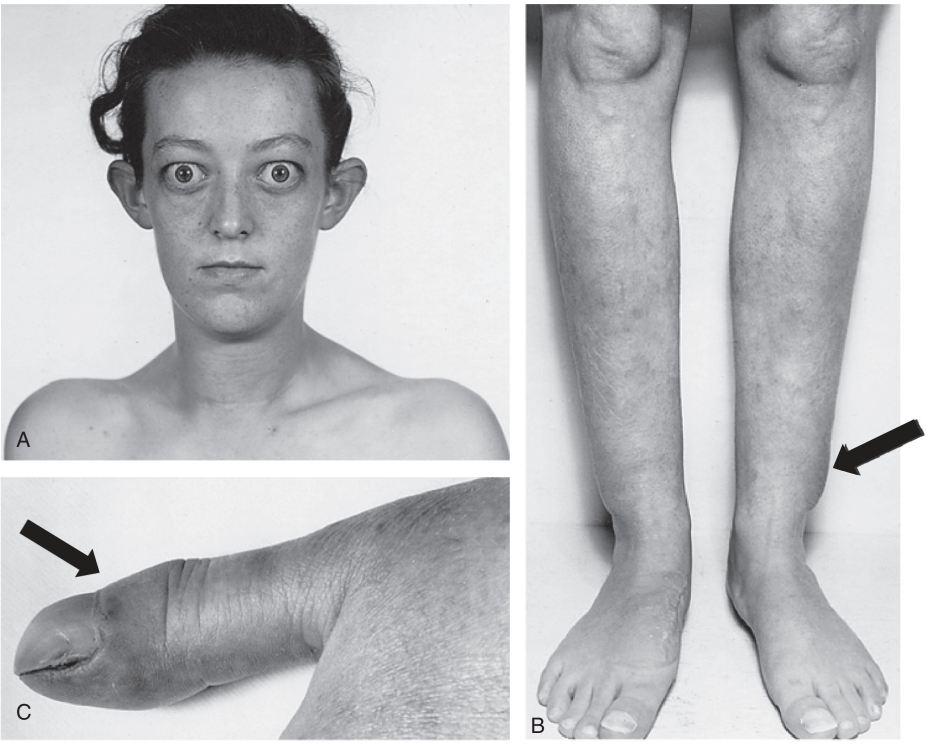

FIGURE 45–3. Features of Graves disease. (**A**) Facial appearance: exophthalmos, eyelid retraction, periorbital edema, and proptosis. (**B**) Thyroid dermopathy over lateral aspects of the shins (*arrow*). (**C**) Thyroid clubbing or acropachy (*arrow*). (From Jameson JL, Weetman AP. Disorders of the thyroid gland. In: Kasper DL, Braunwald E, Fauci AS, et al., eds. Harrison's Principles of Internal Medicine, 16th ed. New York, NY: McGraw-Hill; 2004:2114.)

not be given before radioactive iodine treatment because the iodide will inhibit concentration of the radioactivity in the thyroid. Iodides are also used to protect the thyroid from radioactive iodine fallout after a nuclear accident or attack. Administration of 30- to 100-mg iodide markedly reduces thyroid gland uptake of radioactive iodine. The most frequent toxic effects with iodide therapy are hypersensitivity reactions, "iodism" (characterized by palpitations, depression, weight loss, and pustular skin eruptions), and gynecomastia.

Antithyroid Drugs The thionamide agents propylthiouracil (PTU) and methimazole (MMI) are used in the United States to treat hyperthyroidism.[33,35,41] Carbimazole, an MMI prodrug, is used in some countries (10 mg carbimazole = 6 mg MMI). These drugs inhibit thyroid hormone synthesis by interfering with thyroid peroxidase–mediated iodination of tyrosine residues in thyroglobulin. PTU has the added effect of inhibiting conversion of T_4 to T_3. The thionamides also have immunosuppressant effects. In patients with Graves disease treated with thionamides, TSHR-SAb levels and other immune mediators decrease over time. Both drugs are well absorbed from the gastrointestinal (GI) tract. PTU has a half-life of one to 2.5 hours, whereas half-life of MMI is 6 to 9 hours.

Antithyroid drugs are used as primary therapy for Graves disease or as preparative therapy before surgery or radioactive iodine administration. The decision to use antithyroid drugs as primary therapy must be weighed against the risks and benefits of radioiodine or surgery. Patient preference must be considered.

In most patients, there is no clear efficacy advantage of one thionamide over the other, but in the United States, MMI use has increased dramatically since the mid-1990s in lieu of PTU.[42] Although PTU has the advantage of inhibiting T_4-to-T_3 conversion, MMI can be given as a single daily dose and may have a better overall safety profile, particularly less hepatotoxicity. MMI is preferred to normalize thyroid function before radioactive iodine therapy, although both thionamides increase the failure rate of radioactive iodine therapy.[43] Usual starting dose of MMI is 10 to 20 mg/day (range 5–40 mg based on initial FT_4 level), and usual starting dose of PTU is 50 to 150 mg three times daily. Thyroid hormone levels drop in 2 to 3 weeks, and after 6 weeks, 90% of patients with Graves disease will be euthyroid. Thyroid function testing should be performed every 4 to 6 weeks until stable. After the patient becomes euthyroid, antithyroid drug dose often can be decreased (5–10 mg/day MMI, 100–200 mg/day PTU) to maintain the euthyroid state. Excessive doses of antithyroid drugs will result in hypothyroidism.

Remission of Graves disease occurs in 40% to 60% of patients after 1 to 2 years of therapy. Antithyroid therapy may be stopped or tapered after 12 to 24 months. Relapse usually occurs in the first 3 to 6 months after stopping antithyroid therapy. Levels of TSHR-SAb after a course of treatment may have predictive value for risk of relapse in that antibody-positive patients almost always relapse. However, antibody-negative patients also may relapse after therapy is stopped. About 75% of women in remission who become pregnant will have a postpartum relapse. When therapy is discontinued, a therapeutic strategy should be in place in the event of relapse. Many patients will opt for radioactive iodine as a long-term solution.

Antithyroid drugs are associated with an overall low rate of adverse effects, although serious adverse effects can occur. Current recommendation for choice of antithyroid medication is to use MMI in most patients, while PTU should only be used in patients who cannot tolerate MMI or during first trimester of pregnancy. Skin rash, arthralgias, and GI upset are seen in 5% of patients, with cutaneous reactions somewhat more common with MMI.[35] Although these drugs can be continued in the presence of a minor skin rash, development of arthralgia warrants discontinuation. Hepatotoxicity is an uncommon but potentially serious or fatal adverse effect, occurring in 0.1% to 0.2% of patients, with severe hepatotoxicity more common with PTU.[33-35] Transient rises in aminotransferase enzyme levels are seen in up to 30% of patients treated with PTU. Antineutrophil cytoplasmic antibody (ANCA) vasculitis is another potentially serious but uncommon reaction that is more common with PTU, and patients may develop a drug-induced lupus syndrome.

KEY CONCEPT Agranulocytosis is one of the most serious adverse effects of antithyroid drug therapy. Agranulocytosis must be distinguished from a transient decrease in white blood cell count seen in up to 12% of adults and 25% of children with Graves disease. Agranulocytosis occurs in 0.3% of patients, and incidence may be the same with PTU and MMI therapy. Lower doses of MMI may be associated with a lower incidence.[33] Agranulocytosis, thought to be autoimmune, almost always occurs within the first 3 to 6 months of therapy and occurs suddenly and unpredictably. Patients will present with fever, malaise, and sore throat, and absolute neutrophil count will be less than 1000/mm^3 (1×10^9/L). Patients may develop sepsis and die rapidly. If agranulocytosis occurs, discontinue the antithyroid drug immediately, administer broad-spectrum antibiotics if the patient is febrile, and consider administration of filgrastim. The white blood cell count should recover in 1 or 2 weeks. Patients who develop agranulocytosis should not be switched to another thionamide drug. Monitoring for agranulocytosis is controversial owing to its sudden and unpredictable nature. Most do not recommend routine monitoring of the complete blood count (CBC), although early detection could improve patient outcomes. Patients initiating thionamide therapy must be informed about the signs and symptoms of agranulocytosis and other serious side effects. Patients should be counseled to report signs and symptoms suggestive of infection, such as fever and sore throat lasting more than 2 or 3 days, bruising, pruritic rash, jaundice, dark urine, arthralgias, abdominal pain, nausea, or fatigue.

Radioactive Iodine Radioactive iodine, typically ^{131}I, produces thyroid ablation without surgery. ^{131}I is well absorbed after oral administration. Iodine is concentrated in the thyroid gland and has a half-life of 8 days. Over a period of weeks, thyroid cells that have taken up ^{131}I begin to develop abnormalities and necrosis. Eventually, thyroid cells are destroyed, and hormone production is reduced. After a single dose, 40% to 70% of patients will be euthyroid in 6 to 8 weeks, and 80% will be cured. In most patients, hypothyroidism will develop, and long-term LT_4 replacement will be necessary. Because ^{131}I has a slow onset of action and may cause added release of thyroid hormone, most patients are treated initially with β-blockers and antithyroid drugs to prevent ^{131}I-induced thyroid storm. MMI is the preferred agent before administration of ^{131}I. MMI is discontinued 3 to 5 days before administration of ^{131}I and restarted 3 to 7 days later. MMI is then slowly tapered over the next 4 to 6 weeks as thyroid function normalizes. β-Blockers can be continued during ^{131}I therapy. Dose of ^{131}I is based on the estimated weight of the patient's thyroid gland (typical dose, 10–15 mCi [370–555 MBq]). Radioactive iodine therapy is contraindicated during pregnancy and breastfeeding. Radioactive iodine therapy may acutely worsen Graves ophthalmopathy. Patients with prominent eye disease may be started on prednisone 40 mg/day, with dose tapered over 2 to 3 months. Radioactive iodine also may cause a painful thyroiditis, which may necessitate anti-inflammatory therapy.

Patient Encounter 2, Part 1

A 19-year-old female comes to the clinic stating, "I'm having trouble sleeping. I might be getting a little manic." She first noticed these symptoms a few weeks ago, which have not improved despite the use of over-the-counter sleep aids. She also feels more anxious for no reason, though she says cannabidiol (CBD) helps. She may have lost a little weight, but she is not sure. Sometimes she can feel her heart beating in her chest when she exercises but denies chest pain, syncope, or palpitations at rest. Her medications include lamotrigine and quetiapine for bipolar disorder, a multivitamin product, occasional acetaminophen for headaches, and a hormonal contraceptive. She thinks her mother had some kind of thyroid problem when she was pregnant with her.

PE:

General appearance: Patient appears slightly anxious and responds appropriately to all questions.

Weight 56 kg (123 lb); was 57.5 kg (126.5 lb) at her last visit

VS: Pulse 92 beats/min, BP 108/73 mm Hg, RR 12 breaths/min, T 37°C (98.6°F)

Skin: Warm, moist, and soft

HEENT: Slightly and symmetrically enlarged thyroid, which is nontender and without appreciable nodules; mild exophthalmos

CV: Apical HR: 92/min, RRR

Exts: No tremor

Diagnostic studies

ECG: Slight sinus tachycardia

Labs: Electrolytes, CBC normal. TSH 0.15 mIU/L (µIU/mL; reference range 0.5–4.5 mIU/L [µIU/mL]); FT_4 2.2 ng/dL (28.3 pmol/L; reference range 0.7–1.9 ng/dL, or 9.0–24.5 pmol/L); + TSHR-SAbs. Pregnancy test is negative.

Should this patient be treated for hyperthyroidism?

What therapeutic options exist for this patient's Graves disease?

What pharmacotherapy would you recommend? What if she were pregnant?

How would you initiate and titrate therapy?

What would you tell the patient regarding the cause of her signs and symptoms, significance of her abnormal thyroid function tests, and therapeutic options?

Patient Encounter 2, Part 2

Two years later, the patent is admitted to the hospital for altered mental status and to rule out acute psychosis and sepsis. For the past year, she had been working in Thailand as an English teacher. Due to the COVID-19 situation, she was unable to obtain her medications from home and was only taking a local herbal product. Her coworkers in Thailand noticed she was becoming increasingly fatigued, lethargic, and possibly delusional, saying that the Central Intelligence Agency and Thai police were watching her. Her family arranged for medical evacuation to the United States for further assessment and treatment.

PE:

Wt: 52 kg (114.4 lb)

General appearance: Patient appears sweaty and agitated.

VS: Pulse 146 beats/min, BP 92/66 mm Hg, RR 22 breaths/min, T 40°C (104°F), O_2 saturation 97% (0.97) on room air

Skin: Warm, sweaty, and soft

HEENT: Diffusely enlarged, nontender thyroid without any appreciable nodules; + exophthalmos

CV: Apical HR: 145 beats/min, RRR

Pulm: Clear to auscultation

Exts: + tremor; Reflexes: biceps, triceps, patellar, and Achilles: 3+/4

GI: Hyperactive bowel sounds

Mental status examination: Patient is only oriented to year and familiar persons. Cannot recall date, time, or location.

Diagnostic studies

COVID-19 PCR: neg

ECG: Sinus tachycardia with occasional premature atrial contractions

Labs: Electrolytes, CBC normal. TSH less than 0.1 mIU/L (µIU/mL; reference range 0.5–4.5 mIU/L [µIU/mL]); FT_4 9.4 ng/dL (121 pmol/L; reference range 0.7–1.9 ng/dL, or 9.0–24.5 pmol/L); + TSHR-SAbs. Pregnancy test is negative.

Diagnoses:

1) Thyroid storm.

2) **Sepsis:** rule out communicable diseases endemic to Thailand such as malaria and dengue fever.

What are the signs and symptoms of thyroid storm?

How should this patient be treated?

No long-term carcinogenic effect of ^{131}I has been demonstrated in clinical trials.[33]

Surgery Subtotal thyroidectomy is indicated in patients with very large goiters and thyroid malignancies and those who do not respond or cannot tolerate other therapies. Patients must be euthyroid before surgery, and they are often administered iodide preoperatively to reduce gland vascularity. Overall surgical complication rate is 2.7%. Postoperative hypothyroidism occurs in 10% of patients who undergo subtotal thyroidectomy. After thyroidectomy, serum calcium and intact parathyroid hormone levels should be monitored for early identification of postoperative hypoparathyroidism. Postoperative administration of 1250 to 2500 mg/day of calcium and 0.5 mcg/day of calcitriol may be given and then tapered over 1 to 2 weeks if the patient does not develop hypoparathyroidism.[33]

▶ *Special Conditions and Populations*

Graves Disease and Pregnancy Pregnancy may worsen or precipitate thyrotoxicosis in women with underlying Graves disease owing to the TSH agonist effect of β-hCG.[30] Untreated maternal thyrotoxicosis may result in increased rates of miscarriage, premature delivery, eclampsia, and low-birth-weight infants. Fetal and neonatal hyperthyroidism may occur as a result of transplacental passage of TSHR-SAbs. Because radioactive iodine is contraindicated and surgery is best avoided during pregnancy, most patients are treated with antithyroid drugs. PTU is considered the treatment of choice, particularly in the first trimester. While MMI is thought to have greater teratogenic potential versus PTU, the relative safety of these medications in pregnancy is not clear.[44] Patients receiving prepregnancy MMI are switched to PTU as soon as the pregnancy is confirmed. The lowest possible dose of PTU to maintain maternal euthyroidism should be used. Given the potential maternal adverse effects of PTU (eg, hepatotoxicity), patients should be switched from PTU to MMI for the second and third trimesters.[30,35] Antithyroid therapy in excessive doses may suppress fetal thyroid function. Although PTU and MMI are found in breast milk, nursing mothers should be switched to MMI after delivery because of the risk of hepatotoxicity from PTU in the mother and infant.

Pediatric Hyperthyroidism β-Blockers are administered to children who are symptomatic or have a heart rate greater than 100 beats/min.[33] MMI is the preferred antithyroid drug therapy in children at a dose of 0.2 to 0.5 mg/kg/day (divided doses preferred by some clinicians).[33] Once a euthyroid state is achieved, MMI dose can be reduced by 50% or more to maintain euthyroidism. As in adults, antithyroid drugs are administered to children with Graves disease for 1 to 2 years. If remission does not occur in that time, long-term antithyroid drug therapy, radioactive iodine, or surgical therapy is offered. Long-term studies with ^{131}I use in children show no increased risk of thyroid cancer or leukemia.[32]

Thyroid Storm Thyroid storm is a life-threatening condition caused by severe thyrotoxicosis.[30,45] Signs and symptoms include high fever, tachycardia, tachypnea, dehydration, delirium, coma, and GI disturbances. Thyroid storm is precipitated in a previously

Patient Care Process: Hyperthyroidism

Collect Information:

- Perform a medication history or medication reconciliation for the use of all medications and supplements. Identify adverse drug events, allergies, and hypersensitivities.
- Review the medical history and physical assessment findings.
- Speak with the patient and other caregivers as appropriate to identify issues affecting medication access and other aspects of care.

Assess the Information:

- Identify the potential underlying cause via a constellation of symptoms and signs (eg, nervousness, palpitations, smooth symmetrical goiter; and the presence of eye and/or skin findings in a person with Graves disease).
- Substantiate assessment via a TSH and FT_4 and TSHR-SAbs, if appropriate. A low or undetectable TSH level identifies thyrotoxicosis.

Develop a Care Plan:

- Treat severe or troublesome autonomic signs and symptoms with a nonselective β-blocker such as propranolol 10 to 40 mg four times daily. Titrate β-blocker dose based on signs and symptoms.
- Consider reducing excess thyroid hormone production with an antithyroid drug and/or radioactive iodine. If radioactive iodine is given, make sure that antithyroid drugs are stopped 4 to 6 days before treatment.
- MMI is the antithyroid drug of choice in most patients.
- Refer patients with Graves disease to an ophthalmologist for assessment and monitoring.
- Treat pregnant hyperthyroid women with PTU in first trimester.
- Address any patient concerns regarding therapy.

Implement the Care Plan:

- Educate the patient about any changes in therapy and how to identify, manage, and report adverse effects.
- Review proper medication administration with the patient, including issues related to food and concomitant medications.
- Discuss the importance of adherence and risks of over- and undertreatment.
- Determine if the patient has insurance coverage for prescription medications.
- If patient has been or is currently receiving pharmacotherapy to treat hyperthyroidism, assess efficacy, safety, and patient adherence. Note if there are there any significant drug interactions.
- If patient is not at desired TSH level, determine if pharmacotherapy or a change in pharmacotherapy is indicated.

Follow-up: Monitor and Evaluate:

- Monitor patients on antithyroid drugs for signs and symptoms of adverse effects.
- After baseline CBC with differential and liver profile, repeat CBC when patient has a febrile illness and repeat liver panel if signs or symptoms of hepatotoxicity occur (some recommend routine monitoring during the first 6 months of therapy).
- Assess for any skin rash or development of arthralgias.
- Antithyroid drugs have a delayed effect. After 2 to 4 weeks of therapy, adjust dose if the TSH is not in target range (0.5–2.5 mIU/L [μIU/mL]). When the patient is euthyroid, consider reducing dose of antithyroid drug to avoid hypothyroidism.
- Complete a periodic assessment of TSHR-SAbs.
- Consider stopping antithyroid therapy in patients with Graves disease after 12 to 18 months to see if remission has occurred.
- Several months after radioactive iodine, expect the patient will require permanent LT_4 replacement and evaluate for such.

hyperthyroid patient by infection, trauma, surgery, radioactive iodine treatment, and sudden withdrawal from antithyroid drugs. Patients are treated with a short-acting β-blocker such as IV esmolol, IV or oral iodide, and large doses of PTU (500–1000 mg load; then 250 mg every 4 hours) or MMI (60–80 mg/day). Supportive care with acetaminophen to suppress fever, fluid and electrolyte management, and antiarrhythmic agents are important components of therapy. IV hydrocortisone 300 mg initially and then 100 mg every 8 hours is used often because of the potential presence of adrenal insufficiency.

NONTHYROIDAL ILLNESS (EUTHYROID SICK SYNDROME)

Several changes in the hypothalamic–pituitary–thyroid axis occur during acute illness, termed *nonthyroidal illness* or *euthyroid sick syndrome*.[17,46] Type and degree of abnormalities depend on the severity of illness. Mild-to-moderate medical illness, surgery, or starvation causes a decrease in serum T_3 levels owing to decreased peripheral conversion of T_4 to T_3. Reduced T_3 levels do not correlate with ultimate mortality and are thought to be an adaptive response to stress. Patients with more severe illness, especially those in the intensive care unit, frequently have reduced total T_4 levels, although FT_4 levels often are normal. In critically ill patients, there is a correlation between degree of serum T_4 reduction and mortality. In most acutely ill patients who are euthyroid, TSH level is normal. However, administration of dopamine, octreotide, or high doses of glucocorticoids can reduce TSH levels. During recovery from acute illness, TSH level may become modestly elevated to renormalize serum T_4 levels. During this time, thyroid function tests may be misinterpreted to indicate hypothyroidism. Despite the sometimes very low T_4 levels, there is no evidence that LT_4 administration has any survival benefit.[3,17,47] Patients with possible thyroid abnormalities during acute illness should be evaluated by an endocrinologist.

THYROID CANCER AND LT_4 SUPPRESSION

KEY CONCEPT Growth and dissemination of thyroid carcinoma are stimulated by TSH. As such, LT_4 is an integral component of thyroid carcinoma management as it suppresses TSH secretion. Early in therapy, patients may receive the lowest LT_4 dose sufficient to fully suppress TSH to undetectable levels. Controlled trials show that suppressive LT_4 therapy reduces tumor growth and improves survival.[48] These patients are purposefully "overtreated" with LT_4, sometimes to a fully suppressed TSH level, and rendered subclinically or mildly hyperthyroid. Postmenopausal women and other individuals at high risk for osteoporosis should receive aggressive osteoporosis therapy to prevent LT_4-induced bone loss. Other thyrotoxic complications, such as atrial fibrillation, should be monitored and managed appropriately.

DRUG-INDUCED THYROID ABNORMALITIES

Drugs can affect thyroid function in several ways.[3,12] The effects of drugs on thyroid hormone protein binding, LT_4 absorption, and metabolism have been discussed previously. Several commonly used medications can alter thyroid hormone secretion.

Amiodarone

Amiodarone is a commonly prescribed antiarrhythmic drug that contains two iodide atoms, constituting 38% of its mass.[49] Each 200 mg dose of amiodarone provides 75 mg of iodide. Amiodarone deiodination releases about 6 mg of free iodine daily, 20 to 40 times more than the average daily intake of iodine in the United States. Amiodarone blocks conversion of T_4 to T_3, inhibits entry of T_3 into cells, and decreases T_3 receptor binding. Amiodarone causes rapid reduction in serum T_3 levels, increases free and total T_4 levels, and increases TSH level. After 3 months of therapy, TSH levels usually return to normal, although serum T_3 and T_4 level changes may remain. Most of these patients are euthyroid because FT_3 levels are in the low-normal range.

Amiodarone can frequently cause thyroid abnormalities in previously euthyroid patients. In patients treated with amiodarone for persistent atrial fibrillation, 25% developed subclinical hypothyroidism and 5% developed overt hypothyroidism.[50] Hyperthyroidism occurred in 5%. Thyroid abnormalities, when they occurred, were seen within 6 months of initiation of amiodarone therapy in almost all patients. Amiodarone-induced hypothyroidism is more common in iodine-sufficient areas of the world. Patients with underlying autoimmune thyroiditis are much more likely to develop amiodarone-induced hypothyroidism. Amiodarone-induced hypothyroidism occurs most commonly within the first year of therapy. If amiodarone cannot be discontinued, LT_4 therapy will be effective in most patients. If amiodarone can be stopped, thyroid function will return to normal in 2 to 4 months.

Amiodarone is more likely to cause thyrotoxicosis in iodine-deficient areas. Type 1 amiodarone-induced thyrotoxicosis is caused by iodine excess and typically occurs in patients with preexisting multinodular goiter or subclinical Graves disease. Type 2 amiodarone-induced thyrotoxicosis is a destructive thyroiditis that occurs in patients with no underlying thyroid disease. Amiodarone-induced thyrotoxicosis is more common in men. Because amiodarone has β-blocking activity, palpitations and tachycardia may be absent. In type 1 thyrotoxicosis, amiodarone should be discontinued. If amiodarone therapy cannot be stopped, larger doses of antithyroid drugs may be needed to control thyrotoxicosis. In type 2 thyroiditis, stopping amiodarone may not be necessary because spontaneous resolution may occur. Prednisone 40 to 60 mg/day will quickly improve thyrotoxic symptoms. Prednisone may be tapered after 1 to 2 months of therapy.

KEY CONCEPT Patients receiving amiodarone must receive monitoring for thyroid abnormalities. Baseline measurements of serum TSH, FT_4, FT_3, anti-TPOAbs, and TSHR-SAbs should be performed. TSH, FT_4, and FT_3 should be checked 3 months after initiation of amiodarone and then TSH at least every 3 to 6 months.

Lithium

Lithium is associated with hypothyroidism in up to 34% of patients, and hypothyroidism may occur after years of therapy.[12,51] Lithium appears to inhibit thyroid hormone synthesis and secretion. Patients with underlying autoimmune thyroiditis are more likely to develop lithium-induced hypothyroidism. Patients may require LT_4 replacement even if lithium is discontinued.

Interferon-α

Interferon-α causes hypothyroidism in up to 39% of patients being treated for hepatitis C infection.[3,12] Patients may develop transient thyroiditis with hyperthyroidism before becoming hypothyroid, which may be transient as well. Asian patients and patients with preexisting anti-TPOAbs are more likely to develop interferon-induced hypothyroidism. The mechanism of interferon-induced hypothyroidism is not known. If LT_4 replacement is initiated, it should be stopped after 6 months to reevaluate need for replacement therapy.

Tyrosine Kinase and Immune Checkpoint Inhibitors

TKIs are targeted antineoplastic agents used in several types of malignancies, including thyroid cancer.[13] Several TKIs have significant effects on thyroid function, both in previously hypothyroid patients on LT_4 replacement and in previously euthyroid patients. Imatinib has been shown to cause a fourfold increase in TSH levels in patients being treated for thyroid cancer. Sunitinib and sorafenib have been associated with primary hypothyroidism in 20% to 40% of treated patients. Some sorafenib patients developed mild hyperthyroidism before becoming hypothyroid. Patients receiving TKI therapy should have baseline and periodic thyroid function monitoring.

A variety of immune checkpoint inhibitors are used as targeted anticancer therapy. These agents have different specific mechanisms of action and include ipilimumab, nivolumab, atezolizumab, avelumab, and durvalumab. These agents can cause both hypothyroidism and hyperthyroidism. Incidence of thyroid dysfunction varies among the specific agents and combinations but ranges from 3% to 6% for hypothyroidism and 1% to 4.5% for hyperthyroidism with nivolumab to over 10% for both conditions with combination nivolumab and ipilimumab therapy.[13]

OUTCOME EVALUATION

- Desired outcomes include relieving signs and symptoms and achieving a euthyroid state.
- Success of therapy for thyroid disorders must be based not only on short-term improvement of the patient's clinical status and abnormal laboratory values but also on achievement of a long-term, stable euthyroid state. Maintaining TSH level in the normal range improves symptoms and reduces risk of long-term complications.
- Because pharmacotherapy is often lifelong, especially in patients with hypothyroidism, patients must undergo periodic monitoring to avoid long-term complications. In hypothyroid patients, such monitoring may involve simply asking the patient about signs and symptoms and a yearly measurement of TSH level.
- Any change in the patient's clinical status, such as a new pregnancy or a major change in body weight, necessitates a reevaluation of therapy. Patients at high risk for complications, such as pregnant women, the elderly, and patients with underlying cardiac disease, must be monitored more closely.
- Patients should be educated and periodically reminded about the importance of adherence and long-term tight control, need for periodic clinical and laboratory monitoring, and importance of staying on one LT_4 product.
- In hyperthyroid patients, the method of achieving desired outcomes may change over time with the use of antithyroid drugs versus radioactive iodine.
- Patients who receive antithyroid drugs must be monitored for adverse drug events such as hepatotoxicity and agranulocytosis.
- Patients who receive radioactive iodine must be monitored for development of hypothyroidism.
- In patients with thyroid cancer, desired outcomes with LT_4 therapy are often different from those in hypothyroid patients. LT_4 doses sufficient to suppress tumor growth may result in a suppressed TSH and mild hyperthyroidism. These patients must be monitored closely for complications of the mild hyperthyroid state, such as bone mineral loss and development of atrial fibrillation.

Abbreviations Introduced in This Chapter

ANCA	Antineutrophil cytoplasmic antibody
ANDA	Abbreviated New Drug Application
Anti-TGAb	Antithyroglobulin antibody
Anti-TPOAb	Antithyroid peroxidase antibody
AUC	Area under the (time-concentration) curve
β-hCG	β-Human chorionic gonadotropin
BMI	Body mass index
CBC	Complete blood count
CBD	Cannabidiol
CNS	Central nervous system
FDA	Food and Drug Administration
FT_3	Free T_3
FT_4	Free T_4
GI	Gastrointestinal
hCG	Human chorionic gonadotropin
ICPI	Immune checkpoint inhibitor
IGF-IR	Insulin-like growth factor I receptor
IV	Intravenous
LDL	Low-density lipoprotein
LT_4	Levothyroxine
MMI	Methimazole
NHANES	National Health and Nutrition Examination Survey
NTI	Narrow therapeutic index
PTU	Propylthiouracil
RAIU	Radioactive iodine uptake
SSKI	Saturated solution of potassium iodide
T_3	Triiodothyronine
T_4	Thyroxine
TBG	Thyroid- or Thyroxine-binding globulin
TKI	Tyrosine kinase inhibitor
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone (thyrotropin)
TSHR-SAb	Thyroid-stimulating hormone receptor-stimulating antibodies
TSI	Thyroid-stimulating immunoglobulin

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46 Adrenal Gland Disorders

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the regulation and physiologic roles of hormones produced by the adrenal glands.
2. Recognize the clinical presentation of adrenal insufficiency.
3. Describe the pharmacologic management of acute and chronic adrenal insufficiency.
4. Recommend therapy monitoring parameters for adrenal insufficiency.
5. Recognize the clinical presentation of Cushing syndrome and the physiologic consequences of cortisol excess.
6. Describe the pharmacologic and nonpharmacologic management of Cushing syndrome.
7. Recommend strategies to prevent the development of hypercortisolism and hypocortisolism.
8. Recommend therapy monitoring parameters for Cushing syndrome.

INTRODUCTION

The adrenal glands are important in the synthesis and regulation of key human hormones. They play a crucial role in water and electrolyte homeostasis, as well as regulation of blood pressure, carbohydrate and fat metabolism, physiologic response to stress, and sexual development and differentiation. This chapter focuses on pharmacologic and nonpharmacologic management of the two most common conditions associated with adrenal gland dysfunction: glucocorticoid insufficiency (eg, Addison disease) and glucocorticoid excess (Cushing syndrome). Other adrenal disorders such as congenital adrenal hyperplasia, pheochromocytoma, hypoaldosteronism, and hyperaldosteronism are beyond the scope of this chapter.

PHYSIOLOGY, ANATOMY, AND BIOCHEMISTRY OF THE ADRENAL GLAND

The adrenal gland is located on the upper segment of the kidney. It consists of an outer cortex and an inner medulla. The adrenal medulla secretes the catecholamines, epinephrine (also called adrenaline) and norepinephrine (also called noradrenaline), which are involved in the regulation of the sympathetic nervous system. The adrenal cortex consists of three histologically distinct zones: the outer zona glomerulosa, the zona fasciculata, and an innermost layer called the zona reticularis. Each zone is responsible for the production of different hormones (Figure 46–1).

The zona glomerulosa is responsible for the production of the mineralocorticoids, aldosterone, 18-hydroxy-corticosterone, corticosterone, and deoxycorticosterone. Aldosterone promotes renal sodium retention and potassium excretion. Its synthesis and release are regulated by renin in response to decreased vascular volume and renal perfusion. Adrenal aldosterone production is regulated by the renin–angiotensin–aldosterone system.

The zona fasciculata is the middle layer and produces the glucocorticoid hormone, cortisol. Cortisol is responsible for maintaining homeostasis of carbohydrate, protein, and fat metabolism. Its secretion follows a circadian rhythm, generally beginning to rise at approximately 3 to 4 AM and peaking around 6 to 8 AM. Thereafter, cortisol levels decrease throughout the day, approach 50% of the peak value by 4 PM, and reach their nadir around midnight. The normal rate of cortisol production is approximately 8 to 25 mg/day. Cortisol plays a key role in the body's response to stress. Its production increases markedly during physiologic stress, such as during acute illness, surgery, or trauma. In addition, certain conditions such as alcoholism, depression, anxiety disorder, obsessive-compulsive disorder, poorly controlled diabetes, morbid obesity, starvation, anorexia nervosa, and chronic renal failure are associated with increased cortisol levels. High total cortisol levels are also observed in the presence of increased cortisol-binding globulin (the carrier protein for 80% of circulating cortisol molecules), which is seen in pregnancy or other high-estrogen states (eg, exogenous estrogen administration). Cortisol is converted in the liver to an inactive metabolite known as cortisone.[1]

The zona reticularis produces the androgens, androstenedione, dehydroepiandrosterone (DHEA), and the sulfated form of DHEA (DHEA-S). Only a small amount of testosterone and estrogen is produced in the adrenal glands. Androstenedione and DHEA are converted in the periphery, largely to testosterone and estrogen.

Adrenal hormone production is controlled by the hypothalamus and pituitary. Corticotropin-releasing hormone (CRH) is secreted by the hypothalamus and stimulates secretion of adrenocorticotropic hormone (ACTH; also known as corticotropin) from the anterior pituitary. ACTH in turn stimulates the adrenal cortex to produce cortisol. When sufficient or excessive cortisol levels are reached, negative feedback is exerted on the secretion of CRH and ACTH, thereby decreasing the overall cortisol production. The control of adrenal androgen synthesis also follows a similar negative feedback mechanism. Figure 47–1 in Chapter 47,

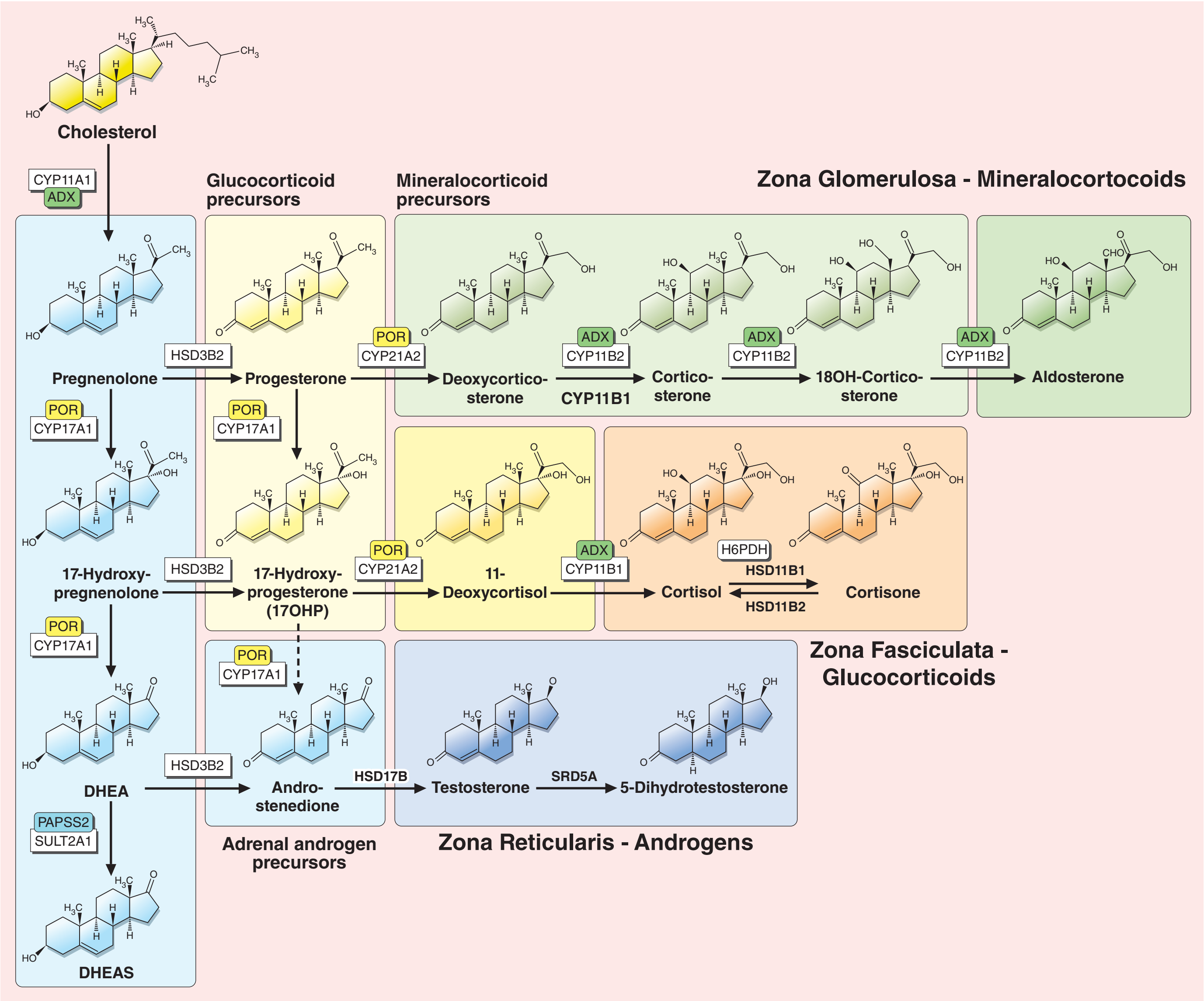
Cholesterol
CYP11A1
ADX
Glucocorticoid precursors
Mineralocorticoid precursors
Zona Glomerulosa - Mineralocortocoids
Pregnenolone
HSD3B2
Progesterone
POR
CYP21A2
Deoxycorticosterone
ADX
CYP11B2
CYP11B1
Corticosterone
ADX
CYP11B2
18OH-Corticosterone
ADX
CYP11B2
Aldosterone
POR
CYP17A1
POR
CYP17A1
17-Hydroxypregnenolone
HSD3B2
17-Hydroxyprogesterone (17OHP)
POR
CYP21A2
11-Deoxycortisol
ADX
CYP11B1
Cortisol
H6PDH
HSD11B1
HSD11B2
Cortisone
Zona Fasciculata - Glucocorticoids
POR
CYP17A1
POR
CYP17A1
DHEA
HSD3B2
Androstenedione
HSD17B
Testosterone
SRD5A
5-Dihydrotestosterone
PAPSS2
SULT2A1
DHEAS
Adrenal androgen precursors
Zona Reticularis - Androgens

FIGURE 46–1. The adrenal cortex consists of three histologically distinct zones: the outer zona glomerulosa, the middle zona fasciculata, and an innermost layer called the zona reticularis. Each zone is responsible for the production of different hormones. The zona glomerulosa is responsible for the production of mineralocorticoids such as aldosterone. The zona fasciculata produces cortisol and the zona reticularis produces androgens. (ADX, adrenodoxin; CYP11A1, side-chain cleavage enzyme; CYP17A1, 17-alpha-hydroxylase/17,20 lyase; CYP21A2, 21-hydroxylase; CYP11B1, 11-beta-hydroxylase; CYP11B2, aldosterone synthase; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; H6PDH, hexose-6-phosphate dehydrogenase; HSD11B1, 11-beta-hydroxysteroid dehydrogenase type 1; HSD11B2, 11-beta-hydroxysteroid dehydrogenase type 2; HSD3B2, 3-beta-hydroxysteroid dehydrogenase type 2; HSD17B, 17-beta-hydroxysteroid dehydrogenase; PAPSS2, PAPS synthase type 2; POR, P450 oxidoreductase; SRD5A, 5-alpha-reductase; SULT2A1, DHEA sulfotransferase.) (Adapted, with permission, from Arlt W. Disorders of the adrenal cortex. In: Longo DL, Fauci AS, Kasper DL, et al., eds. Harrison's Principles of Internal Medicine. New York City, NY: McGraw-Hill, 2018.)

"Pituitary Gland Disorders," depicts hormonal regulation with the hypothalamic–pituitary–adrenal (HPA) axis.

ADRENAL INSUFFICIENCY

Epidemiology and Etiology

Adrenal insufficiency generally refers to the inability of the adrenal glands to produce adequate amounts of cortisol for normal physiologic functioning or in times of stress. The condition is usually classified as primary, secondary, or tertiary, depending on the etiology (Table 46–1).[1-5] The estimated prevalence of primary adrenal insufficiency and secondary adrenal insufficiency are approximately 60 to 143 and 150 to 280 cases per 1 million persons, respectively. Whereas primary adrenal insufficiency is usually diagnosed in the third to fifth decade of life, secondary adrenal insufficiency is commonly detected during the sixth decade.[1,6] Adrenal insufficiency is more prevalent in women than in men, with a ratio of 2.6:1.[1] Chronic adrenal insufficiency is rare.

Pathophysiology

Primary adrenal insufficiency, also known as Addison disease, occurs when the adrenal glands are unable to produce cortisol. It occurs from the destruction of the adrenal cortex, usually

Table 46–1

Etiologies of Adrenal Insufficiency[1-5]

Primary Adrenal Insufficiency (Addison Disease)

- Autoimmune—accounts for 70%–90% of all cases of primary adrenal insufficiency
- Infectious or granulomatous diseases
  - Cytomegalovirus
  - Fungal (histoplasmosis, coccidioidomycosis, cryptococcosis, *Blastomyces dermatitidis* infection)
  - HIV (human immunodeficiency virus), AIDS (acquired immunodeficiency syndrome)
    - Mycobacterial, cytomegaloviral, *Pneumocystis jiroveci*, and *Toxoplasma gondii* infection
  - Sarcoidosis
  - Tuberculosis
- Bilateral adrenal hemorrhage or infarction—usually due to anticoagulant therapy, coagulopathy, thromboembolic disease, or meningococcal infection. Causes acute adrenal insufficiency
- **Adrenalectomy**
- Adrenoleukodystrophy (in men)
- Adrenomyeloneuropathy
- Infiltrative disorders: amyloidosis, hemochromatosis
- Genetic causes
  - Congenital adrenal hyperplasia
  - Familial glucocorticoid deficiency and hypoplasia
- Metastatic malignancy

Secondary Adrenal Insufficiency

- Cushing syndrome
- **Panhypopituitarism**
- Pituitary tumor
- Transsphenoidal pituitary microsurgery
- Pituitary irradiation
- Traumatic brain injury

Tertiary Adrenal Insufficiency

- Hypothalamic dysfunction

Drug-Induced (Most Common Cause of Secondary and Tertiary Adrenal Insufficiency)

- Chronic glucocorticoid administration at supraphysiologic doses
- Steroidogenesis inhibitors
- Megestrol acetate—has glucocorticoid-like activity
- Mifepristone (RU 486)—antagonizes glucocorticoid receptors
- Tyrosine kinase inhibitors
- Inducers of cytochrome P450 enzymes that increase cortisol metabolism (2B1, 2B2, 3A4)

from an autoimmune process. In general, the clinical manifestations are observed when destruction of the cortex exceeds 90%.[4] **KEY CONCEPT** Signs and symptoms of adrenal insufficiency reflect the disturbance of normal physiologic carbohydrate, fat, and protein homeostasis caused by inadequate cortisol production and inadequate cortisol action. Primary adrenal insufficiency usually develops gradually. Patients may remain asymptomatic in the early stages with signs and symptoms present only during times of physiologic stress. Persistent signs and symptoms of hypocortisolism typically occur with disease progression. Additionally, primary adrenal insufficiency may be accompanied by a reduction in aldosterone and androgen production.

Secondary adrenal insufficiency occurs as a result of pituitary gland dysfunction, whereby decreased production and secretion of ACTH leads to a decrease in cortisol synthesis. Tertiary adrenal insufficiency is a disorder of the hypothalamus that results in decreased production and release of CRH, which in turn decreases pituitary ACTH production and release. In contrast to

Clinical Presentation and Diagnosis of Chronic Adrenal Insufficiency[1,3,4,6]

General

- Symptoms develop gradually, especially in the early stages, may be vague, and mimic other medical conditions.
- Patients with autoimmune adrenal insufficiency may have other autoimmune disorders such as type 1 diabetes mellitus or autoimmune thyroiditis.

Symptoms (Percent Prevalence)

- Weakness and fatigue (99%).
- Anorexia, nausea, and diarrhea (56%–90%); may range from mild to severe with vomiting and abdominal pain.
- Hypoglycemia may occur.
- Amenorrhea may occur.
- Salt craving occurs in approximately 22% with Addison disease due to aldosterone deficiency.

Signs

- Weight loss (97%).
- Hypotension (< 110/70 mm Hg) and orthostasis (87%).
- Dehydration, hypovolemia, and hyperkalemia (in primary adrenal insufficiency only) due to aldosterone deficiency.
- Hyponatremia and hypochloridemia levels due to aldosterone deficiency. Hyponatremia can also be present in secondary insufficiency due to cortisol deficiency and increased antidiuretic hormone secretion leading to subsequent water retention.
- Increased serum blood urea nitrogen (BUN) and creatinine due to dehydration.
- Hyperpigmentation of skin and mucous membranes (92%). Usually observed around creases, pressure areas, areolas, genitalia, and new scars. Dark freckles and patches of vitiligo may be present. Hyperpigmentation, due to increased ACTH levels, occurs in most patients with primary but not secondary or tertiary insufficiency.
- Personality changes (irritability and restlessness) due to cortisol deficiency.
- Loss of axillary and pubic hair in women due to decreased androgen production.
- Blood count abnormalities (normocytic, normochromic anemia, relative lymphocytosis, neutrophilia, eosinophilia) due to cortisol and androgen deficiency.

Laboratory Tests (Table 46–2[1,3,4,7])

- Decreased basal and stress-induced cortisol levels.
- Decreased aldosterone level (in primary insufficiency only).
- Lack of increase in cortisol and aldosterone level after ACTH stimulation.

Other Diagnostic Tests

- Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the adrenal glands, pituitary, and/or hypothalamus can aid in determining etiology.
- The presence of antiadrenal antibodies is suggestive of an autoimmune etiology.

Table 46–2

Tests for Diagnosing Adrenal Insufficiency[1,3,4,7]

Test	Procedure	Rationale	Finding in Adrenal Insufficiency	Comments
Screening and Diagnostic Tests for Adrenal Insufficiency				
Unstimulated serum cortisol measurement	Measure serum cortisol at 6–8 AM	Serum cortisol level peaks in the early morning	Serum cortisol < 3 mcg/dL (83 nmol/L)	• Evaluate result in the context of those from other test(s) • Can be performed in conjunction with the rapid ACTH stimulation test (measure baseline serum cortisol before administering 250 mcg of cosyntropin)
Rapid ACTH stimulation test (also called **cosyntropin** stimulation test)	Measure serum cortisol 30–60 minutes after administering cosyntropin 250 mcg IM or IV	Increased cortisol secretion in normal individuals in response to ACTH stimulation but not in adrenal insufficiency	Serum cortisol concentration < 18–20 mcg/dL (497–552 nmol/L)	• Used as gold standard test for diagnosing primary adrenal insufficiency • False-negative results may occur if ACTH deficiency is of recent onset (< 1 month) • If measured serum cortisol concentration is low, measure plasma ACTH, aldosterone, and renin concentrations to differentiate between primary and secondary or tertiary adrenal insufficiency (see below) • A normal response does not exclude mild secondary adrenal insufficiency or recent onset ACTH deficiency. Additional testing (eg, insulin tolerance or metyrapone test) may be required
Insulin tolerance test (insulin-induced hypoglycemia test)	Administer insulin IV to induce hypoglycemia then measure serum cortisol during symptomatic hypoglycemia (confirm that blood glucose is < 40 mg/dL [2.2 mmol/L])	Evaluates ability of entire HPA axis to respond to stress (hypoglycemia)	Serum cortisol concentration < 18 mcg/dL (497 nmol/L) is indicative of secondary adrenal insufficiency	• If the result of the rapid ACTH stimulation test is normal, either this or the overnight metyrapone test is still needed to evaluate for secondary adrenal insufficiency. The insulin tolerance test is considered the gold standard • Contraindicated in patients with a seizure history, aged > 60 years, or cardiovascular or cerebrovascular disease • Requires close medical supervision • Contraindicated in adrenal crisis and primary adrenal insufficiency
Overnight metyrapone test	Administer metyrapone at midnight then measure serum cortisol at 8 AM the next day	Metyrapone inhibits cortisol synthesis. Its administration leads to rise in levels of ACTH and the precursor of cortisol, 11-deoxycortisol. Patients with adrenal insufficiency do not exhibit this	Normal response is a decrease in serum cortisol to < 5 mcg/dL (138 nmol/L) and an increase in 11-deoxycortisol to > 7 mcg/dL (202 nmol/L). Response not seen in secondary adrenal insufficiency	• Distinguishes between normal individuals and patients with secondary adrenal insufficiency • Contraindicated in adrenal crisis and primary adrenal insufficiency
Tests for Differential Diagnosis of Primary, Secondary, and Tertiary Adrenal Insufficiency				
Plasma ACTH concentration	Measure plasma ACTH	In primary adrenal insufficiency, hypocortisolism leads to elevated plasma ACTH concentration via positive HPA axis feedback	• Primary adrenal insufficiency: elevated plasma ACTH • Secondary or tertiary adrenal insufficiency: plasma ACTH low or inappropriately normal	• Evaluate result of test in combination with those from the plasma aldosterone and plasma renin tests

(Continued)

Table 46–2

Tests for Diagnosing Adrenal Insufficiency[1,3,4,7] (*Continued*)

Test	Procedure	Rationale	Finding in Adrenal Insufficiency	Comments
Plasma aldosterone concentration	Measure plasma aldosterone from the same blood samples as those used in ACTH stimulation test	Patients with primary adrenal insufficiency may experience a reduction in aldosterone production	• Primary adrenal insufficiency: low plasma aldosterone • Secondary or tertiary adrenal insufficiency: aldosterone concentration is usually normal (≥ 5 ng/dL [139 pmol/L])	• Evaluate result of test in combination with those from plasma ACTH and plasma renin tests
Plasma renin concentration or activity	Measure plasma renin concentration or activity	Mineralocorticoid deficiency occurs in primary adrenal insufficiency but is usually not present in secondary or tertiary adrenal insufficiency	• Primary adrenal insufficiency: elevated plasma renin • Secondary or tertiary adrenal insufficiency: plasma renin concentration or activity is usually normal	• Evaluate result of test in combination with those from plasma ACTH and plasma aldosterone concentration tests

ACTH, adrenocorticotropic hormone or corticotropin; HPA, hypothalamic–pituitary–adrenal; IM, intramuscularly; IV, intravenously.

Addison disease, aldosterone production is unaffected in the secondary and tertiary forms of the disease. Chronic adrenal insufficiency often has a good prognosis if diagnosed early and treated appropriately.

Acute adrenal insufficiency (ie, adrenal crisis) results from the body's inability to sufficiently increase endogenous cortisol during periods of excessive physiologic stress. Adrenal crisis can occur when patients with chronic adrenal insufficiency do not receive adequate glucocorticoid replacement during stressful conditions such as those experienced during surgery, infection, fever, acute illness, invasive medical procedures, or trauma. Acute adrenal insufficiency can also result from bilateral adrenal infarction due to hemorrhage, embolus, sepsis, or adrenal vein thrombosis. Patients who are critically ill may also experience impaired HPA axis function, with an overall prevalence rate of 10% to 20%, and as high as 60% in those experiencing septic shock. These patients are also at risk for the life-threatening consequences of an adrenal crisis. To better recognize this condition, the term *critical illness–related corticosteroid insufficiency* was coined by the American College of Critical Care Medicine Task Force in 2008.[8] Additionally, abrupt discontinuation or rapid tapering of glucocorticoids, given chronically in supraphysiologic doses, may lead to adrenal crisis. This condition results from prolonged suppression of the HPA axis and subsequent adrenal gland atrophy and hypocortisolemia. Other drugs associated with adrenal insufficiency include those that inhibit production (eg, ketoconazole) or increase metabolism (eg, the cytochrome P450 [CYP] 3A4 inducer rifampin) of cortisol.[4]

Clinical Presentation and Diagnosis of Acute Adrenal Insufficiency (Adrenal Crisis)[1,4,6]

General

- Onset of symptoms is acute and precipitated by excessive physiologic stress or abrupt discontinuation of supraphysiologic doses of chronic glucocorticoid.

Symptoms

- Severe weakness and fatigue.
- Abdominal or flank pain.

Signs

- Severe dehydration leading to hypotension and shock (circulatory collapse). Hypovolemia may not be responsive to intravenous (IV) hydration and may require use of vasopressors.
- Tachycardia.
- Nausea, vomiting.
- Fever.
- Confusion.
- Hypoglycemia.
- Laboratory abnormalities are similar to those observed in chronic adrenal insufficiency.

Laboratory Tests

- The unstimulated serum cortisol and rapid ACTH stimulation tests are useful in diagnosis (Table 46–2). The insulin tolerance test is contraindicated due to preexisting hypoglycemia. The metyrapone test is also contraindicated since metyrapone inhibits cortisol production.

Note: Due to the life-threatening nature of this condition, empiric treatment should be started before laboratory confirmation in patients who present with the clinical picture of acute adrenal crisis.

Regardless of the etiology, patients experiencing an adrenal crisis require immediate glucocorticoid treatment since manifestations such as circulatory collapse can lead to life-threatening sequelae.

Treatment

▶ *Chronic Adrenal Insufficiency*

The general goals of treatment are to manage symptoms and prevent development of adrenal crisis. KEY CONCEPT Lifelong glucocorticoid replacement therapy may be necessary for patients with adrenal insufficiency, and mineralocorticoid replacement therapy is usually required for those with Addison disease. Glucocorticoids with sufficient mineralocorticoid activity are generally required. However, the addition of a potent mineralocorticoid such as fludrocortisone, along with adequate salt intake, is sometimes needed to prevent sodium loss, hyperkalemia, and intravascular volume depletion. Mineralocorticoid supplementation typically is not indicated for the treatment of secondary or tertiary adrenal insufficiency because aldosterone production is often unaffected. Moreover, patients with secondary or tertiary adrenal insufficiency may only require replacement therapy until the HPA axis recovers. Hydrocortisone is often prescribed because it most closely resembles endogenous cortisol with its relatively high mineralocorticoid activity and short half-life and allows the design of regimens that simulate the normal circadian cycle.[3] Other glucocorticoids, however, can be used. Table 46–3 lists the pharmacologic characteristics of commonly used glucocorticoids.[9] Because the primary source of DHEA and androgens is the adrenal cortex, women with adrenal insufficiency may experience decreased libido and energy. Therefore, DHEA supplementation has been advocated as an option for female patients experiencing these effects from adrenal insufficiency. However, a meta-analysis that included 23 randomized controlled trials found that DHEA supplementation was not associated with significant improvement in libido or sexual function.[10] The use of DHEA remains controversial and requires further study. Management strategies for chronic adrenal insufficiency are outlined below:[1-3,6,11,12]

- For the treatment of primary adrenal insufficiency (Addison disease) in adults, hydrocortisone (15–25 mg) or cortisone acetate (20–35 mg) in two or three divided oral doses per day is recommended, with the highest dose given in the morning at awakening to mimic the early morning rise in endogenous cortisol. In a two-dose regimen, the second dose is taken in the early afternoon (2 hours after lunch); and in a three-dose regimen, the second dose is taken at lunch and the third dose is taken no closer than 4 to 6 hours before bedtime. This will avoid insomnia and allow for the lowest concentration in the blood at around midnight. In patients with concerns about adherence, oral prednisolone 3 to 5 mg/day, administered once or twice daily, may be given. Dexamethasone, a long-acting glucocorticoid is not recommended due to the risk of Cushingoid side effects from difficulty in dose titration. Doses of the glucocorticoid replacement therapy may need to be increased or decreased in patients taking CYP 3A4 inducers or inhibitors, respectively. Glucocorticoid therapy at physiologic replacement doses should not lead to the development of Cushing syndrome; however, careful monitoring should still be performed, and the smallest effective dose is used. Patients should be educated regarding the need for increased glucocorticoid dosage during excessive physiologic stress. In addition, administer oral fludrocortisone at a starting daily dose of approximately 0.05 to 0.1 mg in the morning and monitor for resolution of postural hypotension, dizziness, salt craving, dehydration, hyponatremia, and hyperkalemia; increase the dose if needed. Conversely, consider decreasing the dose if adverse reactions from mineralocorticoid administration such as hypertension, hypokalemia, fluid retention, and other significant adverse events occur. In patients receiving hydrocortisone, it should be noted that this drug also possesses mineralocorticoid activity; and patients should be educated to avoid licorice

Table 46–3

Pharmacologic Characteristics of Major Corticosteroids[9]

Corticosteroid	Glucocorticoid (Anti-Inflammatory) Potency	Mineralocorticoid (Sodium-Retaining) Potency	Duration of Action[a]	Equivalent Dose (mg)[b]
Glucocorticoid				
Cortisol (hydrocortisone)	1	1	S	20
Cortisone	0.8	0.8	S	25
Prednisone	4	0.8	I	5
Prednisolone	4	0.8	I	5
Methylprednisolone	5	0.5	I	4
Triamcinolone	5	0	I	4
Betamethasone	25	0	L	0.75
Dexamethasone	25	0	L	0.75
Mineralocorticoid				
Fludrocortisone	10	125	I	c

[a] S, short (ie, 8–12 hour biological $t_{1/2}$); I, intermediate (ie, 12–36 hour biological $t_{1/2}$); L, long (ie, 36–72 hour biological $t_{1/2}$).

[b] These dose relationships apply only to oral or intravenous administration, as glucocorticoid potencies may differ greatly following intramuscular or intra-articular administration.

[c] This agent is used for its mineralocorticoid effects, not for glucocorticoid effects.

Adapted, with permission, from Shimmer BP, Funder JW. Adrenocorticotropic hormone, adrenal steroids, and the adrenal cortex. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Pharmacological Basis of Therapeutics, 13th ed. New York City, NY: McGraw-Hill; 2018: Table 46–3.

Patient Encounter 1, Part 1: Presentation and Medical History

A 38-year-old woman presents to the primary care clinic with complaints of weakness, dizziness, abdominal pain, and upset stomach that have gradually worsened over the last few months. In tracking her home blood pressure readings, she sees her systolic blood pressure has dropped to 95 to 100 mm Hg consistently. Her husband feels she has become more easily irritable.

PMH:

- Graves disease
- Asthma

FH: Father with hypertension and coronary artery disease

SH: Denies smoking and alcohol or illicit drug use

Current Meds:

- Methimazole 5 mg three times daily
- Fluticasone propionate HFA 88 mcg via oral inhalation twice daily
- Albuterol two oral inhalations (90 mcg/actuation) every 4 to 6 hours as needed for shortness of breath

PE:

VS: Sitting BP 100/71 mm Hg, P 68 beats/min, standing BP 94/60 mm Hg, RR 16 breaths/min, Wt 128 lb (58.1 kg) (8 lb [3.6 kg] loss in last 6 months), Ht 5′5″ (165 cm)

Skin: Hyperpigmentation increases in palms

CV: RRR, normal S_1, S_2; no murmurs, rubs, or gallops

Labs (fasting): Serum electrolytes: sodium 137 mEq/L (mmol/L), potassium 4.8 mEq/L (mmol/L), chloride 97 mEq/L (mmol/L), bicarb 29 mEq/L (mmol/L), BUN 24 mg/dL (8.6 mmol/L), serum creatinine 1.1 mg/dL (97 μmol/L), glucose 65 mg/dL (3.6 mmol/L)

Which signs or symptoms of adrenal insufficiency does the patient exhibit?

Does her presentation offer any clues as to etiology or classification of adrenal insufficiency?

Which tests would be most useful for determining etiology and confirming diagnosis of adrenal insufficiency?

and grapefruit juice as they can enhance hydrocortisone's mineralocorticoid effect. Patients taking concurrent phenytoin may need a higher dose of fludrocortisone as it can induce fludrocortisone's metabolism. All patients with Addison disease should also maintain adequate sodium intake. Lastly, although controversial (as indicated above), consider giving DHEA 25 to 50 mg/day (as a single oral dose in the morning) for a 6-month trial to premenopausal female patients who do not experience an improvement in mood and well-being even with adequate glucocorticoid and mineralocorticoid replacement. In these patients, monitor serum DHEA-S (aim for the middle range of normal levels in healthy young people).

- Patients with secondary and tertiary adrenal insufficiency are treated with oral hydrocortisone or another glucocorticoid as described for primary adrenal insufficiency. However, patients with secondary and tertiary adrenal insufficiency may require a lower dose. Some patients (eg, patients with drug-induced adrenal insufficiency or adrenal insufficiency following treatment for Cushing syndrome) will only require glucocorticoid replacement temporarily, which can be discontinued after the recovery of the HPA axis. Fludrocortisone therapy is generally not needed.

► *Acute Adrenal Insufficiency*

KEY CONCEPT During an acute adrenal crisis, the immediate treatment goals are to correct volume depletion, manage hypoglycemia, and provide glucocorticoid replacement. The 2016 Endocrine Society's Clinical Practice Guideline on the Diagnosis and Treatment of Primary Adrenal Insufficiency recommends that adults receive a rapid infusion of 1-L isotonic saline within the first hour or 5% glucose in isotonic saline, followed by continuous IV isotonic saline guided by individual patient needs.[12] For hypoglycemia, dextrose 0.5 to 1 g/kg or 2 to 4 mL/kg of D25W (maximum single dose 25 g) should be infused slowly. Glucocorticoid replacement can be accomplished by hydrocortisone 100 mg IV followed by hydrocortisone 200 mg/day as a continuous infusion for 24 hours, reduced to 100 mg/day the following day.[12] After achieving hemodynamic stability, hydrocortisone can be tapered to a lower maintenance dose by the fourth or fifth day and fludrocortisone can be added if needed. The dose can be increased from 200 to 400 mg/day if there are complications.[1] For the treatment of patients with critical illness-related corticosteroid insufficiency, see the 2017 consensus statements from the Society of Critical Care Medicine and the European Society of Intensive Care Medicine.[13]

KEY CONCEPT Patients with known adrenal insufficiency should be educated about the need for additional glucocorticoid replacement and prompt medical attention during periods of physiologic stress. Although the dosage of glucocorticoid is generally individualized, a common recommendation is to double the maintenance dose of hydrocortisone if the patient experiences fever or undergoes invasive dental or diagnostic procedures.[3] Patients who experience vomiting or diarrhea may not adequately absorb oral glucocorticoids and may benefit from parenteral therapy until symptoms resolve. Prior to surgery, additional glucocorticoid replacement (higher dose and parenteral route) must be given to prevent adrenal crisis. The dose and protocol vary depending on the type of surgery (eg, larger doses for major surgery compared to minor surgery).

Patient Encounter 1, Part 2: Treatment

After appropriate laboratory and diagnostic tests are performed, the patient is diagnosed with Addison disease.

How should her chronic primary adrenal insufficiency be treated?

What monitoring parameters (therapeutic and toxic) should be implemented?

Patient Care Process: Adrenal Insufficiency

Collect Information:

- Perform a medication history of prescription and nonprescription medications.
- Identify allergies.
- Review the medical history and physical assessment findings.
- Identify lifestyle habits, health goals, and socioeconomic factors that affect care.

Assess the Information:

- Evaluate for typical clinical manifestations of chronic or acute adrenal insufficiency.
- Determine if the patient has any etiologies of adrenal insufficiency.
- Assess results from the rapid ACTH stimulation test for the presence of adrenal insufficiency (Table 46–2).
- Assess follow-up tests that differentiate between primary, secondary, and tertiary adrenal insufficiency (Table 46–2).

Develop a Care Plan:

- Determine whether patient will require mineralocorticoid replacement therapy in addition to glucocorticoid supplementation.
- Determine if the patient not previously diagnosed with adrenal insufficiency is presenting with acute adrenal crisis, in which case immediate treatment with injectable hydrocortisone and IV saline and dextrose solutions should be initiated prior to the confirmation of diagnosis.
- Determine and correct the underlying cause of the acute adrenal crisis (eg, infection).
- Devise a strategy for patients with chronic adrenal insufficiency that includes supplemental doses of glucocorticoid when varying degrees of physiologic stress are experienced (eg, minor infection, pending surgery).
- Monitor patient for signs of an acute adrenal crisis and develop a plan to treat this emergency condition.

Implement the Care Plan:

- Educate patient and caregivers on causes of adrenal insufficiency, how to recognize clinical manifestations, and the need to notify all healthcare providers of condition.
- Inform patients how to prevent an acute adrenal crisis: adhere to therapy, do not abruptly stop glucocorticoid treatment and increase glucocorticoid dose during different severity levels of physiologic stress, including childbirth.
- Discuss when to self-administer parenteral glucocorticoid and seek emergency care.
- Suggest wearing or carrying a medical alert (eg, bracelet, card).
- Review dietary and pharmacologic therapy, including duration of treatment and potential adverse consequences of glucocorticoid and mineralocorticoid replacement.

Follow-up: Monitor and Evaluate:

- Monitor for adequacy of treatment and adverse reactions from glucocorticoid and/or mineralocorticoid therapy.
- Determine duration of treatment for patients with secondary and tertiary adrenal insufficiency.

Outcome Evaluation

- Monitor weight, blood pressure, and serum electrolytes, along with symptom resolution and general well-being, in patients with adrenal insufficiency treated with glucocorticoid therapy; adjust dosages accordingly as needed.
- Monitor for adverse drug reactions related to glucocorticoid administration.
- Monitor for the progression of the underlying etiology of adrenal insufficiency in patients with secondary or tertiary adrenal insufficiency.

HYPERCORTISOLISM (CUSHING SYNDROME)

Epidemiology and Etiology

Cushing syndrome refers to the pathophysiologic changes associated with exposure to supraphysiologic cortisol concentrations (endogenous hypercortisolism) or pharmacologic doses of glucocorticoids (exogenous hypercortisolism). Cushing syndrome from endogenous causes is a rare condition, with an estimated incidence of two to five cases per 1 million persons per year.[14] Patients receiving chronic supraphysiologic doses of glucocorticoids, such as those with rheumatologic disorders, are at high risk of developing Cushing syndrome.

Pathophysiology

Cushing syndrome can be classified as ACTH dependent or ACTH independent (Table 46–4).[1,15-17] ACTH-dependent Cushing syndrome results from ACTH-secreting (or rarely CRH-secreting) adenomas. The term *Cushing disease* refers specifically to Cushing syndrome from an ACTH-secreting pituitary adenoma. ACTH-independent Cushing syndrome is due to either excessive cortisol secretion by the adrenal glands (independent of ACTH stimulation) or exogenous glucocorticoid administration. The plasma ACTH concentration is elevated in ACTH-dependent conditions but not in ACTH-independent conditions because elevated cortisol concentrations suppress pituitary ACTH secretion via negative feedback. ACTH and cortisol concentrations are elevated episodically in ACTH-dependent disease due to random hypersecretion of ACTH.[4] In general, patients with Cushing syndrome due to endogenous or exogenous glucocorticoid excess present with similar clinical manifestations. However, patients with ectopic ACTH syndrome may not exhibit the typical signs and symptoms of hypercortisolism due to the acute onset nature of the underlying disease process.[1,9]

Cushing disease and adrenal carcinomas cause adrenal androgen hypersecretion in high enough concentrations to result in signs of androgen excess such as acne, menstrual irregularities, and hirsutism and also cause virilization in women.[4]

Drug-induced Cushing syndrome from glucocorticoid administration occurs most commonly in patients receiving oral therapy, but other routes such as inhalation, dermal, nasal, and intra-articular have also been implicated.[15] Over-the-counter products, including dietary supplements, should also be evaluated since they may contain corticosteroids. Drug-induced Cushing syndrome has been reported with the use of herbal products adulterated with corticosteroids.[18,19] Risk of glucocorticoid-induced Cushing syndrome appears to increase with higher doses and/or longer treatment durations.[15]

Left untreated, patients with Cushing syndrome may experience severe complications of hypercortisolism, resulting in up to a nearly fourfold increase in mortality.[20] Mortality in patients with Cushing is mostly attributed to cardiovascular disease. Hypertension, hyperglycemia, and hyperlipidemia are common findings and can be associated with cardiac hypertrophy, atherosclerosis, and hypercoagulability. Osteopenia, osteoporosis, and increased fractures also have been reported.[20] Prevention and management of these conditions are discussed elsewhere in this chapter. Children may experience linear growth retardation from reduced growth

Clinical Presentation and Diagnosis of Cushing Syndrome[1,14,15,21]

General

- Onset of signs and symptoms ranges from gradual to rapid, depending on etiology.
- Differential diagnoses include diabetes mellitus and the metabolic syndrome because these conditions share several similar characteristics with Cushing syndrome (eg, obesity, hypertension, hyperlipidemia, hyperglycemia, and insulin resistance). In women, the presentations of hirsutism, menstrual abnormalities, and insulin resistance are similar to those of polycystic ovary syndrome. Cushing syndrome can be differentiated from these conditions by identifying the classic signs and symptoms described below.
- True Cushing syndrome also must be distinguished from other conditions that share some clinical presentations (as well as elevated plasma cortisol concentrations) such as depression, anxiety disorder, obsessive-compulsive disorder, alcoholism, obesity, uncontrolled diabetes, eating disorders, and physiologic stress—the so-called pseudo-Cushing states.

Signs and Symptoms (Percent Prevalence)

General appearance

- Weight gain and obesity, manifesting as truncal obesity (90%)
- Rounded and puffy face ("moon facies") (75%)
- Dorsocervical ("buffalo hump") and supraclavicular fat accumulation
- Hirsutism (75%)

Skin changes from atrophy of dermis and connective tissue

- Thin skin
- Facial plethora (70%)
- Skin striae ("stretch marks" that are usually red or purple in appearance and greater than 1 cm) (50%)—not common in patients older than 40 years of age
- Acne (35%)
- Easy bruising (40%)
- Hyperpigmentation—typically with ectopic ACTH syndrome

Metabolic

- Hyperglycemia that can range from impaired glucose tolerance (75%) to diabetes mellitus (20%–50%)
- Hyperlipidemia (70%)
- Polyuria (30%)
- Kidney stones (15%–50%)
- Hypokalemic alkalosis (from mineralocorticoid effect of cortisol)

Cardiovascular

- Hypertension (from mineralocorticoid effect of cortisol) (85%)
- Peripheral edema

Genitourinary

- Menstrual irregularities (typically amenorrhea) (70%)
- Erectile dysfunction (85%)

Other

- Psychiatric changes such as depression, emotional lability, psychosis, euphoria, anxiety, and decreased cognition (85%)
- Sleep disturbances
- Osteopenia (80%) and osteoporosis—usually affecting trabecular bone
- Linear growth impairment in children
- Proximal muscle weakness (65%)
- Avascular necrosis (more common in iatrogenic cases)
- Glaucoma, cataracts
- Impaired wound healing and susceptibility to opportunistic infections
- Hypothyroidism

Laboratory Tests

- Diagnosis is often complex and generally requires the involvement of endocrinologists and specialized testing centers.
- Initial screening tests are listed in **Table 46–5**.[1,21] Typically, a combination of two screening tests is used to establish the preliminary diagnosis.
- After the diagnosis is confirmed, additional tests (eg, midnight serum cortisol or combined dexamethasone suppression plus CRH test) can be performed to determine the etiology or rule out false positive/negative results.

Other Diagnostic Tests

Imaging studies and inferior petrosal sinus sampling may be needed to distinguish between pituitary, ectopic, and adrenal tumors.

Table 46–4

Etiologies of Cushing Syndrome[1,15-17]

ACTH Dependent
- ACTH-secreting pituitary tumor (Cushing *disease*)—70% of endogenous cases
- ACTH-secreting nonpituitary tumors (ectopic ACTH syndrome)— 15% of endogenous cases; usually from small cell lung carcinoma and bronchial carcinoids; also from pheochromocytoma, or from thymus, pancreatic, ovarian, or thyroid tumor. The tumor is usually disseminated (difficult to localize)
- CRH-secreting nonpituitary tumors (ectopic CRH syndrome)—rare

ACTH Independent—15% of endogenous cases
- Unilateral adrenal adenoma
- Adrenal carcinoma
- Bilateral nodular adrenal hyperplasia—rare (< 1%)

Drug-Induced Cushing Syndrome (ACTH independent)—most common cause of Cushing syndrome
- Prescription glucocorticoid preparations (most routes of administration)
- Nonprescription and herbal products with glucocorticoid activity (eg, nonprescription anti-itch products with hydrocortisone, herbal products with magnolia bark or those claiming to contain adrenal cortex extracts, or other byproducts)
- Other drugs with glucocorticoid activity (eg, megestrol acetate, medroxyprogesterone)

ACTH, adrenocorticotropic hormone or corticotropin; CRH, corticotropin-releasing hormone.

Table 46–5

First-Line Screening Tests in Patients with Characteristics of Cushing Syndrome[1,21]

Test	Test Procedure and Measurement	Rationale	Typical Finding in Cushing Syndrome	Comments
24-hour urinary free cortisol	Collect urine over 24 hours and measure unbound cortisol excreted by kidneys	Urinary cortisol is elevated in hypercortisolic states	Elevated urinary free cortisol (value depends on the assay used)	• Easy to perform but should not be used alone since sensitivity and specificity depend on assay used • To exclude periodic hypercortisolism, two or more samples should be obtained (with urinary creatinine measurement to assess completeness of collection) • Distinguishes the effects of Cushing syndrome (elevation) from obesity (no elevation). However, false positive in other pseudo-Cushing states, physiologic stress, if fluid intake ≥ 5 L/day, or taking carbamazepine or fenofibrate (if measured by HPLC) • False negative if moderate to severe renal function, or subclinical hypercortisolism
Overnight dexamethasone suppression test (DST)	Give 1 mg oral dexamethasone at 11 PM, then measure plasma cortisol at 8–9 AM the next morning	Dexamethasone administration suppresses morning plasma cortisol in normal individuals	Plasma cortisol < 1.8 mcg/dL (50 nmol/L) is not suggestive of Cushing syndrome	• Simple to perform and inexpensive • Can be used in conjunction with, or instead of, the urinary free cortisol test • False positive if pseudo-Cushing states, physiologic stress, pregnancy, estrogen treatment (including contraceptives), uremia, taking inducers of dexamethasone metabolism (phenytoin, alcohol, etc), or decreased dexamethasone absorption • False negative if subclinical hypercortisolism, slow metabolism of dexamethasone (eg, CYP3A4 inhibitors), or liver or renal impairment • In pseudo-Cushing states, the 48-hour 2-mg DST (administer 0.5 mg dexamethasone every 6 hours for 48 hours then measure serum cortisol at 8 or 9 AM after the last dose) is preferred
Late-night salivary cortisol	Collect salivary cortisol concentration at 11 PM	Loss of circadian rhythm of cortisol secretion (no nadir at night) in Cushing syndrome but not in pseudo-Cushing states	Elevated late-night salivary cortisol	• Easiest screening test to perform (sample can be collected at home by patient) • To exclude periodic hypercortisolism, two or more samples (on two separate evenings) should be obtained • False positive possible with cigarette smoking, chewing tobacco, licorice ingestion, in pseudo-Cushing states • Adjust collection time in shift workers and others with bedtime significantly after midnight

CYP, cytochrome P450; HPLC, high-performance liquid chromatography.

Patient Encounter 2

A 45-year-old man presents to a clinical pharmacist for asthma education. His medical history is significant for hypertension, hyperlipidemia, and asthma. He complains of insomnia, fatigue, and erectile dysfunction. Physical examination reveals an obese (BMI 39 kg/m^2) man with truncal obesity, dorsocervical fat, and facial plethora. His current medications include valsartan, atorvastatin, fluticasone/vilanterol inhaler, and albuterol inhaler. His fluticasone/vilanterol inhaler dose has increased over the last 2 years in the setting of asthma exacerbations. He has had several walk-in clinic visits this year for asthma exacerbations and was treated with a high-dose prednisone protocol each time. The clinical pharmacist suggests evaluation for possible Cushing syndrome.

Which findings are suggestive of Cushing syndrome?

Aside from Cushing syndrome, what are some major differential diagnoses for clinical presentation?

The patient is diagnosed with drug-induced Cushing syndrome after evaluation and diagnostic testing by the endocrinologist. What patient education points should be provided?

hormone secretion and inhibition of epiphysial cartilage development in long bones.[14,20]

Treatment

The goal of treatment in patients with Cushing syndrome is reversal of hypercortisolism and management of the associated comorbidities, including the potential for long-term sequelae such as cardiac hypertrophy. **KEY CONCEPT** Surgical resection is considered the treatment of choice for Cushing syndrome from endogenous causes if the tumor can be localized and if there are no contraindications. The treatment of choice for Cushing syndrome from exogenous causes is gradual discontinuation of the offending agent.

▶ *Nonpharmacologic Therapy*

Transsphenoidal pituitary microsurgery is the treatment of choice for Cushing disease. Removal of the pituitary tumor can bring about complete remission or cure in 78% to 97% of cases. HPA axis suppression associated with chronic hypercortisolism can result in prolonged adrenal insufficiency lasting for months after surgery and requiring exogenous glucocorticoid administration. Pituitary irradiation or bilateral adrenalectomy is usually reserved for patients who are not surgical candidates or for those who relapse or do not achieve complete remission following pituitary surgery. Because the response to pituitary irradiation can be delayed (several months to years), concomitant treatment with cortisol-lowering medication may be necessary. Bilateral adrenalectomy is also used for the management of adrenal carcinoma and in patients with poorly controlled ectopic Cushing disease in whom the ACTH-producing lesion cannot be localized. Bilateral laparoscopic adrenalectomy achieves an immediate and total remission (nearly 100% cure rate), but these patients will require lifelong glucocorticoid and mineralocorticoid supplementation.[5,22] Nelson syndrome may develop in nearly 20% to 50% of patients who undergo bilateral adrenalectomy without pituitary irradiation. This condition presumably results from persistent hypersecretion of ACTH by the intact pituitary adenoma, which continues to grow because of the loss of feedback inhibition by cortisol. Treatment of Nelson syndrome may involve pituitary irradiation or surgery.[4]

The treatment of choice in patients with adrenal adenomas is unilateral laparoscopic adrenalectomy. These patients require glucocorticoid supplementation during and after surgery due to atrophy of the contralateral adrenal gland and suppression of the HPA axis. Glucocorticoid therapy is continued until the recovery of the remaining adrenal gland is achieved. Patients with adrenal carcinomas have a poor prognosis, with a 5-year survival of 20% to 58%, because of the advanced nature of the condition (metastatic disease). Surgical resection to reduce tumor burden and size, pharmacologic therapy, or bilateral laparoscopic adrenalectomy are the treatment options commonly utilized to manage this condition.[1,5]

▶ *Pharmacologic Therapy*

KEY CONCEPT Pharmacotherapy is indicated when the ectopic ACTH-secreting tumor cannot be localized; to control hypercortisolism to prepare for surgery; in patients who (a) are not surgical candidates; (b) have failed surgery or had a relapse after surgery; or (c) have Cushing disease awaiting the onset of effect of pituitary radiation.[23] The drugs used are classified according to their mechanism and site of action (Table 46–6[22-30]). The most widely used therapeutic class is the adrenal steroidogenesis inhibitors, which can improve hypercortisolism by inhibiting enzymes involved in the biosynthesis of cortisol.[23] Because of their potential to cause adrenal suppression, temporary glucocorticoid replacement, and in some cases mineralocorticoid supplementation, may be needed during and after treatment.

KEY CONCEPT In drug-induced Cushing syndrome, discontinuation of the offending agent is the best management option. However, abrupt withdrawal of the glucocorticoid can result in adrenal insufficiency or exacerbation of the underlying disease.[15] **KEY CONCEPT** Glucocorticoid doses less than 7.5 mg/day of prednisone or its equivalent for less than 3 weeks generally would not be expected to lead to the suppression of the HPA axis.[5,25] However, in patients receiving pharmacologic doses of glucocorticoids for prolonged periods, gradual tapering to near physiologic levels (5–7.5 mg/day of prednisone or its equivalent) should precede drug discontinuation. Administration of a short-acting glucocorticoid in the morning and use of alternate-day dosing may reduce the risk of adrenal suppression. Testing of the HPA axis may be useful in assessing adrenal reserve. In some cases, supplemental glucocorticoid administration during excessive physiologic stress may be needed for up to 1 year after glucocorticoid discontinuation.[15] Table 46–7 lists strategies to prevent the development of hypercortisolism and hypocortisolism.

Outcome Evaluation

- Monitor patients receiving surgical, medical, or radiation therapy for the resolution of the clinical manifestations of hypercortisolism. Symptoms often improve immediately after surgery and soon after initiation of drug therapy. However, it may take months for symptoms to resolve following radiation therapy.
- Monitor for normalization of serum cortisol concentrations.
- Patient Care Process discusses additional evaluation strategies.

Table 46–6

Pharmacologic Treatments for Cushing Syndrome[22-30]

Drug	Mechanism of Action	Dosage[a]: Initial, Usual, Maximum, Dosing Adjustment for Renal and/or Hepatic Failure	Common and/or Major Adverse Reactions	Comment
Inhibitors of Adrenal Steroidogenesis				
Ketoconazole[b] (oral administration)	Inhibits several CYP enzymes, including 17,20-lyase, 17-hydroxylase, and 11β-hydroxylase. Also inhibits cholesterol synthesis	*Adults*: 400–1600 mg/day; every 6–8 hour dosing Extensively metabolized by liver and dosing adjustment should be considered in severe liver disease. Dosing adjustment not needed in renal disease	Generally well-tolerated. Symptoms of adrenal insufficiency (eg, nausea, vomiting, decreased appetite, fatigue) Gynecomastia, decreased libido, and impotence (due to inhibition of testosterone synthesis). Hepatotoxicity	• Effective in a majority of causes; rapid clinical improvement seen • Monitor efficacy with urinary cortisol • Monitor liver transaminases for hepatotoxicity • Useful in women with hirsutism and patients with hyperlipidemia • Requires gastric acidicity for dissolution and absorption, therefore not useful in patients with achlorhydria and those taking proton pump inhibitors or round-the-clock antacids or histamine-2 receptor blockers • Is a CYP3A4 substrate and a strong CYP3A4 inhibitor. Also has other CYP interaction potential. Coadministration with certain medications can lead to QT prolongation and dysrhythmia
Metyrapone[b] (oral administration)	Inhibits 11β-hydroxylase. Also suppresses aldosterone synthesis	*Adults*: 500 mg/day to 6 g/day; every 6–8 hour dosing Dosages in special populations (liver and kidney disease, elderly patients) have not been established	Generally well-tolerated Hirsutism, acne, adrenal insufficiency, GI intolerance, rash, hypokalemia, edema, hypertension	• Used in Cushing disease, ectopic ACTH syndrome, and adrenal carcinoma • Also used as a test to diagnose adrenal insufficiency
Osilodrostat (oral administration)	Inhibits 11β-hydroxylase	*Adults*: Starting dose: 2 mg twice daily. Maximum 30 mg twice daily	Generally well-tolerated. Symptoms of adrenal insufficiency (eg, nausea, vomiting, headache, fatigue, edema)	• FDA-approved in 2020 for adults with Cushing disease for whom pituitary surgery is not an option or has not been curative • Hypocortisolism-related adverse events occurred mainly during dose titration and were considered manageable • There are a number of ongoing clinical trials that will include evaluating long-term effects • Substrate of CYP3A4, CYP2B6, CYP2D6, and UDP-glucuronosyltransferases • Inhibitor of CYP1A2, CYP2C19, CYP2D6, and CYP3A4/5
Etomidate[b] (intravenous infusion administration)	Inhibits 17,20-lyase, 17-hydroxylase, and 11β-hydroxylase	*Adults*: Bolus and adjust dose based on serum cortisol level (typically a loading dose of 3–5 mg followed by 0.01–0.1 mg/kg/hour) Extensively metabolized in the liver to inactive metabolites. Because of changes in protein binding, dosing adjustment may be needed in kidney and liver disease	Injection site pain, nausea, vomiting, myoclonus, hypotension	• Is a general anesthetic and requires careful monitoring in an intensive care unit • Generally reserved for patients with more severe symptoms and in emergency settings

Adrenolytic Agent				
Mitotane (oral administration)	Inhibits steroidogenesis at lower doses and is adrenolytic at higher doses. Inhibits 11β-hydroxylase and cholesterol side-chain cleavage. Reduces aldosterone synthesis	*Adults*: Starting dose: 250 mg; 500 mg/day to 8 g/day. Elderly patients may require a dose decrease Primarily metabolized by the liver and dosing adjustment may be needed in liver disease	GI intolerance (high incidence), fatigue, dizziness, somnolence, gynecomastia Hyperlipidemia requiring lipid-lowering treatment Adrenal insufficiency requiring glucocorticoid replacement therapy	• FDA-approved for treatment of inoperable adrenal cortical carcinoma. Can be used in other types of Cushing syndrome • Efficacy takes several weeks • Lower rate of relapse when used with pituitary radiation. Also enables lower doses and therefore lower rate of adverse reactions • Hypocortisolism (if occurs) may persist several weeks/months after discontinuation as drug is stored in fatty tissues • Strong inducer of CYP3A4
Peripheral Glucocorticoid Antagonist				
Mifepristone (RU 486) (oral administration)	Antagonizes glucocorticoid receptors	*Adults*: 300–1200 mg/day Maximum 300 mg/day with concomitant strong CYP450 inhibitors Do not exceed 600 mg/day in renal impairment or mild-to-moderate hepatic impairment. Do not use in severe hepatic impairment	Nausea, fatigue, headache, hypokalemia, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite, endometrial hypertrophy, prolonged QT interval. Has abortifacient and embryotoxic properties	• FDA-approved for control of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery • Increases cortisol and ACTH levels via antagonism of negative feedback of ACTH secretion • Requires cautious use since limited clinical experiences and cannot use cortisol or ACTH levels to monitor efficacy of treatment • Quicker effectiveness compared to other drug treatment options • Is a CYP3A4 substrate. Also inhibits CYP3A and has other CYP interaction potential
Somatostatin Analog				
Pasireotide (subcutaneous injection)	Binds to somatostatin receptor subtype 5 overexpressed in corticotroph tumor cells resulting in the inhibition of ACTH secretion	*Adults*: 0.6–0.9 mg twice daily Moderate hepatic impairment (Child Pugh B): initial 0.3 mg twice a day, maximum 0.6 mg twice a day. Avoid in severe hepatic impairment (Child Pugh C). No dosage adjustment needed in renal impairment	Hyperglycemia, GI pain, nausea, diarrhea, headache, fatigue, bradycardia, QT prolongation, liver test elevations, cholelithiasis, pituitary hormone (other than ACTH) inhibition	• FDA-approved for treatment of adult patients with Cushing disease for whom pituitary surgery is not an option or has not been curative • Measure response based on 24-hour urinary free cortisol level and/or improvement in signs and symptoms

[a] Dosing guidelines (including age ranges) and safety for children have not been definitively established.

[b] These medications do not have FDA-approved indications for the treatment of Cushing syndrome in either adults or children.

ACTH, adrenocorticotropic hormone or corticotropin; CYP, cytochrome P450; FDA, Food and Drug Administration; GI, gastrointestinal.

Table 46–7

Principles of Glucocorticoid Administration to Avoid Hypercortisolism or Hypocortisolism

To Prevent Hypercortisolism and Development of Cushing Syndrome

- Give the lowest glucocorticoid dose that will manage the disease being treated and for the shortest possible duration
- If feasible, give glucocorticoid via administration routes that minimize systemic absorption (such as inhalation or dermal)
- If feasible, administer glucocorticoid treatment every other day (calculate the total 48-hour dose and give as a single dose of intermediate-acting glucocorticoid in the morning)[4]
- Avoid concurrent administration of drugs that can inhibit glucocorticoid metabolism

To Prevent Hypocortisolism and Development of Adrenal Insufficiency or Adrenal Crisis

- If the patient requires discontinuation from chronic treatment with supraphysiologic doses of glucocorticoid, the following discontinuation protocol can be used:[4]
  - Gradually taper the dose to approximately 20 mg of prednisone or equivalent per day, given in the morning, and then
  - Change glucocorticoid to every other day administration, in the morning
  - Stop the glucocorticoid when the equivalent physiologic dose is reached (20 mg/day of hydrocortisone or 5–7.5 mg/day of prednisone or equivalent)
  - Understand that recovery of the HPA axis may take up to a year after glucocorticoid discontinuation during which the patient may require supplementation therapy during periods of physiologic stress
- Evaluate patients at risk for adrenal insufficiency as a result of treatment(s) of Cushing syndrome and initiate glucocorticoid and mineralocorticoid replacement therapy as appropriate
- Avoid concurrent administration of drugs that can induce glucocorticoid metabolism
- Educate patients about:
  - The need for replacement or supplemental glucocorticoid and mineralocorticoid therapy
  - How to administer parenteral glucocorticoid if unable to immediately access medical care during an emergency
  - Need to wear or carry medical identification regarding their condition (eg, card, bracelet)

HPA, hypothalamic–pituitary–adrenal.

Patient Care Process: Cushing Syndrome

Collect Information:

- Perform a medication history of prescription and nonprescription medications.
- Identify allergies.
- Review the medical history and physical assessment findings.
- Identify lifestyle habits, health goals, and socioeconomic factors that affect care.

Assess the Information:

- Determine whether the patient is taking any glucocorticoids (from prescription or herbal/dietary supplement sources) that may have induced Cushing syndrome.
- Review relevant lab tests (eg, 24-hour urinary free cortisol, overnight dexamethasone suppression test [DST], late-night salivary cortisol).
- Establish diagnosis and etiology based on diagnostic testing.

Develop a Care Plan:

- Evaluate patient for appropriateness of surgery, radiation, and/or pharmacologic therapy depending on etiology.
- If etiology is exogenous administration of glucocorticoid, attempt taper.
- If etiology is endogenous, determine if patient is an appropriate candidate for surgical resection of the tumor or has contraindications to surgical resection such as advanced disease (metastatic adrenal carcinoma).
- Assess response and complications associated with surgery including[22]:
  - Measuring plasma cortisol postsurgery to determine if the patient displays persistent hypercortisolism (surgical-treatment failure) or hypocortisolism (adrenal insufficiency requiring steroid replacement therapy).
  - In patients demonstrating hypocortisolism:
    i. Monitor for signs and symptoms of glucocorticoid withdrawal (headache, fatigue, malaise, myalgia).
    ii. Monitor for signs and symptoms of adrenal insufficiency and develop a treatment plan.
    iii. Monitor morning cortisol or response to ACTH stimulation every 3 to 6 months to assess for HPA axis recovery. Discontinue glucocorticoid replacement therapy when cortisol concentrations are greater than 19 mcg/dL (524 nmol/L) on either test.
    iv. Monitor cortisol, ACTH, low-dose dexamethasone suppression, or other tests to assess for risk of relapse of hypercortisolism.
- If surgical resection does not achieve satisfactory disease control or is not indicated, evaluate the patient for pituitary radiation or bilateral adrenalectomy with concomitant pituitary radiation.
- Evaluate patients with adrenal adenomas for unilateral adrenalectomy.

(Continued)

Patient Care Process: Cushing Syndrome (*Continued*)

- Give glucocorticoid and mineralocorticoid replacement (permanently in the case of bilateral adrenalectomy).

Implement the Care Plan:

- Educate patient and caregivers on causes and possible sequelae of Cushing syndrome, how to recognize clinical manifestations, and the need to notify all healthcare providers of condition.
- Inform patients on how to reduce modifiable cardiovascular and metabolic complications.
- Review advantages and disadvantages of treatment options, including possible adverse consequences.
- Highlight the importance of adherence to therapy.
- Discuss the need for glucocorticoid and mineralocorticoid replacement after treatment, if appropriate.

Follow-up: Monitor and Evaluate:

- Monitor for response to therapy, need for dose adjustments, and the presence of adverse drug reactions.
- Once disease control is achieved, continue to monitor biochemical markers and patient for development of complications of Cushing syndrome, as relapse may occur.
- Monitor patients treated with surgery or pituitary radiation for development of pituitary hormone deficiency.

Abbreviations Introduced in This Chapter

ACTH	Adrenocorticotropic hormone or corticotropin
AIDS	Acquired immunodeficiency syndrome
BUN	Blood urea nitrogen
CRH	Corticotropin-releasing hormone
CT	Computed tomography
CYP	Cytochrome P450
DHEA	Dehydroepiandrosterone
DHEA-S	Sulfated form of dehydroepiandrosterone
DST	Dexamethasone suppression test
FDA	Food and Drug Administration
GI	Gastrointestinal
HIV	Human immunodeficiency virus
HPA	Hypothalamic–pituitary–adrenal
HPLC	High-performance liquid chromatography
IM	Intramuscular
IV	Intravenous or intravenously
MRI	Magnetic resonance imaging

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47

Pituitary Gland Disorders

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and Judy T. Chen

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. List the mediators and primary effects of pituitary hormones.
2. Identify clinical features of patients with acromegaly.
3. Discuss the role of surgery and radiation therapy for patients with acromegaly.
4. Select appropriate pharmacotherapy for patients with acromegaly based on patient-specific factors.
5. Identify clinical features of children and adults with growth hormone (GH) deficiency and select appropriate pharmacotherapy for these patients.
6. Recommend monitoring parameters necessary to assess therapeutic outcomes and adverse effects in patients receiving GH therapy.
7. List common etiologies of hyperprolactinemia.
8. Identify clinical features of patients with hyperprolactinemia.
9. Select appropriate pharmacologic and nonpharmacologic treatments for patients with hyperprolactinemia based on patient-specific factors.

PHYSIOLOGY OF THE PITUITARY GLAND

The pituitary, referred to as the "master gland," is a small endocrine gland located at the base of the brain and is responsible for the regulation of many other endocrine glands and body systems. Growth, development, metabolism, reproduction, and stress homeostasis are among the functions influenced by the pituitary. Functionally, the gland consists of two distinct sections: the anterior pituitary lobe and the posterior pituitary lobe. The pituitary receives neural and hormonal input from the inferior hypothalamus via blood vessels and neurons.

The posterior pituitary is innervated by nervous stimulation from the hypothalamus, resulting in the release of specific hormones to exert direct tissue effects. The hypothalamus synthesizes two hormones, oxytocin and vasopressin. These hormones are stored and released from the posterior pituitary lobe. The anterior pituitary lobe is under the control of several releasing and inhibiting hormones secreted from the hypothalamus via a portal vein system. It synthesizes and secretes six major hormones. Figure 47–1 summarizes the physiologic mediators and effects of each of these hormones.

Hormonal Feedback Regulatory Systems

The hypothalamus is responsible for the synthesis and release of hormones that regulate the pituitary gland. Stimulation or inhibition of the pituitary hormones elicits a specific cascade of responses in peripheral target glands. In response, these glands secrete hormones that exert negative feedback on other hormones in the hypothalamic–pituitary axis (see Figure 47–1). This negative feedback serves to maintain body system homeostasis. In general, high circulating hormone concentrations inhibit the release of hypothalamic and anterior pituitary hormones.

Damage and destruction of the pituitary gland may result in secondary hypothyroidism, hypogonadism, adrenal insufficiency, growth hormone (GH) deficiency, hypoprolactinemia, or panhypopituitarism. A tumor (adenoma) located in the pituitary gland may result in excess secretion of a hormone or may physically compress the gland and suppress adequate hormone release. The type, location, and size of a pituitary tumor often determine a patient's clinical presentation. This chapter discusses the pathophysiology and role of pharmacotherapy in the treatment of acromegaly, GH deficiency, and hyperprolactinemia. The following hormones are discussed elsewhere in this textbook: adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), antidiuretic hormone (or vasopressin; ADH), and oxytocin.

GROWTH HORMONE (SOMATOTROPIN)

Somatotropin or GH, the most abundant hormone produced by the anterior pituitary lobe, is regulated primarily by the hypothalamic–pituitary axis. The hypothalamus releases GH–releasing hormone (GHRH) to stimulate GH synthesis and secretion, whereas somatostatin inhibits it.[1] Release of GH into the circulation stimulates the liver and other peripheral target tissues to produce insulin-like growth factors (IGFs). These IGFs are the peripheral GH targets. There are two types of IGFs, IGF-I and IGF-II. IGF-I is responsible for growth of bone and other tissues, whereas IGF-II is primarily responsible for regulating fetal growth. High concentrations of IGF-I inhibit GH secretion through somatostatin, thereby inhibiting GHRH secretion at the hypothalamus.[1] The hypothalamus also may stimulate the release of somatostatin to inhibit GH secretion. The effects of IGF-I in peripheral tissues are both GH dependent and GH independent.[2]

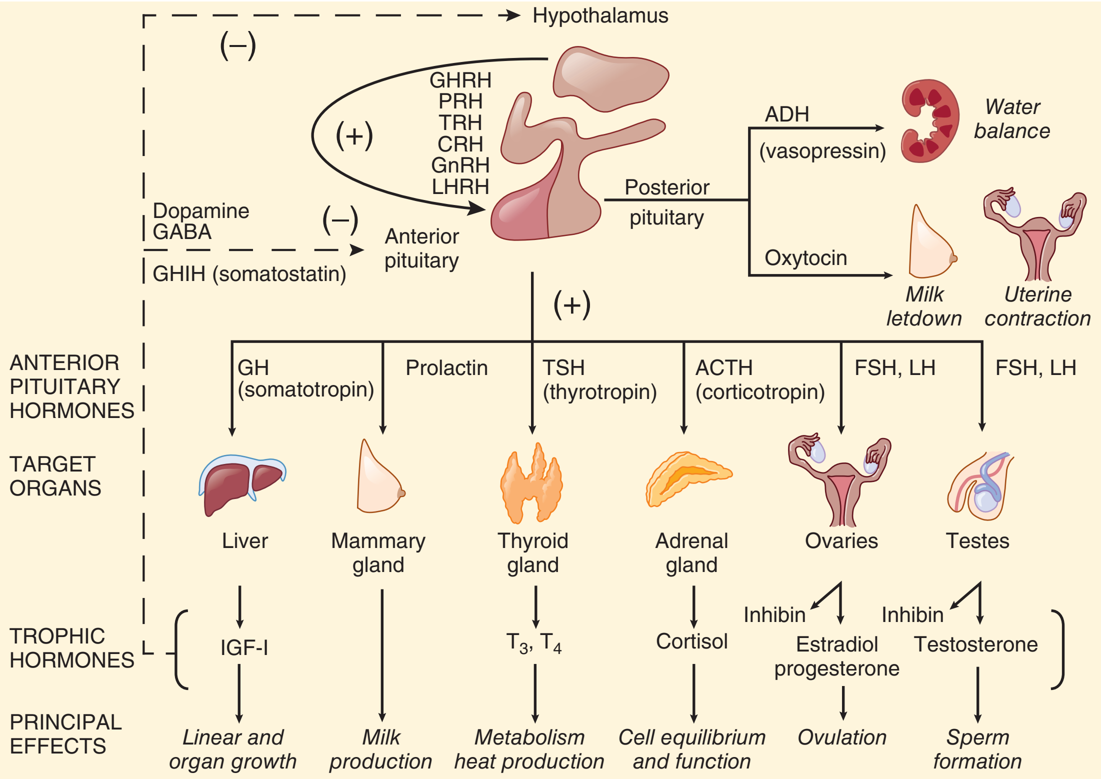
Hypothalamus
(–)
(+)
GHRH
PRH
TRH
CRH
GnRH
LHRH
Dopamine
GABA
(–)
GHIH (somatostatin)
Anterior
pituitary
Posterior
pituitary
ADH
(vasopressin)
Water
balance
Oxytocin
Milk
letdown
Uterine
contraction
(+)
ANTERIOR
PITUITARY
HORMONES
GH
(somatotropin)
Prolactin
TSH
(thyrotropin)
ACTH
(corticotropin)
FSH, LH
FSH, LH
TARGET
ORGANS
Liver
Mammary
gland
Thyroid
gland
Adrenal
gland
Ovaries
Testes
TROPHIC
HORMONES
IGF-I
T3, T4
Cortisol
Inhibin
Estradiol
progesterone
Inhibin
Testosterone
PRINCIPAL
EFFECTS
Linear and
organ growth
Milk
production
Metabolism
heat production
Cell equilibrium
and function
Ovulation
Sperm
formation

FIGURE 47–1. Hypothalamic–pituitary–target-organ axis. The hypothalamic hormones regulate the biosynthesis and release of eight pituitary hormones. Stimulation of each of these pituitary hormones produces and releases trophic hormones from their associated target organs to exert their principal effects. These trophic hormones regulate the activity of endocrine glands. Subsequently, increased serum concentration of the trophic hormones released from the target organs can inhibit both the hypothalamus and the anterior pituitary gland to maintain homeostasis (negative feedback). Inhibin is produced by the testes in men and the ovaries in women during pregnancy. Inhibin directly inhibits pituitary production of follicle-stimulating hormone (FSH) through a negative feedback mechanism. Melanocyte-stimulating hormone (MSH) produced by the anterior pituitary is not illustrated in the figure. (–), inhibit; (+), stimulate. (ACTH, adrenocorticotropic hormone [corticotropin]; ADH, antidiuretic hormone [vasopressin]; CRH, corticotropin-releasing hormone; GABA, γ-aminobutyric acid; GH, growth hormone [somatotropin]; GHIH, growth hormone–inhibiting hormone [somatostatin]; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; IGF-I, insulin-like growth factor-I; LH, luteinizing hormone; LHRH, luteinizing hormone–releasing hormone; PRH, prolactin-releasing hormone; T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone [thyrotropin].)

GH is an anabolic hormone with direct "anti-insulin" metabolic effects. By stimulating protein synthesis and shifting the body's energy source from carbohydrates to fats, GH promotes a diabetic state (Table 47–1).[2] GH controls somatic growth and has a critical role in the development of normal skeletal muscle, myocardial muscle, and bone.

Table 47–1

Effects of Growth Hormone[2]

	Effect(s)
Lipid metabolism	Increases breakdown of fat (lipolysis) Increases circulating fatty acid concentrations Increases lean body mass
Protein metabolism	Increases muscle mass
Carbohydrate metabolism	Decreases glucose utilization Increases insulin resistance Hyperglycemia Increases hepatic glucose output

In healthy individuals, GH is secreted in a pulsatile manner with several short bursts occurring mostly during the night. The amount of GH secretion fluctuates throughout a person's lifetime. Secretion of GH is the lowest during infancy, increases during childhood, peaks during adolescence, and then declines gradually during the middle years.[1] These changes are parallel to an age-related decline in lean muscle mass and bone mineral density.

Growth Hormone Excess

▸ *Epidemiology and Etiology*

Acromegaly affects both genders equally, and the average age of presentation is 44 years. Approximately 125 to 295 people per 1 million are affected, with an estimated annual incidence of five cases per 1 million people.[3] In more than 95% of cases, overproduction of GH is caused by a benign pituitary adenoma, whereas malignant adenomas are rare. Most pituitary adenomas occur spontaneously as a result of a sporadic genetic mutation acquired during life.[4] Depending on tumor size, pituitary adenomas are classified as (a) microadenomas if they are 10 mm or less in diameter; or (b) macroadenomas if they are greater than 10 mm.[4] Although these tumors can produce GH, they more commonly secrete GHRH resulting in excessive GH and IGF-I production.

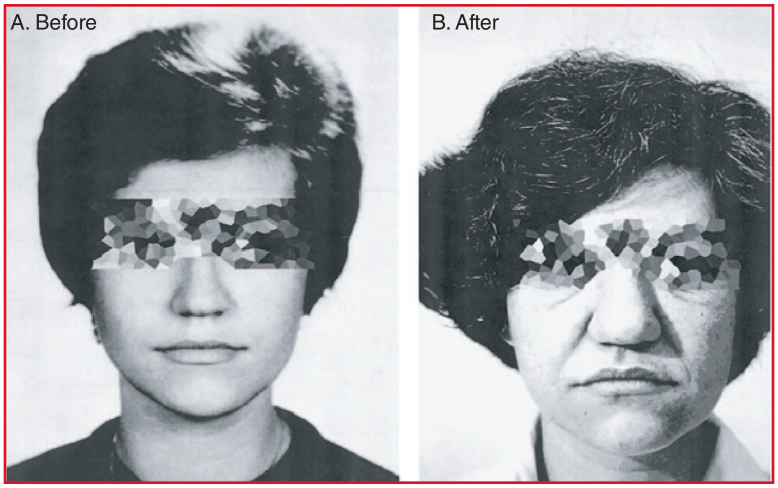

FIGURE 47–2. Before and after photographs of a patient with acromegaly. Compare the photographs **(A)** before the onset of acromegaly and **(B)** after approximately 20 years when the diagnosis was well established. Notice the coarsening of facial features, with an enlarged nose, lips, and forehead.

▶ *Pathophysiology*

Acromegaly is a rare disorder that manifests gradually over time and typically occurs after fusion of the epiphyses (growth plates) of the long bones.[5] The facial and hand features of an acromegalic patient are depicted in Figures 47–2 and 47–3. Gigantism refers to GH excess that occurs during childhood before epiphyseal closure and results in excessive linear growth. Because the signs and symptoms of acromegaly are insidious, diagnosis of this disorder is often delayed for up to 10 years after the initial presentation of symptoms.[5] Therefore, it is important for practitioners to be vigilant in identifying this disease in the early stages.

Diagnosis of acromegaly is based on both clinical and biochemical findings. Because GH fluctuates throughout the day, a single random measurement is never a reliable diagnostic tool to evaluate GH excess.[1] Serum IGF-I concentrations correlate positively with mean GH concentrations and are relatively stable, thus making elevations in IGF-I concentrations an ideal and reliable biochemical marker to monitor disease activity and response to therapy.[5,6] IGF-I serum concentrations are often represented as age- and sex-matched population values.[6] In addition to an elevated serum IGF-I concentration, an oral glucose tolerance test (OGTT) is recommended to confirm the diagnosis.[7] Under normal circumstances, GH is suppressed to less than 1 ng/mL (mcg/L) after administration of a 75-g oral glucose challenge because postprandial hyperglycemia inhibits secretion of GH. However, in patients with acromegaly, there is lack of suppression of GH following an oral glucose load.[7] Therefore, the diagnosis of acromegaly is confirmed if a patient has a random GH concentration greater than 1 ng/mL (mcg/L) or has nadir GH concentration greater than 0.4 ng/mL (mcg/L) 2 hours after the test.[7,8]

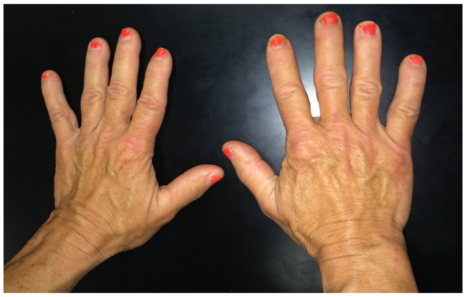

FIGURE 47–3. Photograph of hands from a patient with acromegaly. Soft-tissue swelling and enlargement of the hand in a woman with acromegaly resulting in increased ring and glove size.

▶ *Treatment*

Desired Outcomes Patients with untreated acromegaly experience a two- to threefold increase in mortality rate primarily because of cardiovascular, cerebrovascular, and pulmonary diseases,[5,7] with cancer reported as a cause of death in recent years.[6,8,10] **KEY CONCEPT** Prolonged exposure to elevated GH and IGF-I can lead to serious complications in patients with acromegaly.[10] Comorbid conditions such as hypertension, diabetes, dysrhythmias, coronary artery disease, and heart failure should be aggressively managed to prevent cardiovascular, pulmonary, metabolic, respiratory, musculoskeletal, and neuropathic complications.[6-8,10] Normalization of GH and IGF-I concentrations also normalizes mortality rate and improves overall life expectancy.[10] Goals of therapy are as follows:[5-8]

- Reduce fasting morning GH and IGF-I concentrations as close to normal as possible.
- Reduce tumor size to relieve tumor mass effect.
- Prevent tumor recurrence.
- Preserve normal pituitary function.
- Improve clinical signs and symptoms.
- Alleviate significant morbidities.
- Reduce mortality rates to those of the general population.

It is recommended for patients to receive treatment at the Pituitary Tumor Centers of Excellence to benefit from multimodal management of care with a multidisciplinary team of experts who can offer integrated acromegaly management and utilize the best and most cost-effective care with a personalized approach to treatment.[6,8]

Surgical Treatment According to the Endocrine Society[7] and the American Association of Clinical Endocrinologists (AACE) treatment guidelines for acromegaly,[5] **KEY CONCEPT** surgical resection of the pituitary tumor through transsphenoidal pituitary microsurgery is the treatment of choice for most patients with

Clinical Presentation and Diagnosis of Acromegaly[5-7,9]

General

The patient will experience slow development of soft-tissue overgrowth affecting many body systems. Signs and symptoms may gradually progress over 7 to 10 years.

Symptoms

- Headache and visual disturbances (loss of peripheral vision and blurred vision) caused by the actual tumor mass and its close proximity to the optic structures.
- Weakness, low blood sugar, or weight loss caused by the disruption of adrenal function (ie, ACTH deficiency) by the effect of tumor mass on the pituitary.
- Fatigue and weight gain caused by the disruption of thyroid function (ie, TSH deficiency) by the effect of tumor mass on the pituitary.
- Absence of regular menstrual periods (amenorrhea), impotence, and decreased libido caused by the disruption of the gonadotropin secretion (ie, LH and FSH).
- Excessive sweating, joint pain, nerve pain, and abnormal neurologic sensations (paresthesias) related to elevated GH and IGF-I concentrations.

Signs

- Coarsening of facial features
- Increased hand volume
- Increased ring and shoe size
- Increased spacing between teeth
- Increased acne or oily skin
- Enlarged tongue
- Deepening of voice
- Thick, irregular, and patchy skin discoloration
- Enlarged nose, lips, and forehead (frontal bossing)
- Abnormal protrusion of the mandible (prognathia) and bite abnormalities
- Inappropriate secretion of breast milk (galactorrhea)
- Abnormal enlargement of various organs (organomegaly) such as liver, spleen, and heart
- Carpal tunnel syndrome caused by nerve compression from the swollen tissue

Laboratory Tests

- Elevated IGF-I concentration compared with age-matched control values.
- OGTT: lack of suppression of GH to less than 1 ng/mL (mcg/L) or nadir GH concentration greater than 0.4 ng/mL (mcg/L) following documented hyperglycemia during an OGTT.
- Loss of other hormonal functions caused by tumor mass compression of the anterior pituitary.
- Measuring prolactin concentration in all patients because prolactin cosecretion is common.
- Impaired glucose tolerance and type 2 diabetes mellitus develop in 30% to 50% of patients.

Additional Clinical Sequelae

- Cardiovascular diseases: hypertension, coronary heart disease, cardiomyopathy, left ventricular hypertrophy, and arrhythmia.
- Osteoarthritis and joint damage develop in up to 90% of patients.
- Respiratory disorders and **sleep apnea** occur in up to 80% of patients.
- Vertebral fractures affect up to 60% of patients.
- Increased risk for the development of esophageal, lung, colon, stomach, kidney, and thyroid cancer.

Other Diagnostic Tests

- Perform magnetic resonance imaging (MRI) examination of the pituitary to locate the tumor and validate the diagnosis.
- Obtain serum prolactin concentrations to assess for hyperprolactinemia and **hypopituitarism**.
- Without obvious pituitary tumor but proven acromegaly, measurement of GHRH may be helpful to detect ectopic tumors.

Adapted from Jordan JK, Sheehan AH, Munir K. Pituitary gland disorders. In: DiPiro JT, Yee GC, Posey lM, Haines ST, Nolin TD, Ellingrod V, eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York City, NY: McGraw-Hill; 2020.

GH-producing pituitary adenomas. When performed by experienced surgeons, greater than 85% of patients with microadenomas and greater than 40% of patients with macroadenomas achieve biochemical remission.[7] Complete resection of a macroadenoma may be difficult if the tumor has already invaded the surrounding nerves and tissues. In such cases, debulking of the tumor along with adjunctive radiation and/or pharmacotherapy may improve treatment outcome. Infrequent surgical complications include meningitis, serious visual impairment, spinal fluid leakage, diabetes insipidus, and hypopituitarism.[7] Relative contraindications to surgery include patient frailty, acromegaly-associated comorbidities, and medically unstable conditions such as airway difficulties, severe hypertension, or uncontrolled diabetes.

Pharmacologic Therapy Pharmacologic therapy is often necessary for patients in whom surgery is not an option (Figure 47–4).[8] Somatostatin analogs, GH-receptor antagonists, and dopamine agonists are the primary pharmacologic therapies used for the management of acromegaly (Table 47–2).[1,5,7,8,11-14] Pharmacologic therapy avoids hypopituitarism and other surgical risks.

Somatostatin Analog (GH-Inhibiting Hormone) KEY CONCEPT Somatostatin analogs are the mainstay of pharmacotherapy for the treatment of acromegaly when surgery is not appropriate, or as an adjuvant therapy until patients achieve a sustained response to radiation therapy.[7,8] These agents mimic endogenous somatostatins and bind to somatostatin receptors in the pituitary to cause potent inhibition of GH, insulin, and glucagon secretion. Long-term treatment can sustain GH suppression, alleviate soft-tissue manifestations, and reduce tumor size. The long-acting preparations of somatostatin analogs (octreotide or lanreotide) are considered the cornerstone of therapy because of improved patient

Patient Encounter 1, Part 1

A 45-year-old man presents to your clinic for the first time, as requested by his primary care provider who has concerns that the side effects of his medications are causing bothersome symptoms. The patient complains of weakness, fatigue, excessive sweating, and joint pain. He states he recently scheduled an appointment to see the ophthalmologist because of his worsening blurry vision. The patient has noticeably large facial features, a very deep voice, and oily skin.

PMH: Heart failure, type 2 diabetes mellitus, sleep apnea

FH: Positive for heart disease in father and hypertension in mother

Allergies: No known drug allergies

SH: Janitor at an elementary school

Meds: Atorvastatin 40 mg daily, lisinopril 20 mg daily, metoprolol succinate 25 mg daily, furosemide 40 mg daily, metformin 1000 mg twice daily, liraglutide 1.8 mg daily, empagliflozin 25 mg daily, gabapentin 600 mg three times daily, aspirin 81 mg once daily, lidocaine cream 4% applied three to four times daily to affected area

Based on the information available, what signs and symptoms are suggestive of acromegaly?

What comorbidities are present in this patient as a result of untreated acromegaly?

What diagnostic tests should be performed to confirm the patient's diagnosis of acromegaly?

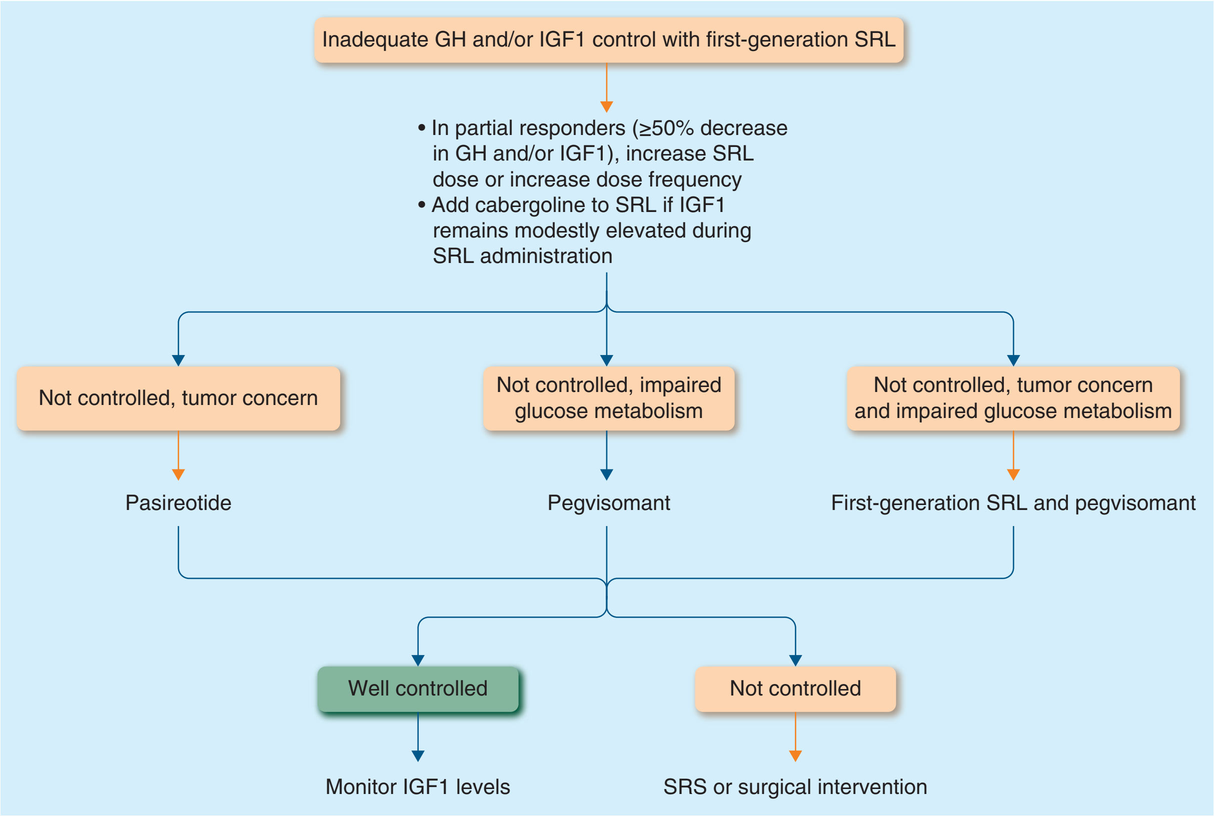
Inadequate GH and/or IGF1 control with first-generation SRL
• In partial responders (≥50% decrease in GH and/or IGF1), increase SRL dose or increase dose frequency
• Add cabergoline to SRL if IGF1 remains modestly elevated during SRL administration
Not controlled, tumor concern
Not controlled, impaired glucose metabolism
Not controlled, tumor concern and impaired glucose metabolism
Pasireotide
Pegvisomant
First-generation SRL and pegvisomant
Well controlled
Not controlled
Monitor IGF1 levels
SRS or surgical intervention

FIGURE 47–4. Medical management of patients with acromegaly.[8] The proposed algorithm presents treatment of acromegaly in patients inadequately controlled with first-generation somatostatin receptor ligands (SRL), lanreotide Autogel and octreotide long-acting release. In partial responders (greater than or equal to 50% decrease in growth hormone [GH] and/or insulin-like growth factor 1 [IGF1]), increase SRL dose and/or dose frequency. If IGF1 remains modestly elevated during SRL administration, add cabergoline to SRL. If disease control is not achieved, patients should be switched to the second-generation SRL pasireotide if there is a clinically relevant residual tumor on imaging and/or clinical concern of tumor growth (tumor concern). Patients with impaired glucose tolerance should be switched to the GH antagonist pegvisomant. Patients with impaired glucose tolerance and tumor concern should be treated with a combination of a first-generation SRL and pegvisomant. Those who remain uncontrolled despite second-line medical therapy should be considered for stereotactic radiosurgery (SRS) or surgical intervention (Reprinted by permission from Creative Commons Attribution License: Melmed S, Bronstein, MD, Chanson P, et al. A Consensus Statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol. 2018;14:552–561. (Licensed under a CC BY 4.0 license. Link available at https://creativecommons.org/licenses/by/4.0/.)

Table 47–2

Comparison of Various Drugs Within Drug Classes for Treatment of Acromegaly[1,5,7,8,11-14]

	Dopamine Agonist	Somatostatin Analog						GH-Receptor Antagonist
Medication	**Cabergoline**	**Octreotide (Sandostatin)**	**Octreotide (Mycapssa)**	**Octreotide LAR (Sandostatin LAR)**	**Lanreotide SR**	**Lanreotide Autogel (Somatuline Depot)**	**Pasireotide (Signifor LAR)**	**Pegvisomant (Somavert)**
Starting dose	1 mg/week orally	50 mcg SC thrice daily	20 mg PO twice daily	20 mg IM every 4 weeks	60 mg IM every 2 weeks	90 mg deep SC every 4 weeks[a]	40 mg IM every 4 weeks	10 mg SC daily after initial loading dose of 40 mg
Maximal dose	7 mg/week orally	100 mcg SC thrice daily	80 mg daily	40 mg IM every 4 weeks[b]	120 mg IM every 7 days	120 mg deep SC every 4 weeks	60 mg IM every 4 weeks	30 mg SC daily[c]
Dosage in hepatic insufficiency	Dosage reduction may be recommended for patients with severe hepatic failure	–	–	Cirrhosis: 10 mg IM every 4 weeks	Dosage reduction may be necessary; no guidelines available	Moderate-to-severe impairment: starting dose 60 mg every 4 weeks	Moderate impairment: starting dose 20 mg every 4 weeks, maximal dose of 40 mg every 4 weeks. Severe hepatic impairment: avoid use	Discontinue therapy if liver function tests are elevated at least five times the upper limit of normal or transaminase at least three times the upper limit of normal with any increase in serum total bilirubin
Dosage in renal failure	None	Dialysis dependent: adjustment may be necessary; no guidelines available	Initial dose in ESRD: 20 mg PO daily	Dialysis-dependent renal impairment: 10 mg IM every 4 weeks	Dosage reduction may be necessary; no guidelines available	Moderate-to severe-impairment: starting dose, 60 mg every 4 weeks	None	None
Side effects	Nausea, GI cramps, headache, drowsiness, dizziness, fatigue	Nausea, GI cramps, diarrhea, flatulence, abdominal pain, constipation, gallstones	Nausea, GI cramps, diarrhea, flatulence, abdominal pain, constipation, gallstones	Nausea, GI cramps, diarrhea, flatulence, abdominal pain, constipation, gallstones	Nausea, GI cramps, diarrhea, flatulence, abdominal pain, constipation, gallstones	Nausea, GI cramps, diarrhea, flatulence, abdominal pain, constipation, gallstones	Nausea, GI cramps, diarrhea, hyperglycemia, fatigue, gallstones, abdominal pain	Headache, fatigue, GI cramps, abnormal liver enzymes, injection-site reactions, sweating
Monitoring suggestions	GH, IGF-I, and prolactin concentration 4–6 weeks after each dose change	GH and IGF-I 3 months after dose change, thyroid function tests and blood glucose	GH and IGF-I 2 weeks after dose initiation or change, thyroid function tests and blood glucose	GH and IGF-I 3 months after dose change, thyroid function tests and blood glucose	GH and IGF-I 3 months after dose change, thyroid function tests and blood glucose	GH and IGF-I 3 months after dose change, thyroid function tests and blood glucose	GH and IGF-I 3 months after dose change, thyroid function tests and blood glucose	Liver function tests (serum transaminase, total bilirubin, alkaline phosphatase) monthly for 6 months, then biannually for the next year; MRI every 6 months, then yearly if no growth; IGF-I (not GH) after the first year, then yearly

[a] In the United States, initiate lanreotide at 90 mg every 28 days for 3 months and then titrate accordingly based on response.

Different labeled dosing guidelines exist for the United Kingdom and Canada.

[b] Product labeling recommends a maximum of 30 mg IM every 4 weeks.

[c] Although higher doses have been used in patients with persistently elevated IGF levels, doses > 30 mg/day are not approved and recommended.[8]

ESRD, end-stage renal disease; GH, growth hormone; GI, gastrointestinal; IGF-I, insulin-like growth factor-I; IM, intramuscularly; LAR, long-acting release; MRI, magnetic resonance imaging; PO, per os (by mouth); SC, subcutaneously; SR, slow release.

Adapted from AACE Medical Guidelines for Clinical Practice for the diagnosis and treatment of acromegaly. Endocr Pract. 2004;10:213–225 by permission of publisher, American Association of Clinical Endocrinologists (AACE) Corp.

adherence and acceptability over the first-generation octreotide. Somatostatin analogs normalize GH and IGF-I concentrations in approximately 55% of patients[5] and modestly reduce pituitary tumor size in more than half of patients with acromegaly.[7] Optimal dose titration of somatostatin analogs is important in disease control.[7] Patients with inadequate biochemical control can benefit from titrating to higher doses with more frequent dosing.[8] The long-acting release (LAR) formulation of pasireotide has been demonstrated to provide superior efficacy compared to octreotide or lanreotide in achieving clinical and biochemical control[11] and is recommended as the second-line therapy in patients with inadequate control with LAR lanreotide or octreotide.[8] The delayed-release oral octreotide is the first and only oral somatostatin analog approved for patients who previously responded to and tolerated octreotide or lanreotide injections.[12-14] The Pituitary Society integrates oral octreotide into the treatment algorithm for those who have demonstrated complete or partial biochemical response on octreotide or lanreotide injections, and recommends initiating it at the time of the previously scheduled injection.[14] While the oral somatostatin analog may improve patient acceptance due to its preferred route of administration, oral octreotide is less effective compared to the long-acting injectable preparations.

Because somatostatin analogs can achieve substantial relief of clinical symptoms with significant reduction in tumor size,[15] it is important to monitor patients for tumor recurrence if treatment is discontinued.[5,7] Use of somatostatin analogs before surgery is not routinely recommended due to insufficient data to suggest additional benefits over surgery alone.[16]

Somatostatin analogs are generally well tolerated. Transient gastrointestinal (GI) disturbances are common but usually subside within the first months of therapy.[17] Somatostatin analogs inhibit gallbladder contractility and decrease bile secretion; therefore, their major adverse effect is development of biliary sludge and asymptomatic gallstones (cholelithiasis).[17] Somatostatin analog–induced gallstones are generally asymptomatic; therefore, prophylactic therapy or routine abdominal ultrasound monitoring is usually not needed.[7,17] Additionally, somatostatin analogs may alter the balance of counterregulatory hormones (ie, glucagon, insulin, and GH), resulting in either hypoglycemia or hyperglycemia. Higher incidence of hyperglycemia and diabetes has been reported with pasireotide compared to other somatostatin analogs;[11] therefore, its use is not recommended in patients with uncontrolled diabetes.[6,8] Somatostatin analogs also may suppress pituitary release of TSH, leading to decreased thyroid hormone secretion and subsequent hypothyroidism. Proactive monitoring of thyroid function and glucose metabolism is recommended. Sinus bradycardia, conduction abnormalities, and arrhythmias have been reported with the use of somatostatin analogs. Because of the potential adverse effects of the somatostatin analogs, concomitant use with insulin, oral hypoglycemic agents, β-blockers, or calcium channel blockers may require careful dosage adjustment. Somatostatin analogs may also alter the bioavailability and elimination of cyclosporine, and monitoring of cyclosporine serum concentration is necessary.

GH-Receptor Antagonist The advent of a GH-receptor antagonist represents a novel approach to the treatment of acromegaly. Pegvisomant is the only genetically engineered GH-receptor antagonist that blocks the action of GH. Pegvisomant is indicated for the treatment of acromegaly in patients who have an inadequate response to surgery or radiation therapy. The effects of pegvisomant work independently of tumor characteristics, somatostatin, and dopamine receptors. To date, pegvisomant is the most effective agent in normalizing IGF-I concentration in acromegaly; it achieved this in 89% to 100% of patients in initial clinical trials, and in 73% in more recent cohorts.[18,19] Long-term safety and efficacy of pegvisomant (10 year follow up) from an ongoing postmarketing surveillance registry (ACROSTUDY) suggest a reasonable benefit/risk balance.[14,20] Pegvisomant therapy has favorable effects on glucose tolerance and insulin sensitivity and should be considered as a treatment option if patients have partial or no response to first-line medical therapy and also present with uncontrolled diabetes.[6] However, use of pegvisomant is associated with significant dose-dependent increases in GH despite declining IGF-I concentrations. The dose-dependent increase in GH is troubling because it has been suggested that persistent elevation of GH concentration may be indicative of tumor growth. Given the incidence of pituitary tumor enlargement is 6.8%, careful monitoring with periodic imaging scans is warranted.[20] **KEY CONCEPT** Pegvisomant is recommended in patients who have inadequate response to somatostatin analogs, or as an adjuvant for patients who have only a partial response to somatostatin analogs.[5,7,8] Patients at risk of visual damage from large tumors impinging on the optic chiasm may consider alternative pharmacologic therapy.[7]

The long-term use of pegvisomant appears to be well tolerated with a low incidence of adverse effects, including self-limiting injection-site reactions (3.1%) and elevated liver enzymes (3%).[20] Although elevations of liver enzymes often are self-limiting and not associated with symptoms,[5,7] hepatotoxicity has been reported in clinical trials, particularly in patients receiving combined pegvisomant and somatostatin analogs.[18] Therefore, serum transaminases, total bilirubin, and alkaline phosphatase should be assessed before initiating therapy and periodically thereafter. Use caution when administering pegvisomant to patients with elevated liver function tests (LFTs), and therapy should be discontinued in patients who present with clinical signs and symptoms of hepatic injury.

Dopamine Agonists Dopamine is one of the neurotransmitters that can increase GH secretion in healthy adults. However, dopamine agonists administered to patients with acromegaly exert the opposite effect and suppress GH release from the tumor. The first dopamine agonist used for acromegaly, bromocriptine, achieved normal IGF-I concentrations in fewer than 10% of patients.[21] The large doses of bromocriptine required to achieve the desired response are often associated with dose-limiting toxicity such as GI discomfort and orthostatic hypotension. Cabergoline is the preferred dopamine agonist for the treatment of acromegaly due to its improved tolerability and extended duration of action. Cabergoline can effectively reduce GH and IGF-I concentrations in approximately 30% of patients but its efficacy appears to decrease over time.[7] Although orally administered dopamine agonists are the least expensive medical therapy for managing acromegaly, the major disadvantage is their relative lack of efficacy compared with existing therapeutic options. **KEY CONCEPT** Cabergoline may be considered for patients with the modest elevation of GH and IGF-I concentrations less than 2.5 times the upper limit of normal (ULN). It may also be used as adjunctive therapy in patients unresponsive to monotherapy with somatostatin analogs or pegvisomant.[7,8] Although cardiac valvular abnormalities have been observed in patients using higher doses of cabergoline for Parkinson disease, patients receiving treatment for acromegaly do not seem to carry increased risk of cardiac valve disease.[5,7,21,22] Nonetheless, echocardiographic monitoring for potential cardiac abnormalities is reasonable for patients who require prolonged, high-dose (> 2 mg/week) cabergoline therapy.[7]

Combination Therapy For patients who are resistant to monotherapy, combination therapies have been beneficial with improved efficacy and reduced side effects associated with individual medication. Addition of pegvisomant or cabergoline may be considered in patients with inadequate response to somatostatin analog.[7,14]

Radiation Therapy Radiation therapy is an important adjunctive therapy in patients with residual GH excess after surgery or pharmacologic therapy.[7] Treatment involves the use of radiation to destroy rapidly growing tumor cells and often results in a reduction in tumor size. A major complication of radiation therapy is hypopituitarism, requiring lifelong hormone replacement.[5] There is also the potential for optic nerve damage if the pituitary tumor is near the optic tracts. Radiation therapy may take 10 to 20 years before its full effects become evident.[5] Owing to this delay in the onset of effectiveness, pharmacologic therapy with a somatostatin analog often is indicated as bridge therapy.[5,7] Men and women who desire to have children should be warned that pituitary irradiation therapy may impair fertility because of subsequent gonadotropin deficiency.[5]

Management of Acromegaly in Pregnancy Due to limited safety data, use of pharmacologic therapy during pregnancy is reserved for tumor and headache control. Substitute long-acting formulation of somatostatin analogs and pegvisomant with short-acting octreotide approximately 2 months prior to conception.[7] Monitoring of IGF-I and GH level during pregnancy is limited in patients with acromegaly because conventional assays are not usually able to distinguish between the variant forms of GH.[7]

▶ *Outcome Evaluation*

- Lifelong biochemical assessment is critical for determining therapeutic outcomes.[19] Although some patients may experience a rapid decline in GH concentrations after surgery, stabilization of IGF-I concentrations usually occurs 3 months after surgery but rarely may be delayed for up to 12 months. Fully assess pituitary function at 12 weeks or later after surgery.[5] Monitor random GH and IGF-I concentrations every 3 to 6 months postoperatively to assess treatment response.[5] Obtain IGF-I concentrations annually in all postsurgical patients to monitor for potential pituitary tumor recurrence.[5,7,19] Measure nadir GH level after glucose load in patients with GH greater than 1 ng/mL (mcg/L).[7]
- Assess MRI at least 12 weeks after surgery to visualize residual tumor.[7]
- For patients treated with somatostatin analogs, assess baseline fasting blood glucose, thyroid function tests, and heart rate. Thereafter, periodically monitor patients for adverse reactions such as GI disturbances, glucose intolerance, signs and symptoms of thyroid abnormalities, bradycardia, and arrhythmias in patients receiving long-term somatostatin analogs. Reevaluate IGF-I and GH concentrations at 3-month intervals to determine therapeutic response and inquire about symptoms of gallbladder disease (eg, intermittent pain in the upper right abdomen) during follow-up appointments.[5,7] If normalization of GH and IGF-I concentrations is not fully achieved after 1 year, perform MRI 6 months later and annually thereafter to monitor tumor mass.[5]
- For patients treated with a GH-receptor antagonist, GH concentrations are not measured because pegvisomant is a modified GH molecule that is detected in commercial GH assays, resulting in falsely elevated GH concentrations. Therefore, monitor IGF-I concentrations to assess response to pegvisomant therapy. After appropriate dose titration, monitor IGF-I concentrations every 6 months.[5,7] Concern for tumor growth requires careful monitoring of tumor size; therefore, perform MRI every 6 months during the first year of therapy. If there is no evidence of growth, then monitor annually thereafter.[7] Because of the potential for hepatotoxicity with pegvisomant therapy, it is mandatory to monitor liver enzymes prior to initiation of therapy, monthly during the first 6 months, biannually thereafter.[7] More frequent monitoring of liver enzymes is warranted in patients with elevated liver enzymes at baseline.[5] Discontinue pegvisomant if LFT is more than threefold elevated.[7]
- For patients receiving dopamine agonists, the maximal suppression of GH and IGF-I concentrations may take up to 3 months to achieve. After stable control of biochemical markers is achieved with dopamine agonists or somatostatin

Patient Encounter 1, Part 2

PE:

VS: BP 142/86 mm Hg, P 87 beats/min, RR 19 breaths/min, T 36°C (96.8°F), Ht 193 cm (6′4″), Wt 106 kg (233 lb), BMI 28.4 kg/m^2

ROS: (+) fatigue, (+) weakness (+) deepening of voice, (+) decreased joint motion, (+) excessive sweating

HEENT: Visual field defects; head is elongated with bony prominence of the forehead, nose, and lower jaw; large fleshy nose

CV: RRR, normal S1 and S2; no murmurs, rubs, or gallops, 2^+ pitting edema of lower extremities, (–) chest pain, palpitation, orthopnea

Pulm: (–) SOB, (–) cough

GI: (–) Nausea, vomiting, and abdominal pain

Abd: Soft, nontender, nondistended; (+) bowel sounds, (–) hepatosplenomegaly

Neuro: A&O × 3. Normal reflexes

Psychiatric: Pleasant

Available Labs: Electrolytes and renal function are within normal limits. Fasting blood glucose concentration is 234 mg/dL (13 mmol/L), glycated hemoglobin A1c ($HgbA_{1c}$) is 8.5% (0.085; 69 mmol/mol Hb), (+) microalbuminuria. GH concentration 2 hours after an OGTT is 72 ng/mL (mcg/L). Elevated IGF-I concentration at 876 ng/mL (mcg/L). TSH 1.2 μU/mL (mU/L) and free thyroxine (FT_4) 1.4 ng/dL (18 pmol/L) are within normal range

MRI: (+) 7 mm benign pituitary adenoma extending toward the optic chiasm; no invasion into the cavernous sinus

Given the patient does not want surgery, what pharmacologic treatment options are available?

What factors need to be considered when choosing a pharmacologic treatment option?

Provide monitoring parameters to assess efficacy and safety to the patient starting on pegvisomant.

Patient Care Process: Acromegaly

Collect Information:

- Review the available diagnostic data to determine pituitary tumor size and location.
- Perform complete medication history. Identify allergies to medications and other substances.
- Determine treatment options the patient has tried in the past.
- Review the medical history, relevant laboratory tests, and physical assessment findings.
- Speak with patient and review records to identify signs and symptoms of acromegaly, preferences and beliefs, health goals, and socioeconomic factors or barriers that affect medication access and other aspects of care.

Assess the Information:

- Assess the patient's clinical signs and symptoms and biochemical disease markers to determine the severity of acromegaly.
- Determine if the patient has a coexisting prolactin-secreting tumor and the impact of the tumor on the optic tract.
- Assess the presence of acromegaly complications. Identify any significant comorbidity associated with acromegaly that requires immediate treatment or early diagnosis.
- Evaluate patient for the presence of surgical contraindications to transsphenoidal microsurgery. Determine if the patient is able or willing to undergo surgical intervention.
- Assess if the patient has any contraindication or allergy to therapies (see Table 47–2).

Develop a Care Plan:

- If surgical intervention does not achieve satisfactory disease control, select subsequent appropriate pharmacologic therapy based on patient-specific factors (see Figure 47–4).
- Determine if selected drug doses are optimal (see Table 47–2). Consider if the patient's therapy requires any dose adjustment.

Implement the Care Plan:

- Discuss potential effectiveness and disadvantages of existing treatment options.
- Address any patient concern about acromegaly, its management, and possible complications.
- Determine whether the patient has insurance coverage and preferred treatments covered.
- Educate patient about changes in drug therapy, proper medication administration techniques, potential new adverse effects, and how to manage and report adverse effects that occur.
- Discuss the importance of medication adherence and how to reduce the modifiable cardiovascular and metabolic risk factors.
- Use motivational interviewing and coping strategies to maximize adherence.

Follow-up: Monitor and Evaluate:

- Monitor patient's biochemical markers (GH and IGF-I concentrations) and complications to surgical intervention.
- Review adherence to treatment plan using multiple sources of information.
- Review physical examination, lab tests, and results of other diagnostic tests to assess changes in clinical status and complications.
- Evaluate safety and efficacy of pharmacologic therapy and the degree of disease control.
- Determine whether the patient is experiencing any adverse reaction or drug interaction.
- Routinely assess acromegaly complications; include blood pressure, glucose tolerance, fasting lipid profile, cardiac evaluations (if clinically indicated), colonoscopy, dual-energy X-ray absorptiometry (DEXA) scan (hypogonadal only), evaluation of residual pituitary function, and sleep apnea.

analogs, monitor GH and IGF-I concentrations annually.[5] Measure GH, prolactin, and IGF-I level 4 to 6 weeks after dose change.[5]

- Monitor GH and IGF-I annually 1 to 3 months after medication withdrawal to assess efficacy of radiation therapy.[7] Assess for hypopituitarism and replace any hormone deficit.[7]

Growth Hormone Deficiency

▸ *Epidemiology and Etiology*

An estimated 2% of the population can be characterized as having short stature, with only 1 in 4,000 primarily caused by GH deficiency.[9] Children may present with GH deficiency at any time during their developmental stages. The evaluation of GH deficiency in a child of short stature should be deferred until appropriate exclusion of other identifiable causes of growth failure, such as hypothyroidism, chronic illness, malnutrition, genetic syndromes, and skeletal disorders, has occurred. Several medications, such as somatostatin analogs, gonadotropin-releasing hormone (GnRH) agonists, methoxamine, phentolamine, isoproterenol, glucocorticoids, cimetidine, methylphenidate, and amphetamine derivatives, may induce GH insufficiency.[23]

▸ *Pathophysiology*

GH deficiency exists when GH is absent or produced in inadequate amounts. GH deficiency may be congenital, acquired, or result from disruption of the hypothalamus–pituitary axis. GH deficiency may be an isolated condition or occasionally be accompanied by another endocrine disorder (eg, panhypopituitarism). Because GH is frequently undetectable with random sampling, a stimulation or provocative test is usually performed to confirm the diagnosis. Historically, the gold standard for diagnosis of adults with GH deficiency has been the insulin tolerance test (ITT); however, because of safety limitations, this test has been used less frequently in recent years.[25,26] The glucagon stimulation test (GST) has become the more commonly used alternative test because of its reproducibility and safety with relatively few contraindications. The macimorelin test, approved in 2017, is a GH

Clinical Presentation and Diagnosis of Growth Hormone Deficiency in Children[9,24]

General

The patient will have a physical height that is greater than two standard deviations below the population mean for a given age and sex.

Signs

- The patient will present with reduced growth velocity and delayed skeletal maturation.
- Children with GH-deficient or GH-insufficient short stature also may present with abdominal obesity, prominence of the forehead, and immaturity of the face.

Laboratory Tests

- Patients will exhibit a peak GH concentration of less than 10 ng/mL (mcg/L) after a GH stimulation test.
- Reduced IGF-I concentration may be present.
- Because GH deficiency may be accompanied by the loss of other pituitary hormones, hypoglycemia and hypothyroidism may be noted.

Other Diagnostic Tests

- Perform MRI of the hypothalamic–pituitary region to detect structural or developmental anomaly.
- Perform radiography of the left wrist and hand for children older than 1 year of age to estimate bone age (knee and ankle for children younger than 1 year of age).

Adapted from Jordan JK, Sheehan AH, Munir K. Pituitary Gland Disorders. In: DiPiro JT, Yee GC, Posey LM, Haines ST, Nolin TD, Ellingrod V, eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York City, NY: McGraw-Hill; c2020.

secretagogue expected to gain popularity, given it is well tolerated with lower likelihood of false-positive results.[26] In prepubertal children, measurement of IGF-I concentrations may be useful in evaluating GH deficiency.[27] The diagnosis of GH deficiency in children, often without the need for provocative testing, is established if the child exhibits all three conditions: (a) auxological criteria, (b) hypothalamic–pituitary defect, and (c) deficiency of at least one additional pituitary hormone.[28] Failure of linear growth is an almost universal presenting feature of childhood GH deficiency.

Childhood GH deficiency may or may not continue into adulthood. Most adults with GH deficiency have overt pituitary disease and present with nonspecific clinical disorders distinct from pediatric GH deficiency. Adult GH deficiency presumably

Clinical Presentation and Diagnosis of Growth Hormone Deficiency in Adults[25,26,29-32]

General

The patient likely will have a history of childhood-onset GH deficiency; hypothalamic or pituitary disorder; or the presence of three or four other pituitary hormone deficiencies caused by head trauma, tumor, infiltrative diseases, surgery, or radiation therapy.

Symptoms

- Reduced strength and exercise capacity
- Defective sweating (eg, reduced sweating)
- Psychological problems
- Low self-esteem
- Depression
- Fatigue or listlessness
- Sleep disturbance
- Anxiety
- Social isolation
- Emotional lability and impaired self-control
- Poor marital and socioeconomic performance

Signs

- Increased fat mass (especially abdominal obesity)
- Reduced lean body mass
- Reduced muscle strength
- Reduced exercise performance
- Thin, dry skin; cool peripheries; poor venous access
- Depressed affect, labile emotions
- Impaired cardiac function as evidenced by abnormal echocardiography or stress test results

Laboratory Tests

- ITT remains the gold standard test using a peak GH cut-point of 5 ng/mL (mcg/L).
- GST is an alternative test using body mass index (BMI)–appropriate cut-points as follows: GH cut-point of 3 ng/mL (mcg/L) for normal-weight and overweight patients (BMI 25 to 30 kg/m^2) with a high pretest probability; GH cut-point of 1 ng/mL (mcg/L) for obese (BMI > 30 kg/m^2) and overweight patients with a low pretest probability.
- A newer alternative is the macimorelin test with a GH cut-point of 2.8 ng/mL (mcg/L).
- The presence of three or more pituitary hormone deficiencies with a low IGF-I concentration does not require further stimulation test.
- Increased low-density lipoprotein cholesterol, total cholesterol, triglycerides; decreased high-density lipoprotein cholesterol.
- Reduced bone mineral density associated with an increased risk of fracture.
- Increased insulin resistance and prevalence of impaired glucose tolerance.
- GH deficiency may be accompanied by the loss of other pituitary hormones.

is associated with an increased risk of death from cardiovascular diseases.[24]

▶ *Treatment*

Desired Outcomes The goal of treatment for GH deficiency is to correct associated clinical symptoms.[23] In children, prompt diagnosis and early initiation of treatment are important to maximize final adult height. In adults, the goal is to achieve normal physiologic GH concentrations in an attempt to reverse metabolic, functional, and psychological abnormalities.[25,29]

Pharmacologic Therapy KEY CONCEPT Recombinant GH therapy is the main pharmacologic treatment for GH deficiency in both children and adults. It promotes skeletal, visceral, and general body growth; stimulates protein anabolism; and affects bone, fat, and mineral metabolism (see Table 47–1).[2] GH therapy requires subcutaneous or intramuscular administrations, given as daily injections. It is recommended to administer GH injections in the evening to mimic physiologic endogenous GH secretion.[26] Many preparations of synthetic GH (somatropin) are available with a variety of injection devices to make administration more appealing and easier. Zomacton is only approved for use in children, and other somatropin products such as Humatrope, Norditropin, Nutropin, Genotropin, Omnitrope, and Saizen are approved in both children and adults. The long-acting GH (LAGH) preparations are available in China and South Korea but currently under development in the United States.[30]

KEY CONCEPT Although comparative trials have not been conducted to date, recombinant GH products appear to have similar efficacy for treating GH deficiency as long as the regimen follows currently approved guidelines.[26] GH secretion decreases with age; therefore, older adults with GH deficiency often require substantially lower replacement doses than younger individuals. The optimal therapeutic approach is to initiate GH therapy at lower doses and titrate according to clinical response, adverse effects, and IGF-I concentrations.[26,30] Table 47–3 lists the recommended GH replacement doses for children and adults.[25,26,28] Conventional weight-based regimens are not recommended in adults due to lack of evidence supporting higher dosages in heavier individuals and greater potential for adverse effects.[25,29,31] For elderly patients, lower GH replacement doses often are adequate because of increased GH sensitivity.[29,31] Women with intact hypothalamic–pituitary–gonadal axis or on estrogen therapy (or oral contraceptives) generally require a higher GH dose than men due to decreased GH concentrations associated with estrogen.[26,31] Carefully monitor patients requiring replacement therapy with estrogens, thyroid hormones, or glucocorticoids because of potential interactions with GH therapy.[29] The potency of GH products is generally expressed as 3 international units (IU or mU) per 1 mg of protein.[25] Selection of an injection device depends on patient preference due to lack of differences in clinical outcomes among the various injection systems.[26]

Evidence has suggested that GH treatment in GH-deficient children can increase short-term growth and improve final adult height.[9] Beneficial effects of GH therapy in adults with GH deficiency have been demonstrated to normalize body composition and metabolic process; improve cardiac risk profile, bone mineral density, quality of life, and psychological well-being; and increase muscle strength and exercise capacity.[25,31] However, evidence for reduction in cardiovascular risks and mortality are still lacking with long-term use of GH replacement therapy.[33]

Practitioners should begin GH therapy as soon as possible to optimize long-term growth. As somatropin is synthetic human GH, there is no evidence that one commercial product is more advantageous than another, apart from differences in devices that are more user-friendly, dose per mg adjustments, and whether the product requires refrigeration. Patients should generally be started on a low dose guided by age, gender, and concomitant medications.[26] It is recommended that GH dose in pediatric patients does not continue beyond achievement of a growth velocity below 2 to 2.5 cm/year.[28] The decision to discontinue therapy prior to this should be individualized on factors such as

Table 47–3

Dose Recommendation for Growth Hormone Deficiency in Children and Adults[25,26,28]

	Growth Hormone Replacement Dose	Dose Titration
Children[28]	**Starting Dose**	• Evaluate every 3–6 months based on height and height velocity.
Prepubertal children	22–35 mcg/kg/day with individualization on subsequent dosing	• Monitor IGF-I and IGFBP-3 yearly. • Monitor TSH and T_4 for hypothyroidism. • Reduce dose if serum IGF-I concentration is substantially above normal after 2 years of therapy.
During puberty	Individualized dosing	• Against routine increase in dose to 700 mcg/kg/week. • Resume growth hormone at 50% of the dose used in childhood during transitions.[26]
Adults[25,26]	**Starting Dose**	• Increase dose by 0.1–0.2 mg/day at 1- to 2-month intervals based on clinical response, serum IGF-I concentrations, and side effects. Longer time intervals and smaller dose titration may be necessary in older adults and those with other comorbidities.
Age < 30 years	0.4–0.5 mg/day[a]	
Age 30–60 years	0.2–0.3 mg/day	
Age > 60 years	0.1–0.2 mg/day	
Concurrent diabetes, obesity, older age, or previous gestational diabetes	0.1–0.2 mg/day	
Hepatic impairment	–	• Clearance may be reduced in patients with severe hepatic dysfunction; specific dosing suggestions are not available.
Renal impairment	–	• Patients with chronic renal failure tend to have decreased clearance; specific dosing suggestions are not available.

[a]Might require a higher dose for patients transitioning from pediatric treatment.

IGFBP-3, insulin-like growth factor-binding protein 3; IGF-I, insulin-like growth factor-I; T_4, thyroxine; TSH, thyroid-stimulating hormone.

Patient Care Process: GH Deficiency in Children

Collect Information:

- Obtain a thorough history and physical examination (weight and height) that may indicate the possible presence of GH deficiency.
- Obtain GH and IGF-I concentrations.
- Review imaging tests of the hypothalamic–pituitary region to detect any anomalies.
- Speak with caregivers to identify signs and symptoms of GH deficiency, preferences and beliefs, health goals, and socioeconomic factors or barriers that affect medication access and other aspects of care.

Assess the Information:

- Assess the child's growth characteristics and compare the physical height with a population standard (eg, Centers for Disease Control and Prevention growth charts).
- Exclude other identifiable causes of growth failure.
- Assess the presence of other pituitary hormone deficiency.
- Assess risk factor for development of malignancy (history of cancer or active cancer).
- Assess if the patient has any contraindication, allergy, or drug interaction with GH therapy.

Develop a Care Plan:

- Calculate the appropriate GH therapy at the lower dosing range based on patient weight (see Table 47–3).

Implement the Care Plan:

- Initiate GH therapy based on patient preference (see Table 47–3).
- Discuss with caregivers and child the potential effectiveness and disadvantages of existing GH treatment options.
- Address any patient concern about long-term complications of GH deficiency, its management, and possible adverse effects of GH therapy.
- Educate regarding potential for lifelong replacement therapy.
- Use motivational interviewing and coping strategies to maximize adherence.

Follow-up: Monitor and Evaluate:

- Review child's medication adherence.
- Monitor response (increase in height and change in height velocity) and adverse effects of GH therapy (intracranial hypertension, slipped capital femoral epiphysis, and scoliosis progression). Individualized dose based on child's response.
- Continue GH therapy until child reaches satisfactory adult height, achieves documented epiphyseal closure, or fails to respond to treatment.
- Review and retest the child using adult GH deficiency diagnostic criteria when the child reaches final adult height.

growth plate fusion or failed response.[28] In patients transitioning from pediatric to adult care, it is important to retest after at least 1 month following discontinuation of GH therapy. In patients with persistent GH deficiency, it is suggested to resume GH therapy at 50% of the dose last used in childhood, and gradually titrate upward to avoid any adverse effect.[26] Resuming GH therapy in these patients is important to obtain full somatic maturation, normalization of body composition, and lipid metabolism in adulthood. The optimal duration of treatment with GH therapy remains unclear, but lifelong therapy may be required. However, if there is no therapeutic benefit after at least 12 to 18 months of treatment, discontinuing GH therapy may be appropriate.[25]

In both children and adults, treatment with GH may mask underlying central hypothyroidism and adrenal insufficiency.[34] Treatment with GH also may induce insulin resistance and lead to the development of glucose intolerance in patients with preexisting risk factors. Adults are more susceptible to dose-related adverse effects of GH-induced symptoms, such as edema, arthralgia, myalgia, and carpal tunnel syndrome, which may necessitate dose reductions in up to 40% of adults.

Children treated with GH replacement therapy rarely experience significant adverse effects. Benign increases in intracranial pressure related to GH therapy may manifest as headaches, visual changes, or altered concentrations of consciousness. This condition is generally reversible upon discontinuation of treatment. Often, GH therapy can be restarted with smaller doses without symptom recurrence. There is still no compelling evidence that GH replacement therapy is associated with an increased risk of cancers in children without prior history or risk factors.[26,35,36] It remains unclear if risk is affected in patients considered high risk. Survivors of childhood cancer may have an increased risk of abnormal growth of tissues with GH treatment, but it does not appear to increase the risk of cancer reoccurrence.[35] The risk of cancer was unrelated to duration or cumulative dose of GH treatment, but cancer mortality risk increases significantly with increasing daily dose of GH in previous cancer survivors.[36]

Nevertheless, GH replacement therapy is contraindicated in all patients with active malignancy.[26] If considering GH therapy, it would be prudent to wait for at least 1 year in children (5 years in adults) after cancer remission with the understanding that GH may potentially increase the risk of tumor recurrence.[26] Because deaths have been reported with the use of GH in children with Prader–Willi syndrome who are severely obese or suffer from respiratory impairments, use of GH is contraindicated in these individuals. Evidence from the long-term surveillance study, Safety and Appropriateness of GH treatments in Europe (SAGhE), remains inconclusive regarding GH therapy and its risk of increased morbidity.[33] Therefore, further surveillance monitoring is warranted.

► *Outcome Evaluation*

- Children with GH deficiency should be evaluated by a pediatric endocrinologist every 3 to 6 months. Monitor for an increase in height and change in height velocity to assess response to GH therapy.[24,26] Every effort should be made to maximize height before the onset of puberty. After final adult height is reached and GH is discontinued for at least

Patient Care Process: GH Deficiency in Adults

Collect Information:

- Obtain a thorough history and physical examination that may indicate the possible presence of GH deficiency, history of childhood GH deficiency, or the presence of other pituitary hormone deficiencies.
- Obtain GH and IGF-I concentrations after appropriate provocative testing.
- Review imaging tests of the hypothalamic–pituitary region to detect any anomaly.
- Perform complete medication history. Identify allergies to medications and other substances.
- Speak with patient to identify signs and symptoms of GH deficiency, preferences and beliefs, health goals, and socioeconomic factors or barriers that affect medication access and other aspects of care.

Assess the Information:

- Assess the patient's clinical signs and symptoms to determine the severity of GH deficiency.
- Assess the presence of other pituitary hormone deficiency.
- Assess the presence of metabolic abnormalities and cardiovascular and fracture risks.
- Assess risk factor for development of malignancy (history of cancer or active cancer).
- Assess if the patient has any contraindication, allergy, or drug interaction with GH therapy.

Develop a Care Plan:

- Determine if GH therapy is indicated. Initiate the appropriate GH therapy at the lower dosing range based on patient characteristics (see Table 47–3).

Implement the Care Plan:

- Initiate GH therapy based on patient preference and characteristics (see Table 47–3).
- Discuss with patient the potential effectiveness and disadvantages of existing GH treatment options.
- Address any patient concern about long-term complications of GH deficiency, its management, and possible adverse effects of GH therapy.
- Discuss with patient how to reduce the modifiable cardiovascular, metabolic, and fracture risk factors.
- Educate regarding potential for lifelong replacement therapy.
- Use motivational interviewing and coping strategies to maximize adherence.

Follow-up: Monitor and Evaluate:

- Review medication adherence.
- Assess the efficacy and adverse effects of GH therapy and consider if the patient's therapy requires any dose adjustment based on IGF-I concentration, patient response, and adverse effects.
- Monitor for improvement of metabolic, cardiovascular, bone mineral density, mood, and body composition parameters to assess response to GH therapy.

1 month, retest and reevaluate the patient using the adult GH-deficiency diagnostic criteria.[25,26]

- Although GH and IGF-I concentrations do not always correlate with growth response, measure IGF-I concentrations yearly to assess adherence to therapy and patient response. If the IGF-I concentration levels are above the laboratory-defined normal range for age or pubertal stage of the patient, the dose should be reduced.[28] IGF-I concentration may be used as a guide to gradually reduce replacement dose after epiphyseal closure.
- Routine monitoring of fasting lipid profile, bone mineral density, and body composition in children is not typically required during GH replacement but should be done before and after discontinuation of therapy.[24,28]
- In adults, measurement of serum IGF-I, along with careful clinical evaluation, appears to be the most reliable way to assess the appropriateness of the GH dose. Measure IGF-I serum concentrations 1 to 2 months during dose titration, and at approximately 6- to 12-month intervals once maintenance doses are achieved.[26] If there is no apparent or objective benefit after at least 12 to 16 months of treatment, therapy may be discontinued.[26]
- Continuously monitor for dose-related adverse effects such as edema, arthralgia, myalgia, and carpal tunnel syndrome.
- Evaluate psychological well-being.
- If initial bone DEXA scan is abnormal, reassess every 2 to 3 years.[26]
- When maintenance therapy is achieved, assess body composition (BMI, waist circumference, waist-to-hip ratio), metabolic status (fasting glucose concentration, FT_4 serum, hemoglobin A1c), cardiac risk factors (eg, fasting lipid profile), and hypothalamic–pituitary–adrenal axis function (eg, morning serum cortisol response to ACTH stimulation) at 6- to 12-month intervals.[26]

PROLACTIN

Prolactin is an essential hormone for normal production of breast milk after childbirth. It also plays a pivotal role in a variety of reproductive functions. Prolactin is regulated primarily by the hypothalamus–pituitary axis and secreted solely by the lactotroph cells of the anterior pituitary gland. Under normal conditions, secretion of prolactin is predominantly under inhibitory control by dopamine. Increases of hypothalamic thyrotropin-releasing hormone in primary hypothyroidism can stimulate the release of prolactin.

Hyperprolactinemia

▶ *Epidemiology and Etiology*

Hyperprolactinemia affects women of reproductive age more than men, and the estimated prevalence in women treated with hyperprolactinemia is 90 cases per 100,000 person years.[37] The etiologies of hyperprolactinemia are presented in Table 47–4.[4,9,23,37] Any medication that antagonizes dopamine or stimulates prolactin release can induce hyperprolactinemia.[9,23] Therefore, it is important to exclude medication-induced hyperprolactinemia from other common causes such as pregnancy, primary hypothyroidism, benign prolactin-secreting pituitary adenoma (prolactinoma), and renal insufficiency. Prolactinomas are the most common pituitary tumors. They are classified as

Patient Encounter 2, Part 1

A 34-year-old man presents to the primary care clinic for his annual wellness visit. He expresses concerns about his difficulty with training for an upcoming triathlon. He states his endurance has significantly decreased over the last few months, and his usual weight training exercises have become too challenging to continue. He started seeing a psychiatrist 3 months ago for symptoms of depression and anxiety. He is experiencing difficulty falling asleep and started taking melatonin. He becomes tearful stating that he had a motorcycle accident last year that resulted in a grade 3 concussion.

PMH: Depression, anxiety

FM: Mother with anxiety; father with hypertension

SH: Married, program analyst; sexually active

Meds: Sertraline 100 mg daily, melatonin 3 mg nightly

ROS: Head injury, weakness, anxiety, depression, sleep problems

PE: Reduced strength

HEENT: Ophthalmic examination reveals normal visual acuity and fields

VS: BP 118/67 mm Hg, P 80 beats/min, RR 16 breaths/min, T 36.6°C (97.9°F)

CV: RRR, normal S1, S2; no murmurs, rubs, or gallops

Abd: Soft, nontender, nondistended

Rectal: Heme (–) stool

Based on the information available, what signs and symptoms are suggestive of GH deficiency?

What could be a possible cause of GH deficiency in this patient?

What diagnostic tests should be performed to confirm the patient's diagnosis of GH deficiency?

microprolactinomas if they are less than 10 mm in diameter and as macroprolactinomas if they are 10 mm or larger in diameter.[37] In general, microprolactinomas rarely increase in size, but macroprolactinomas have the potential to enlarge and invade the surrounding tissues.[38]

Patient Encounter 2, Part 2

Macimorelin test: GH level of 0.9 ng/mL (mcg/L)

Lipid Panel: Total Cholesterol: 207 mg/dL (5.35 mmol/L), low-density lipoprotein (LDL) cholesterol:140 mg/dL (3.62 mmol/L), high-density lipoprotein (HDL) cholesterol: 35 mg/dL (0.91 mmol/L), triglycerides (TG): 160 mg/dL (1.81 mmol/L)

Impaired glucose tolerance test: 105 mg/dL (5.8 mmol/L) while fasting

Given this additional information, what pharmacologic treatment would be appropriate to recommend for this patient?

Table 47–4

Causes of Hyperprolactinemia[4,9,23,37]

Physiologic Causes
Pregnancy
Stress (including exercise and hypoglycemia)
Breast stimulation
Breastfeeding
Coitus
Sleep
Meal

Increased Prolactin Production
Ovarian: polycystic ovary syndrome
Oophorectomy (removal of an ovary)
Pituitary tumors
  Adenomas
  Microprolactinoma (< 10 mm diameter)
  Macroprolactinoma (≥ 10 mm diameter)
  Hypothalamic stalk interruption (prevent dopamine from reaching the pituitary)
Hypophysitis (inflammation)
Ectopic tumors

Hypothalamic Prolactin Stimulation
Primary hypothyroidism
Adrenal insufficiency

Reduced Prolactin Elimination
Chronic renal failure
Hepatic cirrhosis

Neurogenic Causes
Chest wall injury (eg, surgery, herpes zoster, burns)
Spinal cord lesions

Abnormal Molecules
Macroprolactinemia

Medications
Dopamine antagonists: antipsychotics[a], phenothiazines, metoclopramide, domperidone
Prolactin stimulators: methyldopa, reserpine, selective serotonin reuptake inhibitors, 5HT$_1$ receptor agonists, estrogens, progestins, gonadotropin-releasing hormone analogs, benzodiazepines, tricyclic and tetracyclic antidepressants, monoamine oxidase inhibitors, protease inhibitors, histamine$_2$-receptor antagonists, opioids, cocaine
Other: verapamil

Seizures

Idiopathic (Unknown)

[a] Atypicals (olanzapine and clozapine) other than risperidone may cause an early but transient elevation in prolactin.

▶ *Pathophysiology*

Hyperprolactinemia is a condition of elevated serum prolactin. It is the most common endocrine disorder of the hypothalamic–pituitary axis. High prolactin concentrations inhibit the release of gonadotropin-releasing hormone by the hypothalamus and subsequently suppress secretion of LH and FSH from the anterior pituitary (see Figure 47–1). High prolactin concentrations result in reduced gonadal hormone concentrations, often leading to reproductive dysfunction and galactorrhea (inappropriate breast milk production).

In combination with clinical symptoms, one or more serum prolactin concentrations greater than 25 ng/mL (mcg/L) will confirm the diagnosis of hyperprolactinemia in women.[37] A number of physiologic factors such as eating, exercise, and stress can transiently

Clinical Presentation and Diagnosis of Hyperprolactinemia[9,37]

General

Hyperprolactinemia most commonly affects women of reproductive age and is rare in men.

Signs and Symptoms

Premenopause women

- Headache and compromised or loss of vision caused by the prolactin-secreting tumor and its close proximity to the optic structures.
- Oligomenorrhea (infrequent menstruation), amenorrhea, galactorrhea, infertility, decreased libido.
- Increased body weight may be associated with a prolactin-secreting pituitary tumor.
- The degree of hypogonadism generally is proportionate to the degree of prolactin elevation.
- Excessive hair growth (hirsutism) and acne also may be present owing to relative androgen excess compared with low estrogen concentrations.

Men

- Decreased libido, decreased energy, erectile dysfunction, impotence, decreased sperm production, infertility, gynecomastia, and, rarely, galactorrhea.
- Impotence is unresponsive to treatment and is associated with reduced muscle mass, loss of pubic hair, and osteoporosis.

Laboratory Tests

- Prolactin serum concentrations at rest will be greater than 20 ng/mL (mcg/L) in men or 25 ng/mL (mcg/L) in women with at least three measurements.
- Obtain β-human chorionic gonadotropin (β-hCG) concentration to exclude pregnancy.
- Obtain TSH concentration to exclude primary hypothyroidism.
- Obtain blood urea nitrogen and serum creatinine tests to exclude renal failure.

Other Diagnostic Tests

- Perform MRI to locate the tumor, exclude a pseudoprolactinoma, and validate the diagnosis.
- Consider a bone mineral density test in patients with long-term hypogonadism.

Additional Clinical Sequelae

- The prolonged suppression of estrogen in premenopausal women with hyperprolactinemia leads to decreases in bone mineral density and significant risk for development of osteoporosis.
- Risk for ischemic heart disease may be increased with untreated hyperprolactinemia.

Adapted, with permission, from Jordan JK, Sheehan AH, Munir K. Pituitary gland disorders. In: DiPiro JT, Yee GC, Posey LM, Haines ST, Nolin TD, Ellingrod V, eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York City, NY: McGraw-Hill; c2020.

elevate prolactin concentrations.[9] If an intravenous line is present or planned, it is prudent to wait at least 2 hours after line insertion before measuring serum prolactin to decrease detecting transient physiologic increases in prolactin concentration.[9,23,37] Although medication-induced hyperprolactinemia is typically associated with prolactin concentrations of 25 to 100 ng/mL (mcg/L), metoclopramide, risperidone, and phenothiazines have been associated with concentrations greater than 200 ng/mL (mcg/L). However, prolactin concentrations greater than 500 ng/mL (mcg/L) are almost always associated with the presence of a macroprolactinoma.[37]

▶ *Treatment*

Desired Outcomes Because hyperprolactinemia is often associated with hypogonadism, the goals for management of hyperprolactinemia are as follows[37]:

- Normalize prolactin concentration.
- Restore normal gonadal function and fertility.
- Prevent development of osteoporosis.
- If a pituitary tumor is present:
  - Ablate or reduce tumor size to relieve tumor mass effect.
  - Preserve normal pituitary function.
  - Prevent progression of pituitary tumor or hypothalamic disease.

General Approaches to Treatment Management of drug-induced hyperprolactinemia is to discontinue the offending agent, if clinically feasible, and replace it with an appropriate alternative that does not cause hyperprolactinemia.[37] When the offending agent cannot be discontinued or dosage cannot be reduced, cautious use of hormone replacement, oral contraceptives, pharmacologic treatment for osteoporosis, aripiprazole, or dopamine agonists may be considered depending on the patient's clinical circumstances.[39] Treatment options for the management of hyperprolactinemia include (a) clinical observation, (b) pharmacologic therapy with dopamine agonists, (c) transsphenoidal pituitary adenomectomy, and (d) radiation therapy. Clinical observation and close monitoring are justifiable in patients with asymptomatic elevation of prolactin.[37] KEY CONCEPT Dopamine agonists are the first-line treatment of choice for all patients with symptomatic hyperprolactinemia; transsphenoidal surgery and radiation therapy are reserved for patients who are resistant to or severely intolerant of pharmacologic therapy (see Figure 47–5).[4,37] However, in patients with underlying psychiatric symptoms, use of dopamine agonists in addition to antipsychotic therapy may exacerbate the underlying psychosis and should be used with caution in consultation with a mental health clinician.[39]

Pharmacologic Therapy Dopamine is the principal neurotransmitter responsible for the inhibition of prolactin secretion from the anterior pituitary. Thus, dopamine agonists are the main pharmacologic therapy used for the management of hyperprolactinemia. Treatment with dopamine agonists has proven to be extremely effective in normalizing serum prolactin concentration, restoring gonadal function, decreasing tumor size, and improving visual fields.[37] Patients with macroprolactinomas

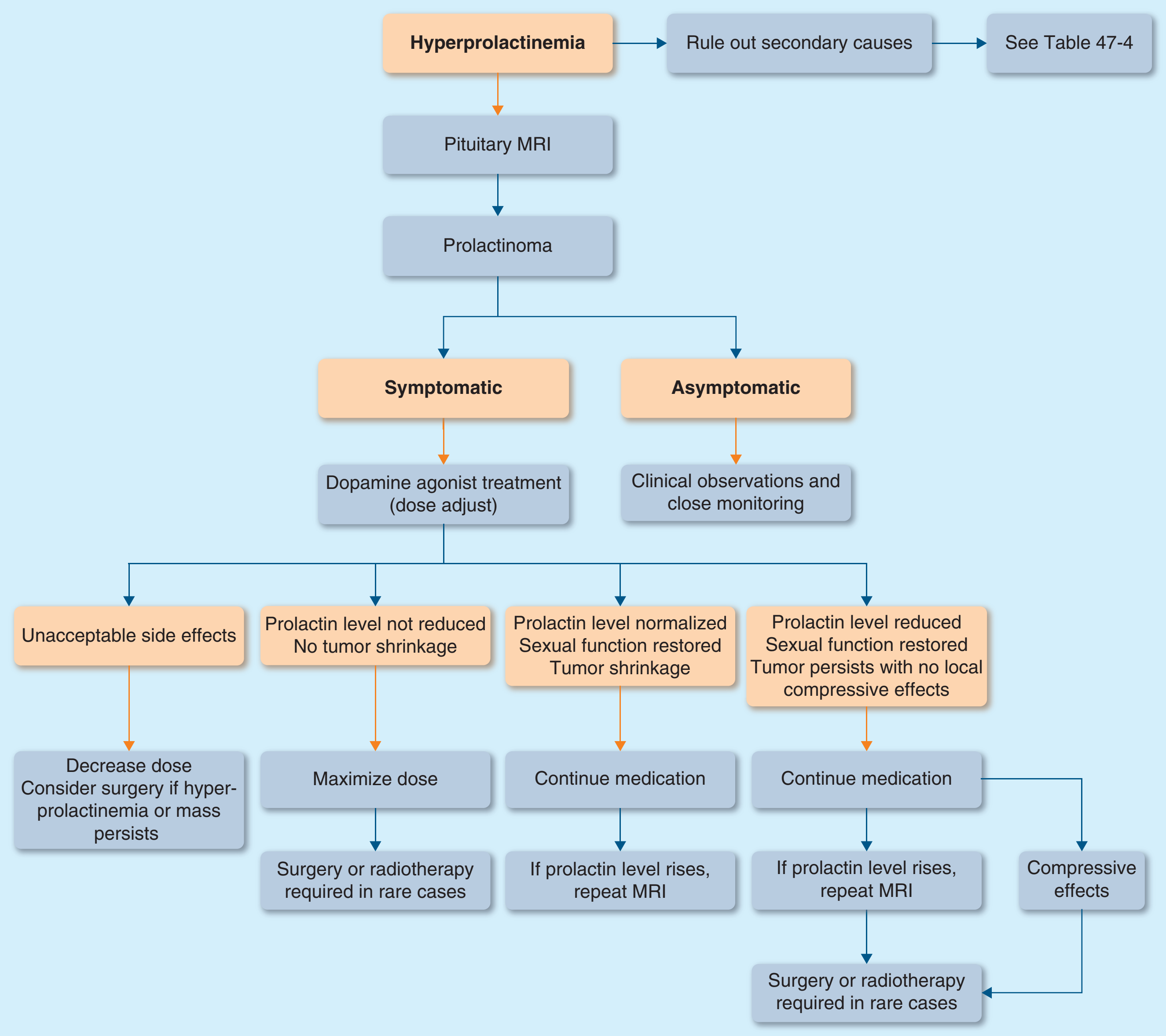
Hyperprolactinemia
Rule out secondary causes
See Table 47-4
Pituitary MRI
Prolactinoma
Symptomatic
Asymptomatic
Dopamine agonist treatment (dose adjust)
Clinical observations and close monitoring
Unacceptable side effects
Prolactin level not reduced No tumor shrinkage
Prolactin level normalized Sexual function restored Tumor shrinkage
Prolactin level reduced Sexual function restored Tumor persists with no local compressive effects
Decrease dose Consider surgery if hyper-prolactinemia or mass persists
Maximize dose
Continue medication
Continue medication
Surgery or radiotherapy required in rare cases
If prolactin level rises, repeat MRI
If prolactin level rises, repeat MRI
Compressive effects
Surgery or radiotherapy required in rare cases

FIGURE 47–5. Approaches to patients with hyperprolactinemia.[4,37] In patients with hyperprolactinemia, the first step is to rule out secondary causes before comprehensive pituitary imaging with magnetic resonance imaging (MRI) and testing. Patients with asymptomatic hyperprolactinemia can be closely monitored with clinical observation without medical treatment. Patients with symptomatic prolactinoma warrant treatment with dopamine agonist. Dosage of the dopamine agonist will need to be adjusted based on patient response; in rare cases, surgery or radiotherapy may be considered in patients with lack of desirable response. (Modified from Melmed S. Pituitary-tumor endocrinopathies. N Engl J Med. 2020;382(10):937–950.)

generally require a higher dose to normalize prolactin concentrations compared with patients with microprolactinomas.[40]

Two dopamine agonists—bromocriptine and cabergoline—are used for the management of hyperprolactinemia (Table 47–5).[41] Because these two dopamine agonists are ergot derivatives, they are contraindicated in combination with potent cytochrome P450 subfamily IIIA polypeptide 4 (CYP3A4) inhibitors, including protease inhibitors, azole antifungals, and some macrolide antibiotics. Furthermore, ergot derivatives can cause constriction of peripheral and cranial blood vessels. These medications are also contraindicated in patients with uncontrolled hypertension, severe ischemic heart disease, or peripheral vascular disorders.

Bromocriptine Bromocriptine directly binds to the D2 dopamine receptors, which helps normalize prolactin concentration and reduces tumor size in patients. Treatment with bromocriptine may also restore menses and fertility in women and improve testosterone secretion, sperm count, and erectile function in men. However, bromocriptine is rarely used in practice due to the inconvenience of daily dosing. Adverse effects such as nausea, dizziness, and orthostatic hypotension further limit 5% to 10% of patients from continuing treatment. To reduce risk of adverse effects and improve patient adherence, bromocriptine may be initiated at bedtime or be administered vaginally (2.5 mg/day) at low dose.[38,42]

Cabergoline Cabergoline has a higher affinity for D2 dopamine receptors than bromocriptine and possesses a long half-life, allowing for once or twice weekly administration. Cabergoline appears to be better tolerated than bromocriptine and may be more effective in normalizing prolactin concentrations and

Table 47–5

Comparison of Dopamine Agonists for Treatment of Hyperprolactemia[41]

	Bromocriptine (Parlodel)	Cabergoline
Starting dose	1.25–2.5 mg/day at bedtime	0.5 mg/week or 0.25 mg twice/week
Titrating dose	2.5 mg increments every 2–7 days	0.25 mg twice weekly increment, up to 1 mg twice weekly every 2–4 months
Usually effective dose	2.5–15 mg/day	1–2 mg/week
Maximal dose	20 mg/day	1 mg twice weekly
Dosing frequency	Two to three divided doses per day	Once or twice weekly
Dosage in hepatic insufficiency	May be required in acute hepatitis or cirrhosis; no guidelines are available	Dose reductions may be recommended for patients with severe hepatic failure (Child-Pugh scores of 10 or higher)
Dosage in renal failure	None	None
Adverse effects	Dizziness, headache, syncope, nausea, vomiting, gastrointestinal cramps, orthostatic hypotension, nasal congestion	Similar but orthostatic hypotension less common
Cost	Moderately expensive	More expensive

restoring menses.[43] It is also effective in treating hyperprolactinemia in patients who are resistant to or intolerant of bromocriptine and in men and women with microprolactinomas and macroprolactinomas.[37,43] Given its favorable safety and efficacy profile and ease of administration, cabergoline has replaced bromocriptine as first-line therapy for the management of hyperprolactinemia.[37] Withdrawal of pergolide from the US market due to increased risk for valvular heart disease raised concerns about the safety of cabergoline. However, to date, cabergoline use in patients with hyperprolactinemia[44] or prolactinoma[45] has not been associated with clinically significant valvular heart disease. However, increased prevalence of asymptomatic mild tricuspid regurgitation was reported in 20% of patients treated with cabergoline; patients should seek cardiac evaluation if cardiac murmurs develop.[44]

Nonpharmacologic Therapy In a small number of patients who have failed or are intolerant of dopamine agonists, transsphenoidal adenomectomy may be necessary.[37] Surgical treatment is also considered in patients with nonprolactin-secreting tumors or macroprolactinomas that jeopardize the optic chiasm.[40] Nonetheless, surgical intervention does not reliably lead to long-term cure and may cause permanent complications. Radiation therapy is reserved for failures of both pharmacologic therapy and surgery.[37] However, normalization of prolactin concentration with radiation therapy may take 20 years to show full benefit, and radiation-induced hypopituitarism may require lifelong hormone replacement.

Management of Hyperprolactinemia in Pregnancy Most women with hyperprolactinemia require dopamine agonist therapy to achieve regular ovulatory cycles and pregnancy. Because restoration of the ovulatory cycle may occur immediately after initiation of therapy, it is necessary to caution patients regarding their potential to become pregnant and ensure adequate contraception when beginning therapy.[40]

Overall, there is reassuring evidence that bromocriptine use during pregnancy does not increase fetal malformations, spontaneous abortions, preterm deliveries, or multiple births.[37,46] Although experience during pregnancy is limited, cabergoline does not appear to be teratogenic.[41] Despite these data, continuation of dopamine agonists during pregnancy is generally not recommended. KEY CONCEPT Women who become pregnant while taking a dopamine agonist should discontinue treatment to minimize fetal exposure.[37]

Microadenomas rarely cause complications during pregnancy. However, untreated macroprolactinomas carry an approximate 31% risk of tumor enlargement.[37] Therefore, monitor female patients with macroprolactinomas closely for the development of headache and visual impairments. Baseline and routine visual field examinations are essential. Evidence of abnormal visual fields may indicate tumor growth and should be followed by an MRI. If tumors enlarge, bromocriptine is the preferred choice over cabergoline because of greater tolerability and efficacy with similar safety experience with this drug during pregnancy.[46]

▶ *Outcome Evaluation*

- Assess patients for tolerability to dopamine agonists.
- Monitor clinical symptoms associated with hyperprolactinemia every month for the first 3 months to assess therapeutic efficacy and assist with dose titration.
- Evaluate the patient for symptoms, such as headache, visual disturbances, menstrual cycles in women, and sexual function in men, to assess clinical response to therapy.[37]
- When the prolactin concentration is normalized and clinical symptoms of hyperprolactinemia have resolved, monitor prolactin concentration every 6 to 12 months.
- If the prolactin concentration is well controlled with dopamine agonist therapy for 2 years with significant tumor reduction, gradually taper therapy to the lowest effective dose or consider discontinuing therapy.[37] Check prolactin concentration after each dose reduction.
- If the prolactin concentrations remain unchanged for 1 year at the reduced dose, dopamine agonist therapy may be discontinued. Prolactin should be measured after 3 months and yearly thereafter.
- In patients with macroprolactinomas, monitor visual field at baseline and repeat the test 1 month after initiation of a dopamine agonist.
- Repeat the MRI in 1 year after initiating therapy or in 3 months in patients with macroprolactinoma or if an increase in symptoms or rise in prolactin concentration suggests the presence of tumor growth.[37]
- Discontinuation of therapy in patients with macroprolactinomas usually leads to tumor regrowth and recurrence of hyperprolactinemia. This decision warrants careful consideration.

Patient Care Process: Hyperprolactinemia

Collect Information:

- Review the available diagnostic data to determine tumor size and location.
- Perform complete medication history. Identify allergies to medications and other substances.
- Review the medical history, relevant laboratory tests, and physical assessment findings.
- Speak with patient and review records to identify signs and symptoms of hyperprolactinemia, preferences and beliefs, health goals, and socioeconomic factors or barriers that affect medication access and other aspects of care.

Assess the Information:

- Assess the patient's clinical signs and symptoms and prolactin level to determine the severity of hyperprolactinemia.
- Exclude other common causes of hyperprolactinemia (Table 47–4).
- Review patient's medication list to exclude medication-induced hyperprolactinemia (Table 47–4).
- Determine if the patient has a coexisting prolactin-secreting tumor and impact of the tumor.
- Assess the presence of hyperprolactinemia complications.
- Assess if the patient has any contraindication, allergy, or drug interaction to dopamine agonists.
- Determine the patient's plan regarding pregnancy because this influences treatment selection.

Develop a Care Plan:

- Initiate the appropriate dopamine agonist at the lowest effective dose for management of hyperprolactinemia (see Table 47–5). Consider if the patient's therapy requires any dose adjustment.

Implement the Care Plan:

- Discuss potential effectiveness and disadvantages of existing treatment options.
- Address any patient concern about long-term complications of hyperprolactinemia, its management, and possible adverse effects of existing dopamine agonists.
- Educate patient about risks associated with hyperprolactinemia.
- Use motivational interviewing and coaching strategies to maximize adherence.

Follow-up: Monitor and Evaluate:

- Evaluate safety and efficacy of dopamine agonist. When appropriate, be sure to make dose adjustments (Table 47–5).
- Monitor patient adherence to treatment plan using multiple sources of information.
- Monitor patients' prolactin level. If the prolactin concentration remains normal for 2 years, reassess the need to continue treatment.
- Consider bone mineral density tests in patient with long-term hypogonadism.

Abbreviations Introduced in This Chapter

AACE	American Association of Clinical Endocrinologists
ACTH	Adrenocorticotropic hormone or corticotropin
ADH	Antidiuretic hormone or vasopressin
β-hCG	β-Human chorionic gonadotropin
BMI	Body mass index
CRH	Corticotropin-releasing hormone
CYP3A4	Cytochrome P450 subfamily IIIA polypeptide 4
DEXA	Dual-energy X-ray absorptiometry
ESRD	End-stage renal disease
FSH	Follicle-stimulating hormone
FT_4	Free thyroxine or T_4
GABA	γ-Aminobutyric acid
GH	Growth hormone or somatotropin
GHIH	Growth hormone–inhibiting hormone or somatostatin
GHRH	Growth hormone–releasing hormone
GI	Gastrointestinal
GnRH	Gonadotropin-releasing hormone
GST	Glucagon-stimulation test
HDL	High-density lipoprotein
$HgbA_{1c}$	Glycated hemoglobin A1c
IGF	Insulin-like growth factor
IGFBP-3	Insulin-like growth factor-binding protein 3
IM	Intramuscular
ITT	Insulin tolerance test
LAGH	Long-acting growth hormone
LAR	Long-acting release
LDL	Low-density lipoprotein
LFT	Liver function test
LH	Luteinizing hormone
LHRH	Luteinizing hormone–releasing hormone
MRI	Magnetic resonance imaging
MSH	Melanocyte-stimulating hormone
OGTT	Oral glucose tolerance test
PRH	Prolactin-releasing hormone
SAGhE	Safety and Appropriateness of Growth hormone treatments in Europe
SC	Subcutaneous
SR	Slow release
SRL	Somatostatin receptor ligand
T_3	Triiodothyronine
T_4	Thyroxine
TG	Triglycerides
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone or thyrotropin
ULN	Upper limit of normal

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48

Pregnancy and Lactation: Therapeutic Considerations

Rebecca H. Stone

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the principles of embryology and teratology.
2. Identify known teratogens and drugs of concern during lactation.
3. Compare the main sources of drug information relevant to pregnancy and lactation.
4. Evaluate and communicate the risks of a drug when taken during pregnancy or lactation.
5. Apply a systematic approach to counseling on the use of drugs during pregnancy and lactation.
6. Recommend the appropriate dose of folic acid to prevent congenital anomalies.
7. Describe physiologic changes during pregnancy and their impact on pharmacokinetics.
8. Choose an appropriate treatment for common conditions in a pregnant or lactating patient.

INTRODUCTION

This chapter will provide the general principles needed to interpret available evidence regarding medication use during pregnancy and lactation, choose an appropriate treatment and dosing strategy for common conditions in pregnancy, and counsel patients in a helpful and supportive way.

EPIDEMIOLOGY AND ETIOLOGY

Background Risks of Anomalies in Pregnancy

Table 48–1 describes the baseline risks of congenital anomalies and some obstetrical complications. This information is essential to evaluate risks associated with medication use and counsel pregnant patients.

Causes of Congenital Anomalies

Although the risk of drug-induced teratogenicity is of concern, the actual risk of birth defects from most drug exposures is small. Medications are associated with less than 1% of all congenital anomalies, although they may also interact with genetic factors.[3] It is important to evaluate and optimize drug use in pregnant patients and patients planning a pregnancy.

Other causes of anomalies include genetic causes in 25% of cases (inherited disease, gene mutation, chromosomal disorder), maternal infections (1%), maternal conditions (1%–3%; eg, pregestational diabetes, obesity), multifactorial heredity (23%–50%), and unknown causes (34%–43%).[3] Theoretical concerns regarding paternal exposure to genotoxic medication are reported, but currently no medication taken by a man has been proven teratogenic.

PATHOPHYSIOLOGY

Age of Pregnancy

The age of pregnancy can be defined as gestational or postconceptional age (PCA). Gestational age (GA) is the term used in clinical practice. It is calculated from the first day of the last menstruation or by ultrasound dating.

PCA, calculated from the day of conception, is 14 days shorter than GA if the menstrual cycle is 28 days. Some references in the field of teratology and embryology refer to PCA to describe stages of pregnancy.

Principles of Embryology

Pregnancy is divided into three development phases: implantation and predifferentiation, organogenesis (or embryogenesis), and

Table 48–1

Occurrence of Select Obstetrical Complications and Risk of Congenital Anomalies in the General Population[1-3]

	Risk of Occurrence in Population (%)
Spontaneous abortion/miscarriage (pregnancy loss that occurs after the pregnancy is known and before 20 weeks of GA; risk increases with higher maternal age)	10–15
Congenital anomalies (percentage of live births):	
• Minor malformations	14
• Major malformations at birth	3
• Major malformations at 2 years old	6
Preterm birth (< 37 completed weeks gestation)[a]	9.9
Low birth weight (< 2500 g)[b]	8.3

[a]United States data from 2016 to 2018.

[b]United States data from 2018.

GA, gestational age.

Table 48–2

Phases of Embryonic and Fetal Development[3]

Phase of Development	Stage of Pregnancy[a]	Development Description	Potential Complications
Implantation and predifferentiation	0–14 days after conception (14–28 days after LMP)	Very little contact between the blastocyst and mother's blood Pluripotent cells, capacity to repair a damage Cells are fragile, miscarriage before pregnancy is detected if too many are destroyed	Spontaneous abortion; even if stopped during this period, long half-life drugs could affect organogenesis
Organogenesis (embryogenesis)	From day 14 until the 9th week after conception (From day 28 until the 11th week after LMP)	Organs are being formed; most critical period for structural anomalies Organs are being formed at different times; sensitivity for each organ differs Refer to Figure 48–1 for the time frame of organ formation	Major or minor structural anomalies; Spontaneous abortion; neurologic impairment
Fetogenesis	After the organogenesis and until birth	The fetus grows Organs begin to function (eg, glomerular filtration) Active cell growth, proliferation, and migration (eg, CNS)	Fetal growth retardation; functional deficit (eg, renal insufficiency), neurologic impairment; spontaneous abortion, stillbirth; neonatal complications

[a] Stage of pregnancy based on a menstrual cycle of 28 days.

CNS, central nervous system; LMP, last menstrual period.

fetogenesis. Table 48–2 describes these phases and possible drug effects if taken during these phases, and Figure 48–1 illustrates the critical periods of human in utero development. KEY CONCEPT The risk of birth defects is usually higher during organogenesis.

▶ *Teratogens*

KEY CONCEPT Health professionals should know which medications have teratogenic risk. A teratogen is an exogenous agent that can modify normal embryonic or fetal development.[3] Teratogenicity can manifest as structural anomalies, functional deficit, cancer, growth restriction, neurologic impairment, or death (spontaneous abortion, stillbirth).

In utero exposure to medication near delivery can also lead to transient neonatal complications, such as withdrawal or side effects (eg, opioids, selective serotonin reuptake inhibitors, antipsychotics, lithium).[4]

Teratogenic exposure is a term preferred over *teratogen* as it considers level (dose) and timing of exposure during pregnancy to determine whether it could lead to a higher risk of a specific malformation.

Criteria have been proposed to determine whether a causal relationship between congenital anomalies and a medication is plausible when analyzing scientific documentation (teratogenic effect).[5,6] Exposure to the medication must have happened during the critical period of development of the organ for which a malformation is noticed (Figure 48–1). In addition, a pattern of anomaly or a specific syndrome must be reproducible in at least two studies conducted in different populations. A rare anomaly associated with a rare exposure is also indicative of a teratogenic effect (eg, ear anomalies and isotretinoin).

Other criteria, listed below, are considered:

- Strength of the association
- Same effects observed in animal studies
- Biological plausibility based on pharmacologic effect

Patient Encounter, Part 1

A 38-year-old patient comes to your office after a positive urine pregnancy test. You collect the following data:

Estimated Gestational Age: 8 weeks, regular menstrual cycles of 30 days

PMH: Type 2 diabetes mellitus (T2DM) diagnosed 8 years ago, hypertension and hypothyroidism diagnosed 2 years ago, obesity (BMI 42 kg/m^2), previous spontaneous singleton preterm birth at 35 weeks gestation

FH: T2DM, hypertension

SH: Latina origin. Paralegal. No use of alcohol or illicit substances. Smokes four to six cigarettes per day. Not very physically active, but tries to respect low-carb diet

Meds: Metformin 1 g orally twice daily with meals, dulaglutide 1.5 mg subcutaneously once weekly, glargine insulin 20 U subcutaneously at night, lisinopril 10 mg daily, levothyroxine 50 mcg orally once daily before breakfast

Allergy: Penicillins

ROS: Morning nausea; tiredness

VS: Wt 284 lb (129 kg), Ht 69 in. (175 cm), BP 118/72 mm Hg with large cuff, pulse 74 beats/min, RR 12 breaths/min

How will you confirm gestational age?

What prenatal workup would you perform at this time?

What is the appropriate counseling at this time?

What are the risks of drugs taken in the first weeks of pregnancy? What resources will you use to find the appropriate information?

What adjustments, if any, are needed for her current medication therapy?

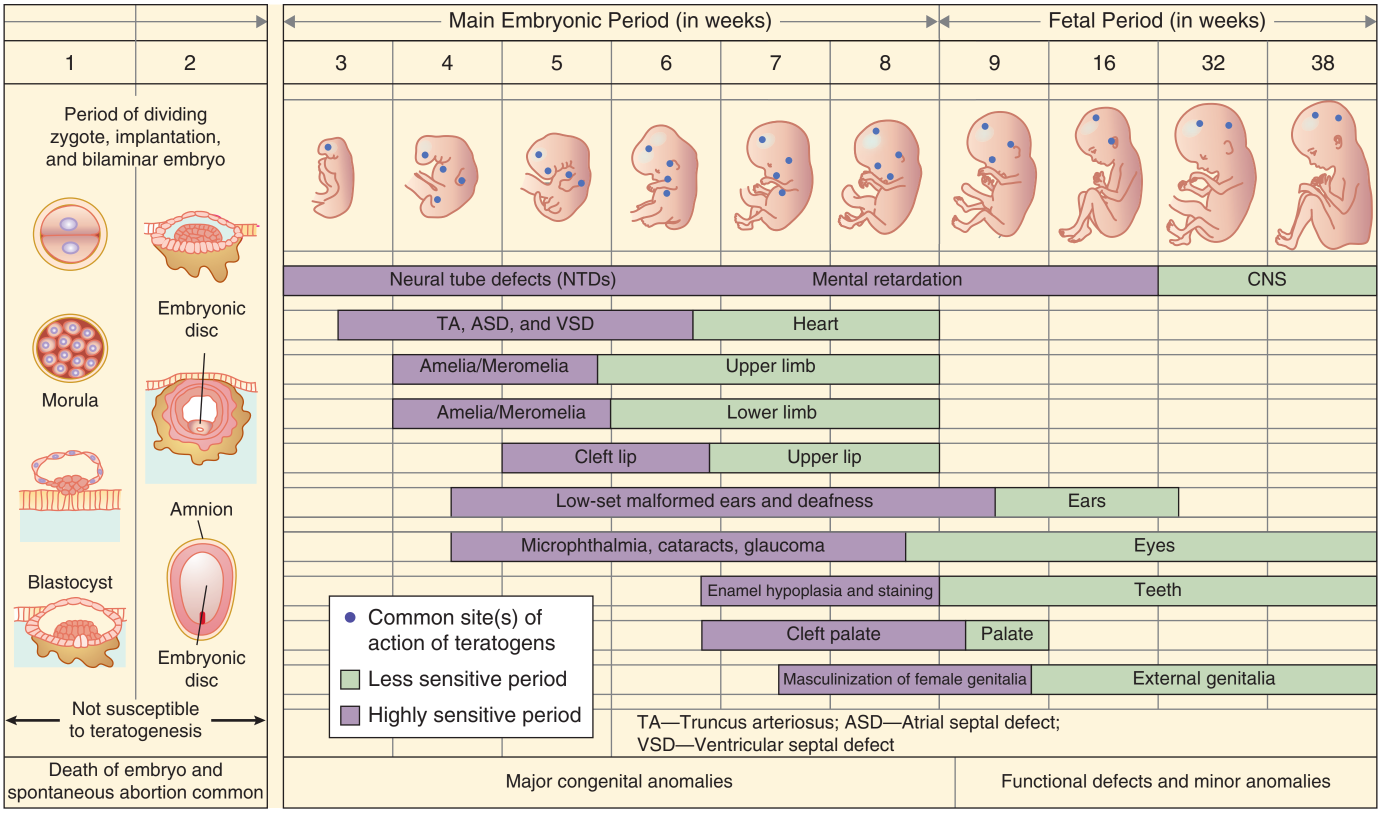
1
2
Period of dividing zygote, implantation, and bilaminar embryo
Morula
Embryonic disc
Amnion
Blastocyst
Embryonic disc
Not susceptible to teratogenesis
Death of embryo and spontaneous abortion common
Main Embryonic Period (in weeks)
Fetal Period (in weeks)
3
4
5
6
7
8
9
16
32
38
Neural tube defects (NTDs)
Mental retardation
CNS
TA, ASD, and VSD
Heart
Amelia/Meromelia
Upper limb
Amelia/Meromelia
Lower limb
Cleft lip
Upper lip
Low-set malformed ears and deafness
Ears
Microphthalmia, cataracts, glaucoma
Eyes
Enamel hypoplasia and staining
Teeth
Cleft palate
Palate
Masculinization of female genitalia
External genitalia
● Common site(s) of action of teratogens
🟩 Less sensitive period
🟪 Highly sensitive period
TA—Truncus arteriosus; ASD—Atrial septal defect; VSD—Ventricular septal defect
Major congenital anomalies
Functional defects and minor anomalies

FIGURE 48–1. Embryonic and fetal development. The horizontal bars represent potential sensitivity to teratogens. The colored areas represent the more critical times. Embryonic period is in postconceptional weeks. (Reprinted with permission from Moore KL. The Developing Human. New York, NY: Elsevier, p. 976: copyright 1974.)

- Higher incidence of the anomaly in the population with the period of use of the medication (eg, thalidomide and limb anomalies)
- Dose–response relationship

With these criteria, there are approximately 30 medications or classes of medications that are considered teratogens (Table 48–3). Others are not necessarily safe: it is important to not interpret a lack of data as an absence of risk. A medication on this list is not necessarily contraindicated as severity and occurrence of malformations vary from one agent to another. Some can be used when benefits outweigh potential risks.

RISK EVALUATION

Desired Outcomes

The goal of drug selection during pregnancy and lactation is to treat conditions effectively when necessary while minimizing risk to the developing embryo/fetus or the neonate.

Medication and Pregnancy

▶ *Data Published on Medication Safety During Pregnancy*

Most available data on drug safety during pregnancy come from postmarketing reports: case reports or case series, epidemiological research using population/prescription databases or using questionnaires, manufacturer registries, or specialized pregnancy registries. Clinicians are encouraged to refer their patients taking medication to a pregnancy registry; a list of pregnancy registries is available on the Food and Drug Administration (FDA) website (www.fda.gov/pregnancyregistries).

Animal studies, now mandatory before marketing a medication, can identify high-risk medications and prevent congenital anomalies. However, they have limitations; different species do not share the same pharmacodynamics and pharmacokinetics, and animal studies usually test much higher doses than those used in clinical settings.[6]

▶ *Sources of Information on the Use of Drugs During Pregnancy and Lactation*

KEY CONCEPT Health-care professionals should be able to compare the main sources of drug information relevant to pregnancy and lactation. Some specialized information sources provide data on the use of medications during pregnancy and lactation (Table 48–4).

The Pregnancy and Lactation Labeling Rule (PLLR), was approved by the FDA and has been in effect since June 30, 2015.[8] This rule requires that the labels of all prescription drugs and biologic products approved after June 30, 2001 include narrative summaries of the risk of using them during pregnancy and lactation, presentation of data supporting the summaries, and an update of the information presented when it is outdated. It replaces the categories A, B, C, D, and X that were required before. Letters have long been criticized by experts because it is too simplistic and can lead to a misinterpretation of risk.

Drugs that were approved before June 30, 2001 do not have to include the information requested by the PLLR in the label, but manufacturers have to remove the categories A, B, C, D, and X. Manufacturers of medication approved between June 30, 2001 and June 30, 2015 have a 3- to 5-year period to comply with the PLLR.[8]

Table 48–3

Medications With Proven Teratogenic Effects in Humans[4-7]

Drug or Drug Class	Teratogenic Effects	Critical Period[a]
Alkylating agents	Malformations of many different organs	Organogenesis
Amiodarone	Transitory hypothyroidism (risk of 17%, goiter in some cases) or transitory hyperthyroidism	From 12th week after LMP
Androgens (danazol, testosterone)	Masculinization of genital organs in female fetus	From ninth week after LMP
Angiotensin-converting enzyme inhibitors; angiotensin II receptor antagonists	Renal failure, anuria, oligohydramnios, pulmonary hypoplasia, intrauterine growth restriction, limbs contracture, skull hypoplasia	Avoid in second and third trimesters. Concern with use in first trimester due to conflicting data
Anticonvulsants (first generation) • Carbamazepine • Phenytoin • Phenobarbital • Valproic acid, divalproex	NTD (carbamazepine and valproic acid); oral cleft, skeletal, urogenital, craniofacial, digital, and cardiac malformations Major malformations: up to 5%–10% depending on the agent used, with variation with dosage used (10%–15% or more for valproic acid) Valproic acid: abnormal neurologic development	Organogenesis for structural anomalies Valproic acid: whole pregnancy for neurologic impairment
Corticosteroids (systemic)	Oral cleft (risk of 3–4/1000 vs 1/1000 in general population)	Organogenesis (most critical period for palate formation: 8 and 11 weeks after LMP)
Diethylstilbestrol	Girls: cervical or vaginal adenocarcinoma, incidence: 1/1000. Structural genital anomalies (eg, of cervix, vagina) Boys: genital anomalies, spermatogenesis anomalies	First and second trimesters
Fluconazole	Skeletal and craniofacial malformations, cleft palate (with chronic oral dose ≥ 400 mg/day); cardiac septal closure anomaly (single oral dose >150 mg); miscarriage (single oral dose ≥150 mg)	Cardiac anomaly during first trimester. Others not defined, cases are reported where exposure was throughout pregnancy
Iodine (supraphysiologic dosage)	Hypothyroidism, goiter	From 12th week after LMP
Isotretinoin, other systemic retinoids (acitretin, bexarotene, etretinate), and high dose of vitamin A (vitamin A > 10,000 IU/day not recommended)	Spontaneous abortion, CNS, skull, eyes and ears malformations, micrognathia, oral cleft, cardiac malformations, thymus anomalies, mental retardation: estimated risk at 25%–30% (may be higher for neurologic development impairment) Isotretinoin and bexarotene: discontinue 1 month before pregnancy, isotretinoin prescribed under a special program called iPLEDGE Acitretin: discontinue 3 years before pregnancy	Organogenesis (risk of teratogenic effect after organogenesis not excluded)
Lithium	Cardiac malformations: risk of 0.9%–6.8% (higher risks in small studies) (baseline risk ~1%) Includes Ebstein anomaly: risk estimated at 0.05%–0.1%	Cardiac organogenesis (5–10 weeks after LMP)
Methimazole/propylthiouracil	Methimazole: aplasia cutis, choanal atresia, esophageal atresia, omphalocele, minor facial anomalies, growth delay; risk of 2%–4% Methimazole/propylthiouracil: fetal hypothyroidism in 1%–5% of newborns, goiter	First trimester Second and third trimesters
Methotrexate	Spontaneous abortion, CNS, and cranial malformations (large fontanelles, hydrocephalia, incomplete cranial ossification, craniosynostosis), oral cleft, ear, skeletal and limb malformations, mental retardation; discontinue at least one ovulatory cycle before pregnancy	Organogenesis (8–10 weeks after LMP for structural anomalies but some exceptions reported)
Misoprostol	Moebius syndrome ± limb anomalies ± CNS anomalies Abortion, preterm birth	Organogenesis Throughout pregnancy for abortion/preterm birth
Mycophenolate mofetil, mycophenolic acid	Anomalies including ear anomalies, oral cleft, micrognathia, ophthalmic, cardiac, and digital anomalies (risk of structural anomalies estimated from 20%–25%); spontaneous abortion (30%–50%)	Organogenesis (risk unknown after)
Nonsteroidal anti-inflammatory drugs	In utero closure of ductus arteriosus (constriction is rare before 27 weeks, 50%–70% at 32 weeks [GA]) and neonatal pulmonary hypertension Renal toxicity and oligohydramnios possible after prolonged use from second half of second trimester from 20 weeks of gestational age	Third trimester
Penicillamine	Cutis laxa Joints and CNS anomalies Risk probably low	Not defined
Tetracyclines	Teeth discoloration	From 16 weeks after LMP

(Continued)

Table 48–3

Medications With Proven Teratogenic Effects in Humans[4-7] (*Continued*)

Drug or Drug Class	Teratogenic Effects	Critical Period[a]
Thalidomide	Limb anomalies (amelia, phocomelia) Cardiac, urogenital, gastrointestinal, and ear malformations Risk of 20%–50% Prescribed under Thalomid REMS program	34–50 days after LMP
Trimethoprim	Cardiac and urogenital malformations, NTD, oral cleft; overall risk probably < 6%	Organogenesis
Warfarin/acenocoumarol	Before 6 weeks: baseline risk of anomalies Taken between 6 and 12 weeks: nasal hypoplasia, epiphysis dysplasia, vertebral malformations, rarely ophthalmic anomalies, scoliosis, hearing loss; risk estimated of 6%–10% and possibly dose-dependent 12 weeks after LMP: rarely, heterogeneous CNS anomalies	Between weeks 6 and 12 after LMP; some risks persist after

[a]Stages of pregnancy in this table are calculated after last menstrual period (gestational age) and not after conception to be more clinically useful.

CNS, central nervous system; LMP, last menstrual period; NTD, neural tube defect.

Communication of Information

Communication of data on medication use during pregnancy can be challenging:[9,10]

- Data may be limited or contradictory.
- Taking medications during pregnancy is a source of anxiety.
- Pregnant patients tend to overestimate their risk of an anomaly associated with medication use and to underestimate their risk associated with undertreating their condition.

KEY CONCEPT Health-care professionals should be able to evaluate and communicate the risks of a drug when taken during pregnancy or lactation. The objective is to give precise data that will help the patient make an informed decision for her health and her baby's health. Information should include a well-grounded assessment of risks, including baseline risks in the general population, risks associated with the medication, and risks of not treating the disease during pregnancy.[9]

When discussing risks[9]:

- Use absolute numbers instead of relative numbers (eg, risk of fetal malformation is approximately 3% at baseline and 6% with exposure to antiepileptic medications. Therefore, exposure to antiepileptic medication increases the absolute risk of malformation by 3%, while the relative risk of malformation doubles).
- Use negatively and positively framed information at the same time (eg, 3% chance of having a child with a malformation; 97% chance of having a child without malformation).
- Use the same denominator when discussing probabilities.

To determine a woman's risk of birth defects, obtain accurate and thorough medical, obstetrical, and pharmacotherapeutic histories (including over-the-counter medications and natural health products) and exposures to alcohol, tobacco, and other recreational drugs.[9]

KEY CONCEPT With all this information, the health-care professional should be able to apply a systematic approach to counseling on the use of drugs during pregnancy and lactation.

Table 48–4

Examples of Sources of Information on Drug Use in Pregnancy and Lactation

Books

- Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, 11th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2017.
- Schaefer C, Peters PWJ, Miller RK. Drugs During Pregnancy and Lactation, Treatment Options and Risk Assessment, 3rd ed. Amsterdam: Elsevier; 2014.
- Hale TW. Medications and Mother's Milk, 17th ed. New York, NY: Springer Publishing Company, LLC; 2017.

Databases

- Reprotox: www.reprotox.org
- Teris (Teratogen Information System): http://depts.washington.edu/terisweb/teris/

Websites/Applications

- www.mothertobaby.org
- www.marchofdimes.org
- www.cdc.gov
- www.fda.gov
- https://www.ncbi.nlm.nih.gov/pubmed/
- List of pregnancy registries: http://www.fda.gov/pregnancyregistries
- Lactmed: https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

Teratology Information Service

- MotherToBaby, a service of Organization of Teratology Information Specialists (OTIS): Go to *www.mothertobaby.org* to find your local Teratogen Information Service, or call National Toll-Free Number: (866) 626–6847

Preconception Care

Adverse pregnancy outcomes, including prematurity, low birth weight, and birth defects, are major health concerns. A late start in prenatal care can delay the identification and modification of risk factors that can affect pregnancy outcomes. Strategies to improve pregnancy outcomes include treating nutritional deficiencies, adequate folic acid, avoiding alcohol, substance abuse and nicotine use, optimizing the management of chronic illnesses and genetic disorders, screening for infections, vaccination (including preconception vaccine optimization and administration of influenza and Tdap during pregnancy), pregnancy planning, and reaching a healthy weight.[11]

Folic Acid

Anencephaly and spina bifida, with an estimated annual prevalence of 6.5 cases per 10,000, are the most common neural tube defects (NTDs) from an inadequate closure of the embryonic neural tube early in pregnancy.[12] Multivitamins containing folic acid reduce NTD and other congenital anomalies including oral clefts and cardiovascular, limb, and urinary tract malformations.[12,13] **KEY CONCEPT** All patients capable of childbearing should be counseled on the appropriate dose of folic acid to prevent congenital anomalies. The American College of Obstetricians and Gynecologists (ACOG) and the US Preventive Services Task Force recommend that all patients capable of pregnancy take 0.4 to 0.8 mg of folic acid daily, beginning 1 month before pregnancy and through the first 2 to 3 months, to prevent NTD.[12,14] Patients at higher risk of NTD (eg, personal or family history of NTDs, use of antiseizure medications [valproic acid and carbamazepine], maternal diabetes, obesity, and mutations in folate-related enzymes) should take higher daily doses of folic acid (eg, 1–5 mg).[12]

▶ *Impact of Physiologic Changes During Pregnancy on Pharmacokinetics*

KEY CONCEPT Several physiologic changes during pregnancy have an impact on pharmacokinetics.

Absorption Decreased gastrointestinal transit can delay drug peak effect, prolonging the time of contact of drugs with the intestinal mucosa, and possibly enhancing absorption of certain drugs. Higher gastric pH may affect absorption of weak bases or acids. Pregnancy physiologic changes may also increase skin, tissue, and lung absorption.[15]

Distribution Volume of distribution increases for most drugs during pregnancy due to plasma volume expansion and the presence of amniotic fluid, the placenta, and the fetus, thus decreasing maximal drug concentrations. In addition, hypoalbuminemia and decreased protein binding increase free fraction (active portion) of some medications.[15]

Metabolism During pregnancy, the activity of some isoenzymes is increased (eg, CYP3A4, CYP2A6, CYP2D6, CYP2C9), while activity of others is decreased (eg, CYP1A2, CYP2C19). Net impact on drug effect is often unpredictable since there is a wide interindividual variability, and some drugs are metabolized by several isoenzymes.[15]

Renal Elimination Renal blood flow and glomerular filtration increase significantly during pregnancy. The impact of this is more important for drugs that are eliminated in the urine, which results in a decrease in their half-lives.

Table 48–5 shows clinical recommendations based on pharmacokinetic changes during pregnancy for several drugs.[15]

Medication and Lactation

According to the latest policy statement from the American Academy of Pediatrics (AAP), mothers should breast-feed exclusively for 6 months and continue for 1 year if possible.[16]

Table 48–5

Altered Pharmacokinetics During Pregnancy: Clinical Implications and Management[15]

Drugs	Pharmacokinetic Changes	Recommendations and Monitoring[a]
Aminoglycosides	↑ V_d, ↑Cl, ↓ $t_{1/2}$	Monitor peaks and troughs; increase doses if necessary
Antiretrovirals	Variable Cl and C_{max}	Monitor clinical response; drug levels can be useful to adjust some drug dosages
Caffeine	↑ $t_{1/2}$ ↓ Cl (T_1, T_2, T_3)	Risk of more frequent and prolonged side effects; decrease caffeine consumption
Carbamazepine	↑ Cl ↓ $t_{1/2}$	Measure free fraction (preferably); increase dose according to clinical response and levels
Digoxin	↑ Cl ↓ C_{max}	Adjust according to clinical response and plasma levels; digoxin-like immunoreactive substance might interfere with measurement
Fluoxetine and other SSRIs	↑ Cl (T_3)	Increase dose according to clinical response
Heparin LMWH	↑ Cl (T_1, T_2, T_3)	For high-risk patients (mechanical valves, new clot on therapeutic dosing) or CKD, follow anti-XA levels. Use twice-daily administration for high-risk patients
Lamotrigine	↑ Cl (T_1, T_2, T_3)	For epilepsy: measure drug levels at least every trimester; increase dose according to clinical response and levels
Levothyroxine (LT_4)	↓ff	Increase dose at the beginning of pregnancy; follow TSH levels every 4–6 weeks until 20 weeks and once in early T_3
Lithium	↑ Cl (T_1, T_2, T_3) ↓ $t_{1/2}$	Measure drug levels every trimester and monthly in T_3; increase dose according to levels if necessary
Nicotine	↓ $t_{1/2}$ ↑ Cl (T_2, T_3)	Higher doses might be required (smoking cessation) at T_2 and T_3; however, higher nicotine plasma levels possible (increased transdermal absorption)
Nifedipine	↑ Cl (T_3)	Monitor clinical effect; increase doses/frequency if necessary. Use twice daily for extended release formulation if > 40 mg/day
Phenytoin	↓ C_{total}, ff ↑ Cl (T_3) ↓ $t_{1/2}$	If benefits out-weigh risks for use during pregnancy, measure free fraction; adjust dose according to clinical response, levels and signs of toxicity.
Valproic acid	↓ C_{total} ↑ ff	If benefits out weigh risks for use during pregnancy, measure free fraction if prepregnancy reference level available; dose will remain the same in most cases. Increase dose according to clinical response and levels

[a]Resume prepregnancy dosage after delivery in case of dosage adjustment for altered pharmacokinetics.

↑, increase; ↓, decrease; ↔, unchanged; CKD, chronic kidney disease; Cl, clearance; C_{max}, maximum serum concentration; C_{total}, total concentration; ff, free fraction; LMWH, low-molecular-weight heparin; SSRI, selective serotonin reuptake inhibitor; T, trimester; $t_{1/2}$, elimination half-life; V_d, volume of distribution.

▶ *Drug Transfer Into Breast Milk*

To study drug effects, breast-fed infant's serum drug levels could be measured to evaluate safety; however, these data are often unavailable. In most instances, the approximate quantity of drug ingested by the breast-fed infant is estimated using published measured drug concentrations in breast milk. With these data, the percentage of pediatric dose or, if a pediatric dose is not available, the relative infant dose (percentage of weight-adjusted maternal dose) can be calculated, assuming an average of 150 mL/kg/day of milk ingested by a breast-fed infant.

Percentage of pediatric dosage =

$$\frac{\text{Quantity of medication taken from milk by the baby (mg/kg/day)}}{\text{Usual initial pediatric dose (mg/kg/day)}} \times 100$$

Weight adjusted maternal dose or relative infant dose =

$$\frac{\text{Quantity of medication taken from milk by the baby (mg/kg/day)}}{\text{Maternal dose adjusted by weight (mg/kg/day)}} \times 100$$

In the latter equation, maternal dose refers to the dose used by patients in a published study or a case report, not to the dose of the actual patient.

Usually, a percentage of less than 10% of the pediatric dose or, when a pediatric dose is not available, a percentage of less than 10% of weight adjusted maternal dose is generally accepted as safe in full-term healthy infants unless a drug has a toxic side-effect profile.[17]

▶ *Drug Pharmacokinetics*

If clinical data are unavailable on drug transfer into breast milk, then drugs that are highly protein bound, have a high molecular weight, have a short half-life, have no active metabolites, and are well tolerated by children could be preferred.[17] In addition, drugs that are not orally absorbed should not cause systemic adverse effects in the breast-fed infant.

▶ *Drugs of Concern During Breast-Feeding*

KEY CONCEPT Most drugs are safe during breast-feeding. However, some drugs are of concern and require a more thorough assessment by the clinician (Table 48–6). One should also consider additive side effects of several medications.

CONDITIONS PREVALENT IN PREGNANCY AND LACTATION

KEY CONCEPT When possible, treat conditions occurring during pregnancy with nonpharmacologic treatments instead of drug therapy.

KEY CONCEPT Evaluate the need for treatment, including benefits and risks, and possibility of delaying treatment after pregnancy or breast-feeding.

For chronic diseases, please refer to the relevant chapters.

Iron-Deficiency Anemia

Anemia during pregnancy is defined as a hemoglobin level less than 11 g/dL (110 g/L; 6.83 mmol/L).[18] Maternal symptoms include fatigue, palpitations, and decreased exercise tolerance and resistance infections. Fetal risks are prematurity, low birth weight, and perinatal death. All pregnant patients should be screened for anemia, and those with iron deficiency should be treated with oral iron preparations in addition to prenatal vitamins.[18] Iron supplementation decreases the prevalence of maternal anemia

Table 48–6

Drugs of Concern During Breast-Feeding[4,17]

Drug or Class	Comments
Drugs that can decrease the breast milk production	
Clomiphene	Has been used to suppress lactation
Ergot derivatives (bromocriptine, cabergoline, ergotamine)	Have been used to suppress lactation
Estrogens	Contraceptives with ethinyl estradiol should be delayed for 3–6 weeks postpartum to decrease effect on lactation and prevent thrombosis
Pseudoephedrine	Do not use in patients with low milk production; a few doses will probably not have effect
Drugs for which use during breast-feeding may expose the neonate to a significant quantity and may necessitate a strict follow-up	
β-Blocking agents (acebutolol, atenolol, sotalol)	Neonatal β-blockade reported Concern for acebutolol, atenolol, and sotalol, but other β-blocking agents such as metoprolol, propranolol, and labetalol are safe
Amiodarone	May accumulate (long half-life); possible neonatal thyroid and cardiovascular toxicity
Antineoplastics	Neonatal myelosuppression possible
Chloramphenicol	Severe adverse effects reported when used to treat babies (blood dyscrasia, gray baby syndrome)
Ergotamine	Symptoms of ergotism (vomiting and diarrhea) reported
Illicit drugs	Unknown contents and effects
Lamotrigine	A breast-fed infant could have blood concentrations between 10% and 50% of maternal blood concentrations (variable but can be in therapeutic range); monitor for CNS side effects (sedation, hypotonia, weight gain, and poor sucking) and rash
Lithium	Up to 50% of maternal serum levels have been measured in infants; cases of infant toxicity (lethargy, cyanosis, electrocardiogram anomalies, dysthyroidism, tremors) reported; if breast-feeding, monitor infant serum lithium, creatinine, urea, and TSH levels every 4–12 weeks and other side effects (jitteriness, feeding problems, signs of dehydration)
Phenobarbital/primidone	Drowsiness and reduced weight gain reported; up to 25% of a pediatric dose can be ingested via breast milk; monitor for CNS adverse effects (sedation, hypotonia, weight gain, and poor sucking)
Radioactive iodine-131	No breast-feeding for days to weeks to achieve nonsignificant radiation levels (long radioactive half-life); monitor radioactive levels in milk before allowing breast-feeding; for diagnostic purposes, prefer Tc99m or iodine-123
Tetracyclines	Chronic use may lead to dental staining or decreased epiphyseal bone growth (theoretical)

CNS, central nervous system, TSH, thyroid stimulating hormone.

at delivery and reduces transfusion requirements. It is unclear whether supplementing nonanemic pregnant patients will improve perinatal outcomes but it reduces maternal fatigue.[18]

Nausea and Vomiting of Pregnancy (NVP)

As many as 80% of pregnant patients suffer from nausea or vomiting.[19] Taking a prenatal vitamin for 1 month before pregnancy may reduce the incidence and severity of nausea and vomiting of pregnancy (NVP). Nonpharmacologic measures, such as lifestyle (rest, avoidance of nausea triggers) and dietary changes (small/frequent meals, fluid restriction during meals, avoiding spicy/fatty foods, consuming crackers upon awakening, high protein snacks) may be considered for initial management. Acupuncture and acupressure may also be helpful.[19]

Early treatment with pyridoxine (vitamin B6) or a combination of pyridoxine and doxylamine is recommended to prevent progression to more severe NVP such as hyperemesis gravidarum. When insufficient, diphenhydramine, prochlorperazine, promethazine, ondansetron, or metoclopramide can be prescribed (Table 48–7).[19]

Pain

Pregnant or lactating patients may experience pain from preexisting conditions or from temporary pathologies (eg, musculoskeletal conditions, fibromas, migraine, etc.).

The general principles of treatment are[4,20]

- Maximize nonpharmacological measures.
- Acetaminophen is the safest analgesic during pregnancy.
- Avoid nonsteroidal anti-inflammatory drugs (NSAIDs) during the third trimester; short-term (< 72 hours) courses can be used under medical supervision during the first and second trimesters.
- Opioids are not associated with a higher risk of malformations. However, close neonatal monitoring is necessary due to possible withdrawal if opioids are taken regularly near delivery.
- Pregnancy and lactation safety data are limited for some medications (eg, pregabalin, gabapentin) and their use should be evaluated on a case-by-case basis.
- For migraine, sumatriptan can be used when other medications are not sufficient or indicated.

Urinary Tract Infections

Urinary tract infections, even asymptomatic, are associated with preterm birth, low birth weight, and preeclampsia, and treatment reduces these risks.[21,22] Untreated bacteriuria leads more often to pyelonephritis due to physiologic changes of the urinary tract.[21] Screening for asymptomatic bacteriuria is performed in the first trimester but may be repeated in high-risk patients (eg. preexistent DM, sickle cell disease, and neurogenic bladder).[21,22] Uropathogens are the same as for nonpregnant patients,[21] including multidrug-resistant strains; antibiograms are warranted. Differential diagnosis of dysuria includes sexually transmitted infections.

Antimicrobial therapy is considered for asymptomatic patients with $\geq 10^8$ colony forming units (cfu)/L or symptomatic patients with $\geq 10^5$ cfu/L of a uropathogen on a clean-catch mid-stream specimen.[22] Treatment options include β-lactams, nitrofurantoin, and fosfomycin (Table 48–7). Trimethoprim-sulfamethoxazole should be avoided during organogenesis (congenital malformations) and near term (theoretical risk of **kernicterus**).[4] Quinolones are reserved for resistant infections due to theoretical concerns of arthropathy.[4] Initiate in-hospital intravenous (IV) antibiotics for pyelonephritis.

Repeat urine culture 7 days after treatment. Suppressive prophylaxis (Table 48–7) up to 6 weeks after delivery is indicated for persistent bacteriuria despite two treatment courses, recurrent cystitis, or after a single pyelonephritis episode.[22]

Preterm Labor

Preterm birth is defined as a delivery before 37 completed weeks (< 259 days). Preterm birth, especially before 32 weeks of pregnancy, is the major cause of short- and long-term neonatal mortality and morbidity. In case of a premature delivery threat, depending on the GA, the following should be started, antenatal corticosteroids for fetal pulmonary maturation, an antibiotic to lower the risk of neonatal group B streptococcal disease, and magnesium sulfate for fetal neuroprotection.[23,24] Tocolytics can be administered in preterm labor and antibiotics in preterm premature rupture of membranes (PPROM) to prolong pregnancy.[24]

▶ *Antenatal Corticosteroids*

Administration of antenatal corticosteroids to the mother to accelerate the maturation of the fetal lungs decreases incidence and severity of neonatal respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and death.[23] Provide a single course of antenatal corticosteroids (betamethasone or dexamethasone) to patients between 24 0/7 and 33 6/7 weeks of gestation at risk of delivery within 7 days (Table 48–7).[23] It may also be considered starting at 23 0/7 weeks or between 34 0/7 and 36 6/7 weeks if they did not receive a previous course. A single repeat course can be considered after 7 to 14 days if at less than 34 0/7 weeks and at risk of delivery within 7 days.[23]

▶ *Tocolytic Agents*

Tocolytics are used when preterm labor occurs before 33 6/7 weeks to delay delivery to complete a course of corticosteroids and allow transfer of the mother to a center with neonatal intensive care facilities. Tocolytics include magnesium sulfate, β-mimetics (terbutaline), prostaglandin inhibitors (indomethacin), oxytocin receptor blockers (atosiban, not available in the United States), and calcium channel blockers (nifedipine) (Table 48–7).[24,25] Tocolytic agents can prolong pregnancy for up to 48 hours. Magnesium sulfate is associated with significant maternal adverse effects, and indomethacin cannot be used after 32 weeks of pregnancy.[24]

FDA issued a warning regarding the use of terbutaline for tocolysis due to the risk of serious maternal adverse effects. Accordingly, its use should be limited to short-term inpatient use.[24]

▶ *Neuroprotection*

Magnesium sulfate given to patients at imminent risk of delivery before 32 0/7 weeks gestation decreases the incidence of subsequent neurologic morbidities like cerebral palsy (Table 48–7).[24,26,27]

▶ *Antibiotics for PPROM*

In the presence of PPROM, 2 days of parenteral ampicillin/erythromycin followed by 5 days of oral amoxicillin and erythromycin are associated with a delay of delivery and reduction in maternal and neonatal morbidity (Table 48–7).[27] Patients with PPROM should receive adequate intrapartum Group B *Streptococcus* (GBS) prophylaxis for the first 48 hours to prevent neonatal infection (refer to section on "GBS infection").[27,28]

Table 48–7

Medication Dosing Recommendations During Pregnancy and Lactation[12,18-50]

Drug	Dosage	Comments
Micronutrients and Vitamins		
Folic acid	0.4–0.8 mg po daily	Dosage necessary to reach RDA: 0.6 mg (pregnancy), 0.5 mg (breast-feeding)
	1–5 mg po daily	If higher risk of having a child with NTD
Iron	60–200 mg (elemental iron) po per day (divided doses if > 60–100 mg of elemental iron)	Doses to treat iron-deficiency anemia
Nausea and Vomiting		
First choices		
Diphenhydramine or dimenhydrinate	25–50 mg po four times daily as needed	Will likely cause sedation. Do not drive under the effect of these medications
Doxylamine	12.5 mg po three to four times daily as needed	
Pyridoxine	25 mg po three times daily as needed	Dose up to 200 mg daily have been used
Doxylamine + pyridoxine	10/10 mg: days 1 and 2 take two pills at bedtime; day 3 may take one pill in the morning and two at bedtime; may increase to one pill in the morning, one in the afternoon and two at bedtime (four pills daily) 20/20 mg: day 1 take one pill at bedtime; day 2 may take one pill in the morning and one at bedtime (two pills daily)	Increase to next dose if nausea persists FDA approved agents: Diclegis (10/10 mg), Bonjesta (20/20 mg) Off label: separate doxylamine and pyridoxine products
Second choices		
Metoclopramide	5–15 mg po three to four times daily as needed	Older maternal age and higher dose increase risk of extrapyramidal effects
Ondansetron	4–8 mg po three times daily as needed	QT prolongation, first trimester use associated with small increase in cardiovascular malformations and cleft palate
Prochlorperazine	25 mg twice daily as needed	Phenothiazine use with metoclopramide increases risk of extrapyramidal effects
Promethazine	12.5–25 mg four times daily as needed	Phenothiazine use with ondansetron increases risk of QT interval prolongation
Urinary Tract Infections		
Asymptomatic bacteriuria and uncomplicated acute cystitis		
Nitrofurantoin	100 mg po four times daily for 3–7 days 100 mg po twice daily (macrocrystalline—Macrobid) for 3–7 days	Avoid use in G6PD deficiency
Cefadroxil	1000 mg po twice daily for 3–7 days	
Cefprozil	500 mg po twice daily for 3–7 days	
Cephalexin	500 mg po twice daily for 3–7 days	
Amoxicillin	500 mg po three times daily for 3–7 days	Check for local resistance before prescribing
Fosfomycin	3 g po single dose	
Acute pyelonephritis		
Ampicillin + gentamicin	1–2 g IV every 6 hours + 1.5 mg/kg/dose IV every 8 hours	Switch to oral antibiotic after 48 hours afebrile and treat for a total of 10–14 days, for example: • Cephalexin 500 mg po four times daily • Cefprozil 500 mg po twice daily • Amoxicillin clavulanate 875/125 mg po twice daily
Cefazolin	1–2 g IV every 8 hours	
Cefuroxime	0.75–1.5 g IV every 8 hours	
Ceftriaxone	1–2 g IV or IM every 24 hours	
Prophylaxis		
Nitrofurantoin	50–100 mg po daily at bedtime or postcoitally as needed	Start after the end of the treatment for pyelonephritis and continue until 4–6 weeks after delivery
Cephalexin	250 mg po at bedtime or postcoitally as needed	Nitrofurantoin should be preferred to prevent resistance to cephalosporins
Fetal Lung Maturation		
Betamethasone	12 mg IM every 24 hours for two doses	A single rescue course may be considered after at least 1 or 2 weeks of treatment if gestational age is < 34 0/7 weeks and the patient is likely to give birth within the next week
Dexamethasone	6 mg IM every 12 hours for four doses	

(*Continued*)

Table 48–7

Medication Dosing Recommendations During Pregnancy and Lactation[12,18-50] (*Continued*)

Drug	Dosage	Comments
Tocolytic Agents		
Indomethacin	50 mg oral load, then 25–50 mg po every 6 up to 48 hours	Avoid after 32 weeks of pregnancy; reports of increased risk of maternal postpartum hemorrhage, and neonatal complications (eg, premature closure of the ductus arteriosus, renal insufficiency, patent ductus arteriosus, necrotizing enterocolitis) are worrisome
Magnesium sulfate	4 g IV over 30 minutes, then continuous IV infusion of 2 g/hour up to 48 hours	Contraindicated in patients with myasthenia gravis; maternal pulmonary edema and cardiac arrest have been reported Monitor blood magnesium levels Use with caution if renal impairment, contraindicated if renal failure
Nifedipine (short acting)	10–30 mg oral load (divided over at least 1 hour if > 10 mg used), then 10–20 mg every 4–8 up to 48 hours	Avoid in patients with hypotension and preload-dependent cardiac lesions such as aortic insufficiency
For neuroprotection or prevention of eclampsia		
Magnesium Sulfate	4 g IV over 30 minutes, then continuous IV infusion of 1 g/hour	Contraindicated in patients with myasthenia gravis; maternal pulmonary edema and cardiac arrest have been reported; treatment limited to 24 hours for neuroprotection Monitor blood magnesium levels Use with caution if renal impairment; contraindicated if renal failure
Preterm Premature Rupture of Membranes		
Ampicillin	2 g IV every 6 hours for 48 hours followed by amoxicillin	Ampicillin/amoxicillin are used with erythromycin
Amoxicillin	250 mg po three times daily for 5 days	
Erythromycin base	250 mg IV every 6 hours for 48 hours followed by 333 mg po three times daily for 5 days	
Preterm Labor Prevention		
17-α-Hydroxyprogesterone	250 mg IM each week	Start at 16–24 weeks' gestation if previous preterm delivery
Progesterone (micronized)	100 mg (capsules) or 90 mg (8% gel) intravaginally daily (previous preterm delivery) 200 mg intravaginally daily (short cervix)	Start at 16–24 weeks' gestation if previous preterm delivery and before 24 weeks if short cervix
Group B *Streptococcus*		
Penicillin G	5 million units IV initially, then 2.5–3 million units IV every 4 hours until delivery	First choice
Ampicillin	2 g IV initially, then 1 g IV every 4 hours until delivery	
Cefazolin	2 g IV initially, then 1 g IV every 8 hours until delivery	
Clindamycin	900 mg IV every 8 hours until delivery	Only if isolate proven sensitive to clindamycin and erythromycin, or sensitive to clindamycin and testing for inducible clindamycin resistance is negative
Vancomycin	1 g IV every 12 hours until delivery	If other options are inappropriate
Cervical Ripening/Induction of Labor		
Misoprostol	25 mcg (1/4 of 100 mcg tablet) vaginally every 3–6 hours	Check for **uterine tachysystole** with or without fetal heart rate changes. Off label use
Dinoprostone	0.5 mg gel in cervical canal, or 1–2 mg vaginal gel 10 mg extended-release vaginal insert in posterior fornix	Do not use if previous uterine surgery including cesarean section Check for uterine tachysystole with or without fetal heart rate changes
Oxytocin	Low-dose regimen: 0.5–2 mU/min, with 1–2 mU/min increase every 15–40 minutes according to contractions High-dose regimen: 6 mU/min with 3–6 mU/min increases every 15–40 minutes according to contractions	Check for uterine tachysystole and water intoxication
Postpartum Hemorrhage Treatment		
Oxytocin	10 U IM or 10–40 U per 500–1000 mL as continuous intravenous infusion	Use normal saline or lactated Ringer's; caution with bolus if cardiac disease
Methylergonovine	0.2 mg IM every 2–4 hours	Do not use in patients with hypertension, preeclampsia or cardiovascular disease

(*Continued*)

Table 48–7

Medication Dosing Recommendations During Pregnancy and Lactation[12,18-50] (*Continued*)

Drug	Dosage	Comments
Carboprost tromethamine	0.25 mg IM or intramyometrial every 15–90 minutes up to eight doses	Use with caution if asthma
Misoprostol	600–1000 mcg PO or PR	Off label use
Tranexamic acid	1 g IV over 10 minutes (repeat once if bleeding persists)	Off label use
Hyperthyroidism		
Methimazole	5–15 mg po once or twice daily (total daily dose: 10–30 mg)	Preferred agent in second and third trimesters Risk of malformation in first trimester
Propylthiouracil	50–100 mg po one to three times daily (100–600 mg divided in three daily doses)	Preferred agent in first trimester Risk of hepatotoxicity
Severe Hypertension		
Labetalol	Start with 10–20 mg IV over 2 minutes; repeated 20–80 mg every 15–30 minutes (max 300 mg/24 hours) Or 1–2 mg/min IV drip Oral formulation can be acceptable if patient is asymptomatic and no other option is available	Can exacerbate asthma symptoms May cause fetal bradycardia
Nifedipine (short acting)	10–20 mg po; could be repeated after 20 minutes, then 10–20 mg every 2–6 hours (max 180 mg/24 hours)	May cause headache, flushing, dizziness, reflex tachycardia, and maternal pulmonary edema
Hydralazine	5 mg IV or IM; repeated 5–10 mg IV every 20–40 minutes (max 20 mg IV) Or 0.5–10 mg/hour IV drip	May cause reflex tachycardia, headaches
Nonsevere Hypertension		
First choices		
Labetalol	200–2400 mg divided in two to three divided doses	Can exacerbate asthma symptoms. May cause tiredness, headaches, hepatotoxicity
Nifedipine extended release	30–120 mg po daily	May cause tachycardia, headaches, lower limb edema
Second choices		
Methyldopa	500–3000 mg divided in two to four daily doses—max 750 mg per dose	Less effective than first line agents, may cause drowsiness, depression, hemolytic anemia, positive antinuclear antibodies
Hydrochlorothiazide	12.5–50 mg po once daily	May cause hypokalemia, dehydration
Bacterial Vaginosis		
Metronidazole	250 mg po three times daily for 7 days or 500 mg orally twice a day for 7 days 0.75% vaginal gel, once or twice daily for 5 days	Can be used in all trimesters For metronidazole and clindamycin, use oral formulation during pregnancy if treatment aim is to prevent PTB
Clindamycin	300 mg po twice daily for 7 days 2% cream, 5 g intravaginally at bedtime for 7 days 100-mg ovules intravaginally at bedtime for 3 days	
Vulvovaginal Candidiasis: Refer to Chapter 85		
Mastitis		
Outpatient treatment		
Dicloxacillin	500 mg po four times daily	Treat for 10–14 days
Cephalexin	500 mg po four times daily	
Amoxicillin 875 mg + clavulanate 125 mg	One tablet po twice daily	
Inpatient treatment for more severe cases		
Oxacillin	2 g IV every 4 hours	Treat IV for 24–48 hours until afebrile then continue with outpatient treatment
Nafcillin	2 g IV every 4 hours	
Clindamycin	600–900 mg IV every 8 hours	
Vancomycin	1 g IV every 8–12 hours	If MRSA suspected or proven
Breast Candidiasis		
Mother		
Clotrimazole, miconazole, or nystatin	Topical cream	After each feeding and for 1 week after symptoms have resolved; also treat infant even if asymptomatic
Fluconazole	200–400 mg po for one dose followed by 100–200 mg po daily	If topical treatment not efficacious, add fluconazole; use until 1 week after symptoms have resolved (minimum of 2 weeks); also treat infant even if asymptomatic

(*Continued*)

Table 48–7

Medication Dosing Recommendations During Pregnancy and Lactation[12,18-50] (*Continued*)

Drug	Dosage	Comments
Infant		
Nystatin oral solution	100,000–200,000 U (1–2 mL) to be swabbed into infant's mouth four times daily, after feedings	
Clotrimazole or miconazole topical cream	Apply in a thin layer in infant's mouth four times daily, after feedings	
Other treatments for candidiasis		
Gentian violet 0.5%–1% solution	To be swabbed into infant's mouth once daily for 5 days before a feeding	Not preferred treatment, may stain clothes and skin, can cause mouth irritation/ulceration If nipples or mouth are not violet after application and the feeding, reapply the treatment

IM, intramuscular; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; NTD, neural tube defect; po, orally; PR, per rectum; PTB, preterm birth; RDA, recommended daily allowance.

Clinical Confirmation and Associated Problems of Pregnancy and Lactation

Confirmation of Pregnancy

- Positive urine or blood human chorionic gonadotropin followed by positive ultrasound, fetal heart sounds, and/or fetal movement.

Pregnancy Dating and Gestational Age

- Calculated from the first day of the last menstrual period (LMP).
- An ultrasound between 10 + 0 and 13 + 6 weeks determines gestational age based on crown-rump length and identifies multiple pregnancies.
- Due dates typically are estimated at 40 weeks of gestation; however, infants delivered between 37 and 42 weeks are considered full term.

Pregnancy Symptoms

- First trimester: Menstrual spotting, missed menses, fatigue, breast tenderness, increased urination, mood swings, nausea/vomiting, headache, heartburn, constipation
- Second trimester: Frequent urination, heartburn, constipation, dry skin, edema, **linea nigra**, **melasma**
- Third trimester: Backache, edema, shortness of breath, insomnia

Routine Pregnancy Visits

- In an uncomplicated pregnancy, visits should occur monthly until 28 weeks of gestation, every 2 to 3 weeks from 28 to 36 weeks of gestation, and then weekly until delivery.
- Assess for each of the following at each visit:
  - Blood pressure
  - Weight
  - Urine protein (dipstick)
  - Uterine size
  - Fetal heart rate
  - Fetal movement

Routine Lab Testing for Normal Pregnancies (First Trimester Unless Otherwise Indicated)

- Hemoglobin and hematocrit for anemia (repeated at 26–32 weeks)
- Blood type, Rh, red blood cell antibody screening
- Human immunodeficiency virus
- Venereal Disease Research Laboratory (VDRL) slide test for syphilis
- Rubella immunity
- Varicella immunity
- Hepatitis B surface antigen
- Urinalysis with culture for bacteriuria
- Gonorrhea and chlamydia
- Cervical cytology
- Screens for Down syndrome and neural tube defects (NTDs) NTDs (between 11 and 20 weeks)
- Gestational diabetes screening (at 24–28 weeks)
- Group B *Streptococcus* (GBS) screening (at 35–37 weeks)
- Patients at high risk for these conditions should be tested at the first visit:
  - Hypothyroidism
  - Type 2 diabetes
  - Sickle cell disease or thalassemia
  - Hepatitis C
  - Tuberculosis
  - Bacterial vaginosis

▶ *Progesterone*

Progesterone is used to reduce the risk of preterm birth in patients with singleton gestation and a prior spontaneous singleton preterm delivery and should be initiated between 16 and 24 weeks of gestation.[29,30] Administration of progesterone is also recommended in the setting of a very short cervix (≤ 20 mm) by transvaginal ultrasound before or at 24 weeks of gestation (Table 48–7).[29,30]

Group B *Streptococcus* Infection

A total of 10% to 30% of pregnant patients are colonized by GBS at term. IV antibiotics are effective in reducing the incidence of early-onset neonatal GBS infection when administered to high-risk groups including patients with GBS vaginal/rectal colonization, GBS bacteriuria in the current pregnancy, and those who previously delivered a neonate with GBS disease.[28]

All patients should be screened for colonization using a vaginal–rectal swab between 36 and 37 weeks. If treatment is indicated, it should be started at the time of membrane rupture or onset of labor, whichever comes first and continued until delivery (Table 48–7). All patients with unknown status should be treated if labor or PPROM occur before 37 weeks. IV penicillin G or ampicillin is preferred treatment. In instances of patient reported penicillin allergy, penicillin allergy testing is recommended, if available, to confirm appropriate therapy.[28] If penicillin-allergic, cefazolin (for nonanaphylactic penicillin reaction) or clindamycin (for anaphylactic penicillin reaction) can be used (refer to Table 48–7 to know when clindamycin can be used). If sensitivity to clindamycin is unknown, vancomycin should be administered.[28]

Induction of Labor

Induction of labor aims to achieve a vaginal delivery by stimulating uterine contractions before spontaneous labor. Cervical ripening is the process of cervical softening, thinning, and dilating, when the cervix is not favorable to delivery.

Mechanical methods for ripening include cervical dilators (hygroscopic dilator, Foley catheter) and extraamniotic saline infusion.[31-33] Pharmacological methods include prostaglandin E1 (eg, vaginal misoprostol) and E2 (eg, vaginal or cervical dinoprostone). Prostaglandins are used both for cervical ripening and induction of labor. The controlled-release vaginal dinoprostone is easily removed in case of uterine tachysystole, which helps to reverse it. Prostaglandins should not be used in patients with a previous cesarean section due to the increased risk of uterine rupture.[32,33]

When the cervix is deemed favorable, nonpharmacological options for producing contractions are membrane sweeping, nipple stimulation, and amniotomy.[31]

Oxytocin is the most frequently used pharmacological method of labor induction.[31] If a prostaglandin has been used, oxytocin needs to be delayed 30 to 60 minutes after the removal of dinoprostone controlled-release insert, 4 hours after the last dose of misoprostol, and 6 to 12 hours after the administration of dinoprostone gel.[31] A rare but serious complication of high cumulative dose of oxytocin is water intoxication due to its antidiuretic action.[32]

Postpartum Hemorrhage

Postpartum hemorrhage is defined by the ACOG as blood loss greater than or equal to 1000 mL or blood loss with signs or symptoms of hypovolemia within 24 hours after birth, regardless of route of delivery.[34] A blood loss greater than 500 mL after vaginal delivery is considered abnormal. Uterine atony accounts for up to 80% of primary postpartum hemorrhage, but other etiologies like genital or cervical trauma, retained placenta, and coagulopathies are also implicated.[34]

Oxytocin and carbetocin (long-acting analog of oxytocin) can prevent excessive blood loss associated with delivery and caesarian section. Of the treatment of postpartum hemorrhage, uterotonics (oxytocin, methylergonovine, carboprost tromethamine, and misoprostol) are effective in the presence of uterine atony. Methylergonovine should not be administered to patients suffering from hypertension or coronary artery disease. Carboprost tromethamine should be used with caution in asthmatic patients.[34] ACOG recommends that tranexamic acid, an antifibrinolytic agent, should be administered when uterotonics fail, and recent data indicate that it reduces mortality when given within 3 hours of birth.[34,35]

Nonpharmacologic approaches are also used, such as uterine massage or compression (tamponade). More invasive procedures ranging from transfusion to hysterectomy are used in unresponsive postpartum hemorrhages.[34]

Thyroid Disorders

Thyroid hormones increase by 50% from 7 to 16–20 weeks' gestation, then plateau until delivery. The thyroxine-stimulating hormone (TSH) reference range shifts downward by 0.5 mIU/L (μIU/mL) in the first trimester because of the beta-human chorionic gonadotropin (β-hCG) effect.[36] Universal screening of thyroid disorders in pregnancy is no longer recommended because identification and treatment of maternal subclinical hypothyroidism has not been shown to result in improved pregnancy outcomes or neurocognitive functioning in children.[36,37] Pregnant patients who are indicated for thyroid function testing are those with risk factors, such as a personal or family history of thyroid disease, type 1 diabetes, or clinical suspicion of thyroid disease. See Chapter 45 for further discussion on thyroid disorders.

Gestational (subclinical) hypothyroidism is defined by a TSH above normal pregnancy range and may be linked to adverse pregnancy outcomes. Replacement therapy is suggested for positive antithyroid peroxidase antibodies (anti-TPOAbs) and TSH above 2.5 mIU/L (strongly if above 4.0 mIU/L) or negative antibodies and TSH above 4.0 mIU/L (strongly if above 10.0 mIU/L).[36,37] To treat chronic hypothyroidism during pregnancy, initially increase prepregnancy levothyroxine dose (LT_4) by 30%. Once treatment is initiated, monitor TSH every 4 to 6 weeks until 20 weeks and once in the early third trimester to aim for TSH under 2.5 mIU/L.[36] Resume prepregnancy dosage at delivery.

Gestational hyperthyroidism is self-remitting and not associated with adverse outcomes. In Graves disease, propylthiouracil (PTU) is used until week 16 and then either continued or changed to methimazole thereafter (Tables 48–3 and 48–7).[37] Administer at the lowest effective dose to target free T_4 (FT_4) at or moderately above the reference range. Monitor fetus and neonate to detect signs of hypothyroidism (if antithyroid drugs) or hyperthyroidism (if mother is positive for thyroid-stimulating hormone receptors-stimulating antibodies [TSHR-Sabs]).

Monitor TSH levels 6 to 8 weeks after delivery in patients with thyroid disorders. Both LT_4 and antithyroid drugs can be used during lactation.[36,37]

Hypertension

Preexisting and gestational hypertension increase the risk of maternal and perinatal morbidity and mortality. Preeclampsia, caused by impaired placentation, may present with hypertension and multiple maternal complications or fetal distress. Delivery leads to cure, although transient flare or *de novo* preeclampsia occur postpartum.[38,39] Timing of delivery depends on maternal and fetal status and GA, but is not deferred past 37 weeks.[38] IV magnesium sulfate is used in prevention of eclampsia (Table 48–7).[26,38,39]

Treat severe hypertension (systolic above 160 mm Hg or diastolic above 110 mm Hg) promptly to avoid target-organ damage (Table 48–7).[38-41] It is recommended to maintain blood pressure levels between 120 to 160 and 80 to 110 mm Hg for pregnant patients with nonsevere hypertension.[40] In nonpreeclamptic hypertension, maintaining blood pressure control benefits the mother without harming the fetus.[42] Labetalol and extended release nifedipine are first-line treatments (Table 48–7).[40] Angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor antagonists, renin inhibitors, or mineralocorticoid receptor antagonists are not recommended.[40]

The ACOG stratifies women into groups of low, moderate, or high risk for preeclampsia based on a prior maternal history of preeclampsia, diabetes, obesity, maternal age, and multiple other patient factors. To prevent preeclampsia and growth restriction, initiation of low-dose aspirin (75–160 mg daily) between 12 and 16 weeks gestation should be considered for moderate risk women and is recommended for high risk women. Additionally, calcium supplements (1.5–2.0 g elemental calcium/day) should be initiated if dietary calcium intake is low.[38,39]

Patients with hypertension around pregnancy and delivery should be instructed to monitor blood pressure up to 10 days postpartum and counseled regarding thresholds or symptoms requiring consultation.[38,39] An appointment 6 to 12 weeks postpartum is recommended to ensure correction of hypertension and proteinuria and for counseling on future pregnancies and long-term care.

Preexisting Diabetes Mellitus

For gestational diabetes mellitus (GDM) discussion, see Chapter 44. Hyperglycemia is teratogenic. Patients of childbearing age with preexistent diabetes should achieve a preconception hemoglobin A_{1c} less than 7% (0.07; 53 mmol/mol Hb) (ideally < 6.5% [0.065; 48 mmol/mol Hb]) to minimize risks of spontaneous abortions and malformations.[43] Refer to folic acid recommendations above.

Patients with preexisting DM should be screened for diabetic nephropathy and retinopathy.[43] Type 1 DM (T1DM) are tested for gestational hypothyroidism and anti-TPOAbs. Low-dose aspirin is indicated to reduce preeclampsia risks for patients with type 1 and type 2 diabetes and should be initiated as early as 12 weeks gestation and continued until delivery.[39]

Optimal control of glycemia throughout pregnancy reduces risks of macrosomia, delivery complications, fetal demise, preeclampsia, and neonatal complications.[43] Self-monitoring of blood glucose (SMBG) goals during pregnancy are fasting less than 95 mg/dL (5.3 mmol/L), premeal less than 100 mg/dL (5.6 mmol/L), 1 hour post meal less than 140 mg/dL (7.8 mmol/L), or 2 hour post meal less than 120 mg/dL (6.7 mmol/L). Standard treatment is insulin. Oral hypoglycemics are not as efficacious, cross the placenta, and long-term safety data are missing.[4,43] Continue medication until the patient is safely switched to insulin.

Intrapartum glucose is maintained between 70 mg/dL (3.9 mmol/L) and 110 mg/dL (6.1 mmol/L) to avoid fetal acidosis and neonatal hypoglycemia. Postpartum, resume two-thirds of prepregnancy insulin dosage. Metformin and insulin are safe during breast-feeding.[4]

Anticoagulation

Thromboembolic risk increases during pregnancy and up to 12 weeks postpartum. Anticoagulation with low-molecular-weight heparins or unfractionated heparin may be required antepartum and/or postpartum for some patients, even when not anticoagulated before pregnancy.[4,44] Dosage is specific to the underlying condition.

Warfarin is associated with a dose-dependent embryopathy when used between 6 and 12 weeks' gestation and with fetal and maternal bleeding when used near delivery (Table 48–3).[4,44] Its use is still recommended during pregnancy (except during those periods), in addition to low-dose aspirin, for prosthetic heart valves, which are highly thrombogenic.[44] Warfarin and heparins are safe to use during breast-feeding.[17] Direct oral anticoagulants (DOACs), which include direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, betrixiban), should be avoided during pregnancy and breast-feeding due to insufficient human safety and efficacy data.[44] Additionally, studies have demonstrated that these agents likely cross the placenta and are detectable in breast milk.[44]

Bacterial Vaginosis

Bacterial vaginosis is associated with spontaneous abortion, PPROM, chorioamnionitis, preterm birth, postcesarean wound

Patient Encounter, Part 2

Urine culture screening at 12 weeks reports more than 10^8 cfu/L of sensitive *Escherichia coli*. The patient was successfully treated with oral nitrofurantoin for 3 days, and urine culture a week later was negative. She tested negative for chlamydia and gonorrhea in the first trimester. At 20 weeks, she presents with polyuria and dysuria without fever or systemic symptoms. Urinalysis shows leucocytes and glycosuria, and urine culture is positive for *E. coli* again, and antibiogram does not indicate resistance to any antibiotic agents. Bacterial vaginosis testing is positive, with the presence of a homogenous, thin grayish-white vaginal discharge, vaginal pH greater than 4.5, positive whiff-amine test, clue cells on saline wet mount, and negative for pseudohyphae. She reports a history of repeated urinary tract and yeast infections, but denies symptoms after sexual intercourse or new sexual partner. Home blood glucose monitoring is at target in the fasting state and 1-hour post meals, but is elevated around 120 mg/dL (6.7 mmol/L) before lunch and dinner. Blood pressure is 148/84 mm Hg. She successfully quit smoking at 10 weeks.

Meds: Insulin glargine 40 U subcutaneously at bedtime, insulin aspart 10 U subcutaneously before every meal, labetalol 400 mg orally twice daily, aspirin 81 mg orally at bedtime, levothyroxine 75 mcg orally before breakfast, 17-α-hydroxyprogesterone 250 mg IM weekly until 36 weeks, and multivitamin containing folic acid 1 mg.

What treatment do you recommend at this time?

infection, postpartum endometritis, and pelvic inflammatory disease.[45-47] Oral or topical treatment with metronidazole or clindamycin is recommended for symptomatic pregnant and lactating patients.[45,46] Oral metronidazole or clindamycin is recommended to prevent preterm delivery in patients at high risk (Table 48–7).[46] Culture should be performed 1 month after completion of therapy since the cure rate is approximately 70%.[46]

Vulvovaginal Candidiasis

Only symptomatic vulvovaginal candidiasis should be treated in pregnant or lactating patients (Table 48–7).[45] Refer to Chapter 85.

Six- to seven-day treatments for intravaginal antifungal azoles are recommended during pregnancy to prevent recurrent episodes, but shorter courses are appropriate during breast-feeding. Oral flucanazole may be considered during lactation or if intravaginal azoles cannot be used, but should be used with caution because recent data indicate exposure during pregnancy may increase the risk of miscarriage.

Sexually Transmitted Infections

Table 48–8 presents the management of sexually transmitted infections during pregnancy and lactation, associated risks, and

Table 48–8

Management of Sexually Transmitted Infections During Pregnancy and Lactation[45,46]

	Indications for Treatment	Associated Risks During Pregnancy	When to Repeat Testing During Pregnancy	Other
Chlamydia trachomatis	All patients with a positive test, even if asymptomatic	Preterm labor; neonatal infection	Third trimester: < 25 years of age, those at increased risk of infection	Repeat testing 3–4 weeks and 3 months after therapy
Treatment	First choice: Azithromycin 1 g po once Alternative choices: Amoxicillin 500 mg po three times daily for 7 days Erythromycin base 500 mg po four times daily for 7 days or 250 mg po four times daily for 14 days Erythromycin ethylsuccinate 800 mg po four times daily for 7 days or 400 mg po four times daily for 14 days Doxycycline 100 mg po twice daily for 7 days only during lactation (contraindicated during pregnancy)			
Gonorrhea	All patients with a positive test, even if asymptomatic	Preterm labor, neonatal infection	Third trimester: if first screening positive or if at risk of reinfection	Repeat testing 2 weeks and 3 months after treatment
Treatment (uncomplicated infection of pharynx, cervix, urethra, rectum)	First choice: ceftriaxone 250 mg IM once + azithromycin 1 g po once Second choice during breast-feeding: ceftriaxone 250 mg IM once + doxycycline 100 mg po twice daily for 7 days (doxycycline contraindicated during pregnancy)			
Genital herpes simplex	Active lesions, disseminated; Starting at 36 weeks: prevention of recurrence at term	Neonatal infection, especially if acquired near time of delivery (30%–50%)	No routine testing recommended	Cesarean section if active genital lesions at delivery; evaluate newborn for herpes infection
Treatment	**First episode:** Acyclovir: 400 mg po three times daily for 7–10 days, or 200 mg five times daily for 7–10 days Valacyclovir: 1000 mg po twice daily for 7–10 days **Recurrent episodes:** Acyclovir: 400 mg po three times daily for 5 days, or 800 mg twice daily for 5 days, or 800 mg three times daily for 2 days Valacyclovir: 500 mg po twice daily for 3 days **Suppressive therapy:** start at 36 weeks of gestation (or earlier if at risk of preterm delivery) until delivery Acyclovir: 400 mg po three times daily Valacyclovir: 500 mg po twice daily			
Syphilis	All patients with confirmed positive serology	In utero fetal and neonatal infection; congenital malformations	At 28–32 weeks and at delivery if at risk of reinfection, if untested before, if positive serology in the first trimester, or if was previous stillborn at > 20 weeks	Therapy is efficacious to treat the fetus and prevent transmission; be aware of Jarisch–Herxheimer reaction; fetal evaluation should include ultrasounds
Treatment	Desensitize penicillin-allergic patients Primary, secondary, or early latent: Benzathine penicillin G 2.4 million units IM once Late latent or of unknown duration or tertiary: Benzathine penicillin G 2.4 million units IM three times at 1-week interval			
Trichomoniasis	Symptomatic patients	PPROM, preterm birth, low birth weight; neonatal infection		Therapy does not decrease perinatal mortality
Treatment	Metronidazole: 500 mg twice daily for 7 days, or 2 g po single dose Consider deferring breastfeeding for 12–24 hours after single 2 g dose			

IM, intramuscular; IV, intravenous; po, orally; PPROM, preterm premature rupture of membranes.

Patient Encounter, Part 3

At 38 weeks' gestation, the patient presents with rapidly progressing edema, unusual headache, blurry vision, and blood pressure persistently over 160/100 mm Hg. Her reflexes are brisk. 24 hour urine collection shows 350 mg/dL (3.5 g/L) protein, serum creatinine is 1.5 mg/dL (133 μmol/L). Remaining preeclampsia workup (complete blood count [CBC], liver enzymes, lactate dehydrogenase, and creatinine) is normal. Nonstress test is reassuring and cervix. Cervix is closed. The fetus had an estimated fetal weight at 50th percentile and was in cephalic position. Vaginal–rectal swab was positive for group B *Streptococcus* (GBS). She has a confirmed allergy to penicillin.

Meds: Insulin glargine 20 U subcutaneously at awakening, 25 U subcutaneously at bedtime, insulin aspart 20 U subcutaneously before every meal, labetalol 400 mg orally three times daily, aspirin 81 mg orally at bedtime, levothyroxine 100 mcg orally before breakfast, and multivitamin containing folic acid 1 mg.

What is your assessment of this patient's condition and what will you recommend now?

recommended follow-up.[45] Treatment of all recent sexual partners is mandatory.

Patient Encounter, Part 4

After 12 hours of labor, the patient delivers vaginally a 7.8 lb (3.5 kg) baby. She is not sure if she should breast-feed because of her chronic medications.

What treatment plan do you recommend after delivery?

What surveillance do you suggest for the newborn/baby?

Can she breast-feed while taking her medications?

Enhancement of Lactation

Insufficient milk production is diagnosed when breast-feeding cannot meet neonate's requirements. Several factors affect milk production including fatigue, stress, smoking, premature delivery, cesarean section, pain, and some medications (Table 48–6). Optimization of breast-feeding techniques is the first-line strategy. Prolactin is the main hormone linked to milk production. No drug is currently approved by the FDA or recommended by the American Academy of Breastfeeding for lactation enhancement, but dopamine antagonists, metoclopramide, and domperidone (not available in the United States), which increase prolactin levels, have been used for this purpose.[48,49] Metoclopramide's maternal adverse effects include fatigue, irritability, headache, and extrapyramidal symptoms. Domperidone has been associated with abnormal heart rhythm and sudden cardiac death in susceptible individuals; caution is advised when prescribing it with other drugs that prolong the QT interval or that inhibit its metabolism or for patients with underlying cardiac conditions.[48] Very few adverse effects in the infant have been reported.

Patient Care Process

Collect Information:

- Complete medical and obstetrical history.
- Inquire about disorders evolution and last follow-up with the treating physician.
- Conduct medication history (past/current treatments, compliance, efficacy, and safety).
- Verify immunization status.
- Assess for pregnancy signs and symptoms.
- Perform physical examination.
- Evaluate nutritional status and socioeconomic environment.
- Perform first trimester routine lab testing.
- Order serum drug levels.

Assess the Information:

- Evaluate benefits and risks for mother and fetus of continuing medications.
- Assess efficacy, safety, and patient adherence, and screen for drug interactions.
- Evaluate whether safer and more effective alternative are available.

Develop a Care Plan:

- Choose treatments with evidence of benefit and safety during pregnancy or that cannot be delayed until after delivery and/or after breast-feeding is finished (Table 48–7).
- Address patient concerns (risks of medication or of relapse if condition is untreated, prescription coverage and access to care).
- Treat pregnancy symptoms (eg, nausea) if needed.
- When possible, use nonpharmacologic treatments.

Implement the Care Plan:

- Recommend appropriate folic acid and multivitamins.
- Counsel on lifestyle (healthy diet, exercise, avoidance of tobacco, alcohol, and illicit or unnecessary drugs).
- Encourage breast-feeding. If breast-feeding, choose drugs with the best safety profile.
- Communicate information to all other health-care professionals to ensure continuity of care.

Follow-up: Monitor and Evaluate:

- Assess adherence, effectiveness, and safety of treatment at each prenatal visit.
- Review and repeat assessments as necessary.
- Monitor infants for birth defects, developmental delays, or unusual reactions, and report suspected drug-related reactions to the FDA or pharmaceutical companies.

Mastitis

Bacterial mastitis, seen typically within the first 6 weeks of breast-feeding, is characterized by localized signs of inflammation and engorgement. Fever, shivering, and malaise can occur. The most commonly encountered bacteria include *Staphylococcus aureus* (including methicillin-resistant), followed by *Streptococcus*, *Staphylococcus epidermidis*, and *Escherichia coli.*[50]

Cold or warm compresses and more frequent breast-feeding/breast pumping should be encouraged. Antibiotics (Table 48–7) and analgesics (eg, acetaminophen, NSAIDs) can be used to relieve pain.[17,50] Confirm abscess suspicion with ultrasound before surgical drainage.

Breast Candidiasis

Candidiasis (most commonly *Candida albicans*) presents with severe and persistent nipple pain, usually more intense during and immediately after breast-feeding. Breast-fed infants can be symptomatic or asymptomatic. It is recommended to breast-feed more frequently for a short period of time. Clothes and towels in contact with breasts and infant's mouth should be washed in hot water. Antifungal treatment must be given to mother and neonate simultaneously (Table 48–7). Analgesics (eg, acetaminophen, NSAIDs) can be used.[50]

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Abbreviations Introduced in This Chapter

AAP	American Academy of Pediatrics
ACEi	Angiotensin-converting enzyme inhibitors
ACOG	American College of Obstetricians and Gynecologists
anti-TPOAbs	Antithyroid peroxidase antibodies
β-hCG	Beta-human chorionic gonadotropin
CNS	Central nervous system
DM	Diabetes mellitus
GA	Gestational age
GBS	Group B *Streptococcus*
GDM	Gestational diabetes mellitus
LMP	Last menstrual period
LT_4	Levothyroxine
NSAID	Nonsteroidal anti-inflammatory drug
NTD	Neural tube defect
OTIS	Organization of Teratology Information Specialists
PCA	Postconceptional age
PPROM	Preterm Premature Rupture of Membranes
PTU	Propylthiouracil
SMBG	Self-monitoring of blood glucose
STEPS	System for Thalidomide Education and Prescribing Safety
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
T_4	Thyroxine
TSH	Thyroxine-stimulating hormone
TSHR-Sabs	Thyroid-stimulating hormone receptors-stimulating antibodies
VDRL	Venereal Disease Research Laboratory

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49 Contraception

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Discuss the physiology of the female reproductive system.
2. Compare the efficacy of oral contraceptives with that of other methods of contraception.
3. State the mechanism of action of hormonal contraceptives.
4. Discuss adverse effects, risks, and contraindications associated with the use of contraceptives and recommend strategies for minimizing or eliminating such risks.
5. Describe advantages and disadvantages of various contraceptives, including oral and nonoral formulations.
6. Cite important drug interactions that may occur with oral contraceptives.
7. Provide appropriate patient education regarding the use of oral and barrier methods of contraception.
8. Discuss how emergency contraception may be employed to prevent unintended pregnancy.

INTRODUCTION

Historically, the 1950s was an important time in the control of human fertility. It was during that decade that the first combination hormonal contraceptives (CHCs) were developed. Shortly after the discovery that the exogenous administration of hormones such as progesterone successfully blocked ovulation, the use of hormonal steroids quickly became the most popular method of contraception worldwide. CHCs are the most commonly used reversible form of contraception in the United States today, with an estimated 9.1 million women users.[1] Studies of women of childbearing age (15–49 years) in the United States estimate that 64.9% are currently using a contraceptive method.[1] Since the introduction of oral contraceptives, many additional contraceptive forms have been developed and are available for use in the United States, including transdermal systems, transvaginal systems, and intrauterine devices (IUDs). These additional forms of contraception offer women effective and potentially more convenient alternatives to oral contraceptives.

EPIDEMIOLOGY

According to the National Survey of Family Growth, approximately 6.37 million pregnancies occur annually in the United States.[2] It is estimated that nearly half of all pregnancies that occur each year in the United States are unintended, often either due to lack of or imperfect contraceptive use.[2,3] A survey of women of reproductive age in the United States between 2015 and 2017 revealed that approximately 35% were not using any form of contraception.[1] In addition, many women may use their chosen method of contraception imperfectly, which can increase the risk of unintended pregnancy. For patients with certain medical conditions, such as epilepsy, hypertension, ischemic heart disease, sickle cell disease, lupus, or thromboembolic mutations, unintended pregnancy can further increase the risk for adverse health events.[4,5] The provision of appropriate and adequate instruction to patients regarding how to use contraceptive methods effectively is essential to reduce the risk of unintended pregnancy and, for some women, the associated increase in risk for adverse health-related events.

Exposure to sexually transmitted infections (STIs) is also a concern for women who are sexually active. A 2019 STI surveillance report from the Centers for Disease Control (CDC) indicated that newly reported cases of chlamydia, gonorrhea, and syphilis are on the rise.[6] Given that not all methods of contraception protect the user against STIs, the provision of proper patient education by healthcare professionals regarding this risk is absolutely essential.

PHYSIOLOGY

The female menstrual cycle is divided into four functional phases: follicular, ovulatory, luteal, and menstrual.[4] The follicular phase begins the cycle, and ovulation generally occurs around day 14. The luteal phase then begins and continues until menstruation occurs.[4] The menstrual cycle is regulated by a negative-feedback hormone loop between the hypothalamus, anterior pituitary gland, and ovaries[4] (Figure 49–1).

Initially, the hypothalamus releases gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary to produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The levels of FSH and LH released vary depending on the phase of the menstrual cycle. Just prior to ovulation, FSH and LH both are at their peak levels. The FSH helps to promote growth of the follicle in preparation for ovulation by causing granulosa cells lining the follicle to grow and produce estrogen. LH promotes androgen production by theca cells in the follicle, promotes ovulation and oocyte maturation, and converts granulosa cells to cells that secrete progesterone after ovulation.

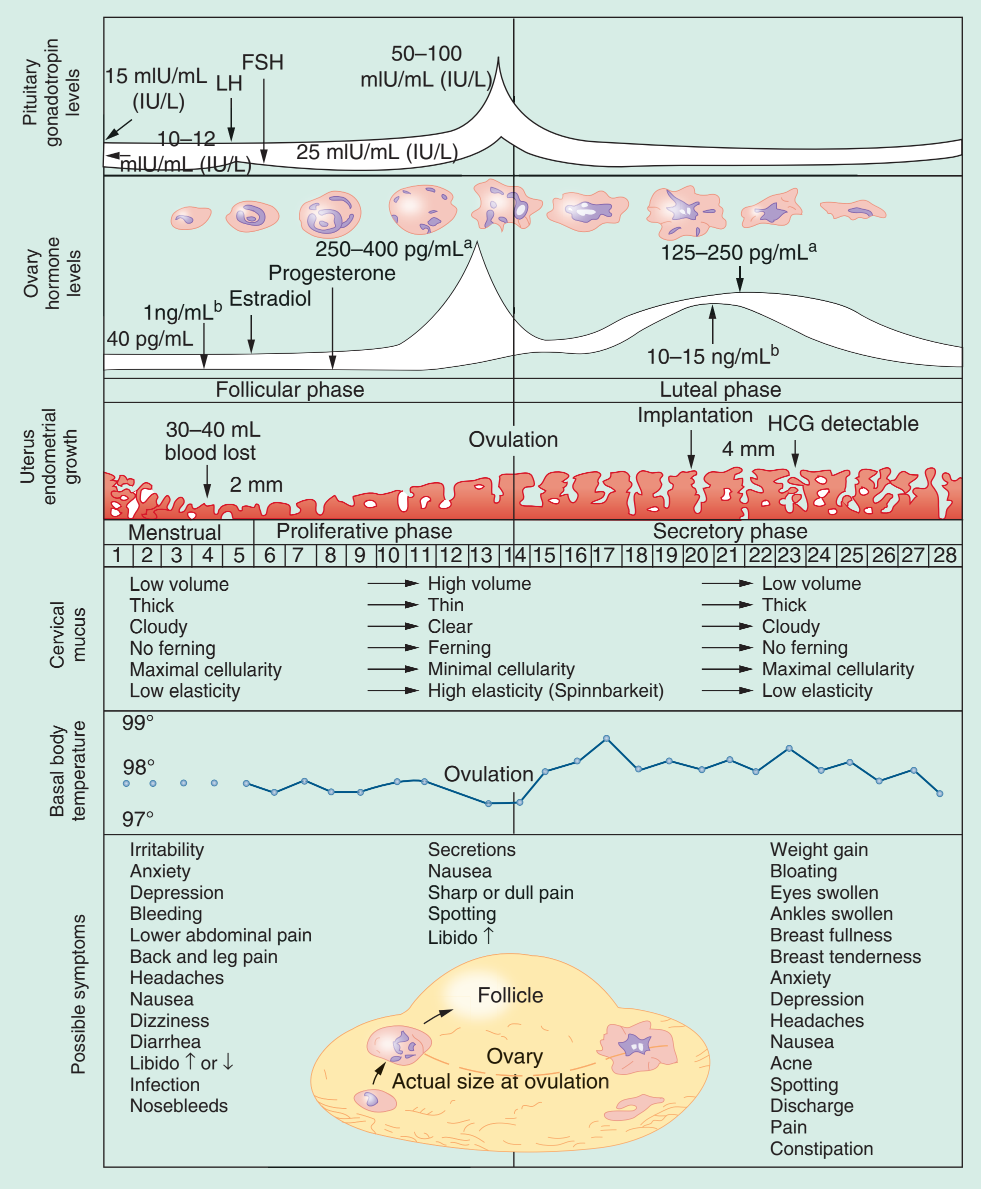
Pituitary gonadotropin levels
15 mIU/mL (IU/L)
LH
FSH
50–100 mIU/mL (IU/L)
10–12 mIU/mL (IU/L)
25 mIU/mL (IU/L)
Ovary hormone levels
250–400 pg/mL[a]
Progesterone
Estradiol
1ng/mL[b]
40 pg/mL
125–250 pg/mL[a]
10–15 ng/mL[b]
Follicular phase
Luteal phase
Uterus endometrial growth
30–40 mL blood lost
2 mm
Ovulation
Implantation
HCG detectable
4 mm
Menstrual
Proliferative phase
Secretory phase
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
Cervical mucus
Low volume → High volume → Low volume
Thick → Thin → Thick
Cloudy → Clear → Cloudy
No ferning → Ferning → No ferning
Maximal cellularity → Minimal cellularity → Maximal cellularity
Low elasticity → High elasticity (Spinnbarkeit) → Low elasticity
Basal body temperature
99°
98°
97°
Ovulation
Possible symptoms
Irritability
Anxiety
Depression
Bleeding
Lower abdominal pain
Back and leg pain
Headaches
Nausea
Dizziness
Diarrhea
Libido ↑ or ↓
Infection
Nosebleeds
Secretions
Nausea
Sharp or dull pain
Spotting
Libido ↑
Follicle
Ovary
Actual size at ovulation
Weight gain
Bloating
Eyes swollen
Ankles swollen
Breast fullness
Breast tenderness
Anxiety
Depression
Headaches
Nausea
Acne
Spotting
Discharge
Pain
Constipation

FIGURE 49–1. Menstrual cycle events. [a]Estradiol: 40 pg/mL = 147 pmol/L; 250 to 400 pg/mL = 918 to 1468 pmol/L; 125 to 250 pg/mL = 459 to 918 pmol/L. [b]Progesterone: 1 ng/mL = 3.18 nmol/L; 10 to 15 ng/mL = 32 to 48 nmol/L. (FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HCG, human chorionic gonadotropin LH, leutinizing hormone.) (Adapted with permission from Nelson AL, Shulman L. Menstrual cycle: normal patterns, menstrual disorders, and menstrually related problems. In: Hatcher RA, Nelson AL, Trussel J, et al. Contraceptive Technology, 21st ed. New York, NY: Ayer Company Publishers, Inc.; 2018:1–61.)

Conception is most likely to occur when viable sperm are present in the upper region of the reproductive tract at the time of ovulation. Fertilization occurs when a spermatozoan penetrates an ovum. Approximately 6 to 8 days after ovulation, attachment of the early embryo to the lining of the uterine cavity—implantation—occurs.

CLINICAL PRESENTATION AND DIAGNOSIS

Goals of Contraception/Desired Outcome

The most common goal of contraception is the prevention of pregnancy. However, some patients use contraceptive methods for other benefits, such as menstrual cycle regulation, reduction of premenstrual symptoms, or treatment of acne.

Choice of Contraceptives: Important Considerations

When helping a patient with contraceptive selection, the most important goal is selecting a safe, effective, and patient-centered option. It is imperative to explain the side effects, safety concerns, and noncontraceptive benefits of each alternative to the patient so that she may make an informed decision. Fertility goals vary for each patient. It must be determined whether the goal is to postpone conception, space out the next pregnancy, or avoid further pregnancy altogether. Also, a clinician must understand the patient's desire to have or not have a regular bleeding pattern, because many contraceptives will affect menses.

As discussed later in this chapter, contraindications exist for various forms of contraception. Patients may be evaluated by a healthcare professional to rule out medical contraindications to certain contraceptives, although a physical examination is not required and pharmacists can prescribe contraceptives in some states. Clinicians also should review family history for potential risks with certain forms of birth control.

Sexual behavior of the female must be determined to understand the risk for STIs. Women not in a monogamous relationship must consider their risk of STIs as a factor in their contraceptive decision. Some barrier methods protect against STIs, but hormonal contraceptives do not prevent STIs if used alone.

Personal preference plays a large role when determining the best contraceptive option. For instance, if a woman is not interested in using a method that interrupts sexual activity, then a diaphragm would be an inappropriate choice. Preference of the sexual partner may also be important. Certain agents such as male condoms require the male partner to play an active role in contraception. Patients must also consider their religious beliefs and cultural practices as some forms of birth control may violate certain religious rules or cultural beliefs.

Cost may also be an issue for patients. Insurance may not cover all forms of contraception, and patients may have to bear the entire cost for certain options.

Efficacy of Contraceptives

Table 49–1 shows the percentage of women who experience unintended pregnancy within 1 year of contraceptive use with ongoing sexual activity.[4]

TREATMENT

Oral Contraceptives (Combination)

CHCs contain a synthetic estrogen (either ethinyl estradiol [EE], which is pharmacologically active, or estradiol valerate, which is metabolized to estradiol and valeric acid) and one of several steroids with progestational activity. Progestins found in various oral contraceptives can include norethindrone, norethindrone acetate, ethynodiol diacetate, norgestrel, levonorgestrel, desogestrel, norgestimate, drospirenone, or dienogest.

The primary mechanism by which CHCs prevent pregnancy is through inhibition of ovulation. FSH and LH regulate the production of estrogen and progesterone by the ovaries. Secretion of estrogen and progesterone by the ovaries occurs in a cyclic manner, which determines the regular hormonal changes that occur in the uterus, vagina, and cervix associated with the menstrual cycle. Cyclic changes in the levels of estrogen and progesterone in the blood, together with FSH and LH, modulate the development of ova and the occurrence of ovulation. The estrogen component of CHCs is most active in inhibiting FSH release.[4] However, at sufficiently high doses, estrogens also may cause inhibition of LH release. In low-dose CHCs (≤ 35 mcg EE), the progestin component causes suppression of LH.[4] Ovulation is prevented by this suppression of the midcycle surge of both FSH and LH and mimics the physiologic changes that occur during pregnancy.

Although suppression of FSH and LH is the primary mechanism by which CHCs prevent ovulation, there are other mechanisms by which these hormones work to prevent pregnancy. Other mechanisms include reduced penetration of the egg by sperm, reduced implantation of fertilized eggs, thickening of cervical mucus to prevent sperm penetration into the upper genital tract, and slowed tubal motility, which may delay transport of sperm.[4]

Table 49–1

Unintended Pregnancy Rates: Percentage of Women Experiencing Unintended Pregnancy Within First Year of Use[4,7]

Method	Typical Use[a]	Perfect Use[b]
No method	85	85
Spermicide alone	21	16
Withdrawal	20	4
Fertility awareness–based methods	24	
Standard days method	12	5
Two-day method	14	4
Ovulation method	23	3
Symptothermal method	2	0.4
Sponge		
Parous women	27	20
Nulliparous women	14	9
Diaphragm with spermicide	17	16
Cervical cap	16–32	9–26
Condom with spermicide		
Female	21	5
Male	13	2
Combination pill and progestin-only pill	7	0.3
Transdermal patch	7	0.3
Vaginal ring	7	0.3
Depo-Provera	6	0.2
IUD		
ParaGard	0.8	0.6
Kyleena	0.2	0.2
Mirena	0.1	0.1
Liletta	0.1	0.1
Skyla	0.4	0.3
Implanon	0.05	0.05
Female sterilization	0.5	0.5
Male sterilization	0.15	0.1

[a] Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

[b] Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

IUD, intrauterine device.

Thus, in addition to inhibiting ovulation, CHCs induce changes in the cervical mucus and endometrium that make sperm transport and implantation of the embryo unlikely.[4]

Table 49–2 contains a partial listing of the many oral contraceptives available in the United States.[7] Since the mid-1960s, EE has been the primary estrogen used in most CHCs. However, the amount of EE used in CHCs has been reduced since that time, with most products now containing 35 mcg or less of EE. In addition, to reduce side effects and improve tolerability associated with oral contraceptive use, newer progestins and different routes of administration have been explored. In an attempt to minimize the undesirable androgenic side effects associated with the progestins of CHCs, the original synthetic progestins were modified to create "third generation" progestins (eg, desogestrel and norgestimate), and "fourth generation" progestins with antiandrogenic properties (eg, drospirenone).

Table 49–2

Selected Available Oral Contraceptives[7]

Estrogen (mcg/tablet)	Progestin (mg/tablet)	Examples of Brand Names
Monophasic Preparations		
EE (20)	Norethindrone acetate (1)	Blisovi Fe 1/20, Blisovi 24 Fe, Junel 1/20, Junel Fe 1/20, Junel Fe 24, Larin 1/20, Larin Fe 1/20, Larin 24 Fe, Loestrin 21 1/20, Loestrin Fe 1/20, Lomedia 24 Fe, Mibelas 24 Fe, Microgestin 1/20, Microgestin Fe 1/20, Minastrin 24 Fe, Tarina Fe 1/20, Taytulla
EE (20)	Levonorgestrel (0.09)	Amethyst
EE (20)	Levonorgestrel (0.1)	Aviane, Balcoltra[a], Falmina, Lessina, Lutera, Orsythia, Sronyx, Vienva
EE (20)	Drospirenone (3)	Beyaz[a], Gianvi, Loryna, Nikki, Vestura, Yaz
EE (20)	Desogestrel (0.15)	Azurette
EE (25)	Norethindrone (0.8)	Generess Fe, Kaitlib Fe
EE (30)	Desogestrel (0.15)	Apri, Desogen, Emoquette, Enskyce, Reclipsen
EE (30)	Levonorgestrel (0.15)	Altavera, Kurvelo, Levora, Marlissa, Portia
EE (30)	Drospirenone (3)	Ocella, Safyral[a], Syeda, Tydemy[a], Yasmin, Zarah
EE (30)	Norgestrel (0.3)	Cryselle, Elinest, Lo/Ovral-28, Low-Ogestrel
EE (30)	Norethindrone acetate (1.5)	Blisovi Fe 1.5/30, Junel 1.5/30, Junel Fe 1.5/30, Larin 1.5/30, Larin Fe 1.5/30, Loestrin 21 1.5/30, Loestrin Fe 1.5/30, Microgestin 1.5/30, Microgestin Fe 1.5/30
EE (35)	Norgestimate (0.25)	Estarylla, Femynor, Mili, Mono-Linyah, MonoNessa, Previfem, Sprintec
EE (35)	Norethindrone (0.4)	Balziva, Briellyn, Femcon Fe, Gildagia, Ovcon 35, Philith, Vyfemla, Wymza Fe, Zenchent, Zenchent Fe, Zeosa
EE (35)	Norethindrone (0.5)	Modicon, Nortrel 0.5/35, Wera
EE (35)	Norethindrone (1)	Alyacen 1/35, Cyclafem 1/35, Dasetta 1/35, Norinyl 1/35, Nortrel 1/35, Pirmella 1/35
EE (35)	Ethynodiol diacetate (1)	Kelnor 1/35, Zovia 1/35E
EE (50)	Norgestrel (0.5)	Ogestrel
EE (50)	Ethynodiol diacetate (1)	Zovia 1/50E
Biphasic Preparations		
EE (10)	Norethindrone acetate (1,0)	Lo Loestrin Fe[b]
EE (20,0,10)	Desogestrel (0.15,0,0)	Azurette[b], Bekyree[b], Kariva[b], Kimidess[b], Pimtrea[b], Viorele[b]
Triphasic Preparations		
EE (20,30,35)	Northindrone acetate (1)	Estrostep Fe, Tilia Fe, Tri-Legest Fe
EE (30,40,30)	Levonorgestrel (0.05,0.075,0.125)	Enpresse, Levonest, Myzilra, Trivora
EE (35)	Norgestimate (0.18,0.215,0.25)	Tri-Estarylla, Tri Femynor, Tri-Mili, Tri-Linyah, Tri-Nessa, Tri-Previfem, Tri-Sprintec
EE (35)	Norethindrone (0.5,1,0.5)	Aranelle, Leena, Tri-Norinyl
EE (35)	Norethindrone (0.5,0.75,1)	Alyacen 7/7/7, Cyclafem 7/7/7, Dasetta 7/7/7, Nortrel 7/7/7, Pirmella 7/7/7
EE (25)	Norgestimate (0.18,0.215,0.25)	Tri-Lo-Estarylla, Tri-Lo-Marzia, Tri-Lo-Sprintec
EE (25)	Desogestrel (0.1,0.125,0.15)	Caziant, Cyclessa, Velivet
Quadriphasic Preparations		
Estradiol valerate (3,2,2,1)	Dienogest (0,2,3,0)	Natazia
Extended Cycle Preparations		
EE (20)	Levonorgestrel (0.1)	Amethia Lo, Camrese Lo
EE (30)	Levonorgestrel (0.15)	Introvale, Jolessa, Quasense, Seasonale, Setlakin
EE (20,25,30,10)	Levonorgestrel (0.15,0)	Fayosim, Rivelsa, Quartette
EE (20,10)	Levonorgestrel (0.1)	LoSeasonique
EE (30,10)	Levonorgestrel (0.15)	Amethia, Ashlyna, Camrese, Daysee, Seasonique
Progestin-Only Preparations		
None	Norethindrone (0.35)	Camila, Errin, Deblitane, Heather, Jencycla, Jolivette, Nora-BE
None	Drospirenone (4,0)	Slynd

[a] Each tablet also contains 451 mcg of levomefolate calcium.

[b] Some references may classify as monophasic since the variation in hormone content does not occur during the first 3 weeks of the pill pack.

EE, ethinyl estradiol

CHCs are available in monophasic, biphasic, triphasic, and quadriphasic preparations. Monophasic preparations contain fixed doses of estrogen and progestin in each active pill. Although all four preparations contain both estrogens and progestins, biphasic, triphasic, and quadriphasic preparations contain varying proportions of one or both hormones during the pill cycle. These preparations were introduced to reduce a patient's cumulative exposure to progestins, as well as to mimic more closely the hormonal changes of the menstrual cycle. However, there is no evidence to suggest that the multiphasic preparations offer significant clinical advantage over monophasic pills.[7]

Most traditional CHCs are packaged as 21/7 cycles (ie, 21 days of active pills and 7 days of placebo). However, newer regimens offer either fewer hormone-free days per traditional, 28-day pill cycle, or extended (or in some cases continuous) cycles (84- or 365-day pill cycle), which may allow for fewer withdrawal bleeds per year and fewer menstrual-related side effects (eg, menstrual pain, bloating, headaches) for some women.

▶ Noncontraceptive Benefits of Combination Hormonal Contraceptives

In addition to preventing pregnancy, there are several noncontraceptive benefits associated with the use of CHCs.

Reduction in the Risk of Endometrial Cancer The risk of endometrial cancer among women who have used oral contraceptives for at least 1 and 10 years is approximately 40% and 80% less than the risk in women who have never used oral contraceptives, respectively.[4,8] There is additional evidence to suggest that this reduced risk may persist for up to 20 years following discontinuation of oral contraceptives.[4,8]

Reduction in the Risk of Ovarian Cancer When compared with women who have never used oral contraceptives, women who have used oral contraceptives for at least 1 year are less likely to develop ovarian cancer than those who have never used oral contraceptives. While there is evidence to suggest the reduced risk of ovarian cancer may persist for years following discontinuation of oral contraceptives,[9] a recent study suggested possible attenuation of the protective effect of CHCs against ovarian cancer with use after 35 years of age.[10]

Improved Regulation of Menstruation and Reduction in the Risk of Anemia Women who take oral contraceptives typically experience more regular menstrual cycles. In general, oral contraceptive use is associated with less cramping and dysmenorrhea.[4,7] Also, women who take oral contraceptives experience less blood loss with each menstrual period.[4,11] Some studies suggest that oral contraceptive use decreases overall monthly menstrual flow by 60% or more and conserves hemoglobin and ferritin levels, which may be particularly beneficial in women who are anemic or at risk for anemia.[4] In addition, some CHC formulations contain iron, which may also minimize the risk for anemia. (See **Unique Oral Contraceptives** section.) For more information on menstruation-related disorders, see Chapter 50.

Reduction in the Risk of Fetal Neural Tube Defects While CHCs are not 100% effective at preventing pregnancy, it is possible that a woman may conceive while taking a CHC. In addition, many women may become pregnant very soon after discontinuing a CHC. To decrease the risk of neural tube defects in the fetuses associated with such pregnancies, a CHC formulation that contain a source of folate in every pill is also available.[4]

Relief from Symptoms Associated with Premenstrual Dysphoric Disorder CHCs have been widely used for the treatment of premenstrual dysphoric disorder (PMDD). Current evidence suggests that these agents are most effective at targeting the physical symptoms associated with the disorder and less effective in treating mood-related symptoms.[12] Although multiphasic CHCs have been used effectively in the treatment of PMDD, monophasic preparations may yield fewer mood swings and may be easier to manage. Several drospirenone-containing CHCs now carry a US Food and Drug Administration (FDA)-approved indication for PMDD, including Yaz, Beyaz, Gianvi, Loryna, Nikki, and Vestura.[7]

Prevention of Benign Breast Disease Women who use oral contraceptives are less likely to develop benign breast cysts or fibroadenomas and experience progression of such conditions.[4,7,13]

Prevention of Ovarian Cysts Because oral contraceptives suppress ovarian stimulation, women who take them are less likely to develop ovarian cysts.[7]

Decrease in Symptoms Related to Endometriosis CHC use has been linked to a decreased incidence of symptomatic endometriosis.[13] In women who suffer from endometriosis, the extended-cycle CHCs may provide the most effective relief from menstrual pain by reducing the total number of painful episodes per year.[4]

Improvement in Acne Control All CHCs can improve acne by increasing the quantity of sex hormone–binding globulin and thereby decreasing free testosterone concentrations.[14] Third-generation progestins, such as desogestrel and norgestimate, are believed to have less androgenic activity compared with older progestins, and drospirenone and dienogest are considered to be antiandrogenic.[14] However, it is not clear that CHCs containing any of these progestins confer any advantage over other CHCs with respect to their ability to improve acne control. Tri Femynor, Tri-Linyah, Tri-Mili, TriNessa, Tri-Previfem, and Tri-Sprintec (EE and norgestimate); Estrostep Fe, Tilia Fe, and Tri-Legest Fe (EE and norethindrone acetate); Yaz, Beyaz, Nikki, Loryna, and Gianvi (EE and drospirenone) each carry an FDA-approved indication for the treatment of acne.[4,7]

▶ Potential Risks of Combination Hormonal Contraceptives

Although there are many noncontraceptive benefits associated with the use of CHCs, their use is not without risk or potential for adverse effects.

Sexually Transmitted Infections Because the use of CHCs may decrease the use of selected barrier contraceptive methods (eg, latex condoms) that do protect against STIs, one of the most common potential risks associated with the use of oral contraceptives is the increased risk of acquiring an STI.[5] However, studies have failed to show an increased risk of HIV transmission, and there is no restriction on the contraceptive method per CDC.

Cardiovascular Events and Hypertension A World Health Organization (WHO) collaborative study found that high-dose (50 mcg or more of EE) oral contraceptive users with uncontrolled hypertension have an increased risk of experiencing a myocardial infarction or stroke.[15] Women who had the lowest risk for experiencing a myocardial infarction or stroke were those who did not smoke, took low-dose (containing ≤ 35 mcg of EE) oral contraceptives, and had their blood pressure checked prior to beginning oral contraceptives. Hypertension secondary to oral contraceptive use is thought to occur in up to 3% of women and believed to be attributed to the effect of estrogens and progestins on aldosterone activity.[4] Given this and the risk for cardiovascular events, women should have their blood pressure checked prior to initiating oral contraceptives, as well as periodically throughout oral contraceptive use. If blood pressure is ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic, the risks outweigh advantages and there should be consideration to discontinue CHCs; if blood pressure is ≥ 160 mm Hg systolic or ≥ 100 mm Hg, then CHC use is not recommended.[5] Estrogen-containing contraceptives are not recommended for smokers who are 35 years of age or older or for women who experience migraine headaches with aura.[5]

Venous Thromboembolism It is believed that the estrogen component of CHCs stimulates enhanced hepatic production of clotting factors. CHCs have been associated with a two- to three-fold increase in the risk of venous thromboembolism compared with women who do not use oral contraceptives.[7] Contraceptive users at greatest risk for the development of VTE include those who are ≥ 40 years of age, obese, smoke, or have an inherited thrombophilia or a history of prior thromboembolism. It is important to note, however, that the increase in risk of VTE in oral contraceptive users is lower than that associated with pregnancy and the postpartum period.[7,16] Less androgenic progestins, such as desogestrel and drospirenone, have been reported to be associated with a higher risk of VTE.[17,18] Studies validating this risk have produced conflicting results. Two studies published in 2011 reported a two- to threefold greater risk of venous thromboembolic events in women using oral contraceptives containing drospirenone when compared with women using levonorgestrel-containing contraceptives.[19,20] A more recent 2015 case-control study of > 10,000 women with VTE also found that exposure to drospirenone and desogestrel was associated with a higher risk of VTE compared to exposure to levonorgestrel.[21] Conversely, the results of the International Active Surveillance Study of Women Taking Oral Contraceptives, published in 2014, demonstrated similar rates of venous and arterial thromboembolism in women taking CHCs containing drosperinone, levonorgesterol, or other progestins.[22] Most recently, a systematic review and meta-analysis of the association of CHCs on the risk of VTE demonstrated that compared to levonorgestrel-containing CHCs, all others showed a significant increase in risk.[23] In general, progestin-only contraceptives are preferred for women who are at increased risk of cardiovascular or thromboembolic complications, including women with a prior history of thromboembolic disease.[5,7]

Gallbladder Disease In women with preexisting gallstones, low-dose estrogen-containing oral contraceptives may enhance the potential for the development of symptomatic gallbladder disease and may worsen existing gallbladder disease.[4,5] Although this risk has not been demonstrated with the use of higher-dose oral contraceptives, CHCs containing estrogen should be used with caution in patients with a history of gallbladder disease or current gallbladder disease, especially if known cause is related to CHCs.

Hepatic Tumors Although the use of oral contraceptives is not associated with an increased risk for the development of hepatocellular carcinoma, long-term use of high-dose oral contraceptives has been associated with the development of benign liver tumors.[3] Because even benign liver tumors may pose significant risk to the patient, oral contraceptives should be discontinued if liver enlargement is noted on physical examination. In cases of either benign hepatocellular adenoma or hepatoma (malignancy), the use of CHCs is contraindicated.[5]

Cervical Cancer There appears to be an increased risk for the development of cervical cancer among long-term users of oral contraceptives, particularly among women who test positive for human papilloma virus (HPV), a known risk factor for cervical cancer.[4] It is uncertain whether this increase in risk is directly attributed to the use of oral contraceptives. Oral contraceptive users may use condoms less frequently, and as a result, this may increase their susceptibility to infection with HPV.

Breast Cancer Studies demonstrating a link between CHCs and breast cancer have generally produced conflicting results. A recent study suggested a small potential increase in risk for breast cancer development in both current and recent users of CHCs compared to women who had never used CHCs. In that study, an increased risk for breast cancer development was also associated with longer duration of CHC use as well as with CHC use before age 20 or before the first full-term pregnancy.[24] A recent retrospective cohort study evaluating the impact of family history on breast cancer risk in CHC users showed that in women with a family history who were considered to be a high or intermediate risk for breast cancer, CHC use did not increase the risk for breast cancer.[25]

KEY CONCEPT Medical eligibility criteria for contraceptive use (MEC) were first developed in 1996 and provide the clinician with guidance from the WHO on the safety of using various contraceptives in patients with select concomitant medical conditions or specific characteristics.[5] Clinicians can utilize the MEC to identify absolute and relative contraindications to the use of oral contraceptives.

Absolute and relative contraindications are listed in Table 49–3.[4,5]

Table 49–3

Conditions with Unacceptable Health Risk or with Theoretical or Proven Risks That Usually Outweigh the Advantages of CHC Use[3,4,5]

Conditions that represent an unacceptable health risk with CHC use

History of thromboembolic disease
History of stroke (or current cerebrovascular disease)
History of (or current) coronary artery disease, ischemic heart disease, or peripheral vascular disease
History of carcinoma of the breast (known or suspected)
History of any estrogen-dependent neoplasm (known or suspected)
Undiagnosed abnormal uterine or vaginal bleeding
Pregnancy (known or suspected)
Breastfeeding < 21 days postpartum
Heavy smoking (defined as 15 cigarettes or more per day) by women who are 35 years of age or older
History of hepatic tumors (benign or malignant)
Active liver disease
Migraine headaches with focal neurologic symptoms (aura)
Postpartum (during the first 21 days in women with additional risk factors for thromboembolism, including age ≥ 35 years, history of previous venous thromboembolism, preeclampsia, recent cesarean delivery, obesity, and smoking)

Conditions for which the theoretical or proven risks usually outweigh the advantages of CHC use

Smoking (< 15 cigarettes per day) at any age
Migraine headache disorder without focal neurologic symptoms
Hypertension (NOTE: WHO considers health risk posed by CHC use to be "unacceptable" when either systolic blood pressure is 160 mm Hg or more, or diastolic blood pressure is 90 mm Hg or more)
Fibroid tumors of the uterus
Breastfeeding > 21 days postpartum (with other risk factors for VTE such as > 35 years, previous VTE, transfusion at delivery, peripartum cardiomyopathy, obesity, postpartum hemorrhage, postcesarean delivery, preeclampsia, or smoking)
Superficial venous thrombosis (acute or history)
Multiple sclerosis with prolonged immobility
Diabetes mellitus
Family history of dyslipidemia
Sickle cell disease
Active gallbladder disease
Age > 50 years
Elective major surgery requiring immobilization (planned in the next 4 weeks)
Postpartum (during days 21 through 42 in women with additional risk factors for thromboembolism, including age ≥ 35 years, history of previous venous thromboembolism, preeclampsia, recent cesarean delivery, obesity, and smoking)

CHC, combination hormonal contraceptive; VTE, venous thromboembolism; WHO, World Health Organization

Adverse Effects of Oral Contraceptives and Their Management As with all medications, there are potential adverse effects with CHCs. KEY CONCEPT Many side effects can be minimized or avoided by adjusting the estrogen and/or progestin content of the oral contraceptive. It is also important to individualize the selection of oral contraceptives, because some women are at increased risk for potentially serious side effects.[26]

Common complaints with CHCs include headaches, nausea, vomiting, mastalgia, and weight gain, although a similar percentage of patients taking placebo also experience these side effects.[27] Given that oral contraceptives often are discontinued owing to side effects, proper counseling before initiation of CHCs is necessary.

Between 30% and 50% of women experience breakthrough bleeding or spotting when oral contraceptives are initiated. All side effects tend to resolve by the third or fourth cycle.[4] Before changing formulations, other more serious causes of bleeding or spotting, such as pregnancy, infection, and poor absorption of the oral contraceptive owing to drug interaction or gastrointestinal problems, should be ruled out. Once these causes have been ruled out, the timing of the spotting must be determined to adjust the formulation appropriately.

The most common side effects and ways to adjust therapy to minimize these side effects are listed in Table 49–4.[4,7,26]

As highlighted in Table 49–4, many of the side effects of CHCs may be minimized by adjusting the estrogen or progestin content of the preparation.

Table 49–4

Management of Adverse Effects of Oral Contraceptives[4,7,26]

Adverse Effect	Cause	Adjustment	Notes
Spotting/bleeding before finishing active pills	Insufficient progestin	Monophasic with increased progestin or triphasic with increasing progestin	
Continued bleeding after menses	Insufficient estrogen	Increase estrogen or triphasic with lower early progestin	
Midcycle bleeding	Difficult to determine	Increase estrogen and progestin	
Increased breakthrough bleeding in general	Insufficient estrogen	Increase estrogen or triphasic formulation	Will increase amount of withdrawal bleeding during menses
Acne, PMDD, hirsutism	Progestin with higher androgenicity (eg, norgestrel, levonorgestrel)	Switch to progestin with lower androgenicity such as norgestimate, norethindrone, or drospirenone	
Nausea, vomiting	Related to estrogen	Take at bedtime or with food; decrease estrogen or switch to a progestin-only product	Symptoms often resolve in 1–3 months
Constipation, bloating, distention	Related to progestin	Decrease progestin	Symptoms often resolve in 1–3 months
Headache	Must be evaluated because of warning sign for stroke – monitor blood pressure	If determined to not be serious, but still troublesome consider: a. Discontinue oral contraceptive b. Decrease estrogen c. Decrease progestin d. Eliminate pill-free interval for 2–3 cycles (when headaches occur during pill-free interval)	Discontinue oral contraceptive immediately if any neurologic symptoms or blurred vision
Decrease in libido, decreased vaginal lubrication	Insufficient estrogen	Increase estrogen or consider vaginal hormonal ring (NuvaRing)	Feelings of depression may coincide
Dyslipidemia in general	Progestin with higher androgenicity (eg, norgestrel, levonorgestrel)	Switch to progestin with lower androgenicity such as norgestimate, norethindrone, or drospirenone	Obtain a baseline lipid panel in women with risk factors for dyslipidemia—smoking, hypertension, family history of heart disease
Triglycerides > 350 mg/dL (3.96 mmol/L)	Related to estrogen	Decrease estrogen to 20–25 mcg or a progestin-only formulation[3]	
Mastalgia	Related to estrogen	Decrease estrogen or switch to an extended cycle formulation (see Unique Oral Contraceptives, later) if it occurs prior to menses	
Weight gain, fluid retention	Excess estrogen and progestin with higher androgenicity (eg, norgestrel, levonorgestrel)	Decrease estrogen and switch to progestin with lower androgenicity such as norgestimate, norethindrone or drospirenone	
Visual changes or disturbances with contact lenses	Related to estrogen	Use saline eye drops	Referral to ophthalmology if eye drops do not help
Melasma, chloasma	Related to estrogen stimulation of melanocyte production	Consider progestin-only product and use of sunscreen	Women with darker pigmentation are more susceptible; melasma may not be completely reversible on discontinuation

Patient Encounter Part 1

A 21-year-old nulliparous woman presents to your clinic requesting information on contraception. She specifically inquires about options that allow for fewer or no menstrual periods. You begin to take a history and determine that the patient is currently sexually active and not using any method of birth control. She weighs 125 lb (56.7 kg), is 67 in. (170 cm) tall, and has a blood pressure of 108/70 mm Hg. She has no history of smoking. She has a history of migraines without aura and anxiety. Her only medication is propranolol. On further questioning, you discover that she has a positive family history of breast cancer (her mother) and ovarian cancer (maternal grandmother), but no personal history. As you discuss various contraceptive options with the patient, it is clear that she has a preference for an oral contraceptive agent.

What additional information do you need to know before recommending a contraceptive for this patient?

Based on the information provided by the patient, what oral contraceptive agent would you recommend for the patient and why?

What education would you provide to this patient regarding risks associated with oral contraceptive use?

Progestin-Only Pills

For women unable to take estrogen-containing oral contraceptives, there are alternatives: oral contraceptives containing only a progestin, either norethindrone (Camilla, Errin, Heather, Jencycla, Jolivette, or Nora-BE) or drospirenone (Slynd). These agents are slightly less effective than CHCs but have other advantages over CHCs. Norethindrone-only products have generally not shown the same thromboembolic risk as estrogen-containing products. Therefore, women at increased risk for or with a history of thromboembolism may be candidates for norethindrone-only oral contraceptives. While CHCs containing drospirenone and EE have been linked to an increased risk for VTE, whether drospirenone-only oral contraceptives also increase this risk is not yet known.[28] In general, these products can minimize menses, and many women have amenorrhea after six to nine cycles. Drospirenone is antiandrogenic, so it may help improve acne in some women. Progestin-only products have been found safe to use in women who are nursing, so they are a viable option for women who breastfeed and desire hormonal contraception. In such patients, it should not be initiated until 42 days postpartum. Spotting or irregular bleeding may occur in some women, and this is a common cause for discontinuation. These products should be started on the first day of menses and taken at the same time every day to minimize risk for pregnancy. There is no pill-free or hormone-free period.

Unique Oral Contraceptives

Along with varying doses of estrogen and different progestins, formulation modifications among select CHC products may yield certain benefits in some patient situations.

Lo-Loestrin Fe (norethindrone/EE) is a biphasic product that contains a low-dose estrogen, a high amount of progestin, and medium androgenic activity. Similar to other low-dose estrogen CHCs, Lo-Loestrin Fe may offer a smaller margin of error when pills are missed but provide the potential advantage of fewer estrogen-related side effects (eg, nausea and breast tenderness). Unlike the typical 28-pill packs that contain 21 active tablets and seven placebo tablets, Lo-Loestrin Fe contains 24 combination hormone tablets, two estrogen-only tablets, and two placebo (iron-only) tablets. This product provides a shorter hormone-free interval and may allow for shorter menstrual periods and fewer menstrual-related symptoms, such as menstrual-related headaches, menorrhagia, and anemia.

There are several monophasic combinations that are packaged as a 91-day treatment cycles with 84 active tablets that are taken consecutively followed by seven placebo tablets. These include Amethia Lo, Camrese Lo, Introvale, Jolessa, Quasense, Seasonale, and Setlakin (levonorgestrel/EE). The extended cycle length of these products allows for one menstrual cycle per "season," or four per year. This type of formulation may be appealing to women with perimenstrual side effects or those at higher risk for anemia with menstrual bleeding. These products may improve anxiety, headache, fluid retention, dysmenorrhea, breast tenderness, bloating, and menstrual migraines. The risk of intermenstrual bleeding and/or spotting may be higher for patients taking these extended-cycle combinations than for patients taking typical 28-day-regimen CHCs.[4]

Amethia, Ashlynna, Camrese, Daysee, Seasonique, and LoSeasonique (levonorgestrel/EE) are also extended cycle preparations that are similar to those mentioned earlier, but instead these preparations contain seven tablets with low-dose estrogen rather than placebo. Menstruation-related problems that may improve with these extended-cycle preparations include menstrual-related headaches, menorrhagia, and anemia. In addition, endometriosis-related menstrual pain may be relieved by providing a continuous regimen without a pill-free interval.[29]

Yasmin and Yaz (drospirenone/EE) are examples of unique CHCs that contain the progestin drospirenone, which has antiandrogenic properties, but also showed antimineralocorticoid activity such as diuresis and hyperkalemia. Slynd (drospirenone) is the first approved progestin-only contraceptive containing drospirenone. Drospirenone has a unique application in young women who experience problems associated with producing too much androgen. Drospirenone is a spironolactone analog, and the 3-mg dose available in CHC preparations has antimineralocorticoid activity equal to 25 mg of spironolactone. Drospirenone can affect the sodium and water balance in the body, although it has not shown superior efficacy for side effects such as bloating compared with other oral contraceptives. Caution should be used in women with chronic conditions or in women taking other medications that may affect serum potassium. Yaz contains 24 active tablets and four placebo tablets, allowing for shorter menstrual periods and fewer menstrual-related symptoms, such as menstrual-related headaches, menorrhagia, and anemia.

In 2003, the FDA Advisory Committee for Reproductive Health Drugs recommended the development of a CHC tablet containing folic acid to minimize the risk of neural tube defects in cases of contraceptive failure. Beyaz, Safyral, and Tydemy are each combination tablets containing drospirenone and EE and 451 mcg of levomefolate calcium, the primary metabolite of folic acid. Beyaz has a shorter hormone-free pill interval, which may allow for shorter menstrual periods and fewer menstrual-related symptoms.

In addition to the prevention of pregnancy, Yaz, Beyaz, Safyral, Nikki, Loryna, and Gianvi; Tri-Femynor, Tri-Linyah, Tri-Mili, Tri-Previfem, and Tri-Sprintec (norgestimate/EE); and Estrostep Fe, Tilia Fe, and Tri-Legest Fe (norethindrone acetate/EE) each carry an FDA-approved indication for treatment of moderate acne vulgaris in females 15 years of age or older desiring contraception who have not responded adequately to conventional antiacne medication. This can help clinicians to streamline medications by serving dual purposes.

Bekyree, Kariva, Kimidess, Pimtrea, and Viorele (desogestrel/EE) have a unique dosing schedule. After the usual 21 active tablets, there are only two tablets with inert ingredients. The last five tablets in the package have 10 mcg of EE. In theory, this may minimize bleeding during the menstrual cycle, although the clinical significance of this dosing schedule has not been established. With each of these products, it is important to counsel patients to complete the entire pack and not to discard the last 7 days of medication.

Another unique formulation is a chewable tablet available to women who have difficulty swallowing medications. Femcon Fe (norethindrone/EE) has all 28 tablets in chewable form and has added spearmint flavoring.

Natazia is a quadriphasic CHC containing estradiol valerate and the progestin, dienogest. Estradiol valerate is metabolized endogenously to estradiol, and dienogest is a strong progestin with antiandrogenic activity. Natazia provides a unique estrogen step-down (estradiol valerate dose gradually decreases from 3 mg to 1 mg)/progestin step-up regimen (dienogest dose gradually increases from 0 mg to 3 mg), and this CHC offers the advantage of a shorter hormone-free interval. This results in fewer days of withdrawal bleeding and may help with menstrual-related headaches.

Finally, Quartette, Fayosim, and Rivelsa (levonorgestrel/EE) are extended-cycle, quadriphasic preparations that contain increasing doses of EE throughout the 91-day pill period. The increasing dose of EE is intended to reduce the rate of breakthrough bleeding or spotting.

Patient Encounter Part 2: Adverse Effects

After 2 months of taking Camrese Lo, she returns to your clinic complaining of heavy spotting during her sixth week of active pills. She reports no change or increase in frequency of her migraine headaches, and her blood pressure is 110/72 mm Hg. She is frustrated with the breakthrough bleeding and wants to explore other contraceptive options.

What are some potential causes of the breakthrough bleeding that the patient has been experiencing?

What strategy would you recommend to eliminate or minimize the potential adverse effects experienced by the patient?

Drug Interactions with Oral Contraceptives

EE is metabolized in the liver primarily via cytochrome P-450 (CYP450) 3A4. **KEY CONCEPT** When reviewing drug interactions of oral contraceptives, clinicians should be aware of the many drugs that may potentially interact with contraceptives—especially those that may reduce the effectiveness of contraceptives. Refer to Table 49–5

Table 49–5

Drug Interactions with CHCs[4,30]

Medication	Mechanism	Clinical Effect[a]
Anticonvulsants (carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone, topiramate, and felbamate)	Increase metabolism of CHCs via induction of various cytochrome P450 enzymes	Decrease efficacy of CHCs (EE doses < 35 mcg are not recommended in women on these medications)
Bosentan	Increase metabolism of CHCs via induction of cytochrome P450 3A4 enzyme	Decrease efficacy of CHCs
Griseofulvin	Increase metabolism of CHCs	Decrease efficacy of CHCs; backup method of contraception is recommended
Lamotrigine	CHCs increase metabolism of lamotrigine via induction of glucuronidation	Decrease efficacy of lamotrigine; dose adjustment may be necessary
Nonnucleoside reverse transcriptase inhibitors (efavirenz, etravirine, nevirapine, rilpivirine)	Increase metabolism of CHCs	Decrease efficacy of CHCs; alternative method of contraception may be considered with efavirenz and consider continued contraception for 12 weeks after discontinuation of efavirenz
Protease inhibitors (atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir)	Increase or decrease in metabolism of CHCs	Decrease efficacy of CHCs or increase side effects of CHCs; alternative method of contraception is recommended with fosamprenavir and may be considered with ritonavir-boosted protease inhibitors, atazanavir, and nelfinavir
Rifampin, rifabutin	Increase metabolism of CHCs	Decrease efficacy of CHCs; backup method of contraception is recommended
St. John's wort	Increase metabolism of CHCs via induction of various cytochrome P450 enzymes	Decrease efficacy of CHCs; avoid use with CHCs
Theophylline	CHCs decrease theophylline clearance by 34% and increase half-life by 33%	Increase side effects of theophylline
Modafinil, armodafinil	Increase metabolism of CHCs via induction of cytochrome P450 3A4 enzyme	Decrease efficacy of CHCs
Pitolisant	Increase metabolism of CHCs via induction of cytochrome P450 3A4 enzyme	Decrease efficacy of CHCs; use an alternative nonhormonal method of contraception during treatment and for at least 21 days after discontinuation

[a] With medications that decrease efficacy of CHCs, an alternative nonhormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of the interacting medication is generally recommended, unless otherwise noted in the table

CHC, combined hormonal contraception; EE, ethinyl estradiol.

Data compiled in part from Ethinyl Estradiol/Levonorgestrel. Micromedex Solutions. Ann Arbor, MI: Truven Health Analytics, Inc.. Available at: http://www.micromedexsolutions.com. Accessed August 14, 2021.

for a list of some of the most common drug interactions seen with oral contraceptives.[4,26,30]

Nonoral Hormonal Contraceptives

KEY CONCEPT As an alternative to oral contraceptive pills, which must be taken daily to reliably prevent pregnancy, nonoral contraceptives in the form of transdermal, transvaginal, and injectable preparations are available and offer patients safe and effective alternatives to the pills for prevention of pregnancy. These formulations also do not require daily administration, making them more convenient than pill formulations.

Xulane and Twirla are transdermal patches that contain both an estrogen and a progestin. Xulane contains 35 mcg of EE and 150 mcg of norelgestromin, while Twirla contains 30 mcg of EE and 120 mcg of levonorgestrel. A new patch is applied to the abdomen, buttocks, back, or upper (outer) arm once weekly for 3 weeks, followed by 7 patch-free days. Although some women have noted irregular bleeding during the first two cycles of patch use, the patch has been demonstrated to provide similar menstrual cycle control and contraceptive efficacy to that of CHCs. It is important to note, however, that higher contraceptive failure rates are seen when the patch is used in women weighing more than 90 kg (about 198 lb).[7] Furthermore, manufacturer prescriber information indicates that women who take transdermal contraception are exposed to approximately 60% more estrogen than women who take CHCs with 35 mcg of estrogen.[31] Although the clinical significance of this is not well defined, studies have suggested a link between the use of the patch and an increased risk for VTE. It is not recommended to use Xulane in women with a body mass index of 30 kg/m^2 or more due to an increased risk for developing VTE.[32] A slightly higher reported incidence of breast discomfort and local skin irritation has also been reported with the patch.[7,33]

NuvaRing and EluRyng are both a transvaginal delivery system that provides 15 mcg of EE and 120 mcg of etonogestrel for the prevention of ovulation. Annovera is a newly approved transvaginal delivery system that contains 150 mcg of segesterone, instead of etonogestrel as the progestin, along with 13 mcg of EE. Transvaginal delivery systems are inserted into the vagina on or before day 5 of the menstrual cycle and removed from the vagina 3 weeks later.[7] Seven days after the ring is removed, a new ring should be inserted. In clinical trials, this transvaginal delivery system demonstrated comparable efficacy and cycle control to CHCs as well as a similar side-effect profile.[7,34] Transvaginal rings should not be removed during intercourse. In addition to the brand name products available for transvaginal delivery, there is also a generic product that also contains 15 mcg of EE and 120 mcg of etonogestrel.

Depo-Provera is a progestin-only, injectable contraceptive that contains depot medroxyprogesterone acetate. Depo-Provera is administered intramuscularly as a 150-mg injection once every 3 months. An advantage of Depo-Provera is that it provides an estrogen-free method of contraception either for women in whom estrogens are contraindicated or for women who cannot tolerate estrogen-containing preparations. Depo-Provera is extremely effective in preventing pregnancy. However, the incidence of menstrual irregularities (including amenorrhea) and weight gain appears to be much greater than that seen with CHCs.[35] Recent data has also shown when women gain 5% of their body weight during the first 3 to 6 months of treatment they are at increased risk for additional weight gain with continued use of the injectable contraceptive.[36] The use of Depo-Provera also has been demonstrated to result in significant loss of bone mineral density (BMD).[38] Although the effect is known to be reversible following product discontinuation, a black-box warning within the product labeling cautions against the risk of potentially irreversible BMD loss associated with long-term use (eg, > 2 years) of the injectable product. Although injectable contraceptives offer no protection against STIs, it is important to note the CDC finds that the risk of HIV acquisition does not outweigh the benefit of contraceptive use in a patient at high risk of HIV infection. Although the extended duration of activity of this product may offer women the advantage of less frequent administration, it is important to note that on discontinuation of Depo-Provera, the return of fertility can be delayed by approximately 10 to 12 months (range 4–31 months).[7]

Depo-SubQ Provera 104 is also an injectable contraceptive product that contains only progestin (depot medroxyprogesterone acetate). This product differs from Depo-Provera in that it is given subcutaneously rather than intramuscularly and contains only 104 mg of medroxyprogesterone acetate (~30% less hormone) administered every 3 months for the prevention of pregnancy. Clinical trials have demonstrated that the subcutaneous formulation of depot medroxyprogesterone acetate is as effective as the intramuscular formulation in the prevention of pregnancy.[37] This product carries the same warning in its package labeling regarding possible effects on BMD as Depo-Provera. It is also used for the management of endometriosis-associated pain along with its use for contraception.

Long-Acting Reversible Contraception

The currently available products for long-term reversible contraception (LARC) are listed in Table 49–6.[38] Surveys have shown that LARC has the highest satisfaction rate among patients using reversible contraceptives, and use within the United States is on the rise.[1]

The primary mechanism of action for IUDs is by preventing fertilization. It is believed that copper-containing IUDs may interfere with sperm transport and fertilization and prevent implantation by releasing toxic copper ions.[38] Progestin-containing

Table 49–6

Long-Acting Reversible Contraception[38]

Product	Ingredient	Dosage Form	Dose	Duration
Mirena	Levonorgestrel	Intrauterine device	52 mg	Up to 6 years
Skyla	Levonorgestrel	Intrauterine device	13.5 mg	Up to 3 years
Kyleena	Levonorgestrel	Intrauterine device	19.5 mg	Up to 5 years
Liletta	Levonorgestrel	Intrauterine device	52 mg	Up to 6 years
ParaGard	Copper	Intrauterine device	380 mm^2	Up to 10 years
Nexplanon	Etonorgestrel	Implantable device	68 mg	Up to 3 years

implantable contraceptives can have direct effects on the uterus, such as thickening of cervical mucus and alterations to the endometrial lining. If an implanted embryo is established, IUDs do not cause destruction of the embryo.[38]

It is important to evaluate a patient to determine whether she is an appropriate candidate for an implantable contraceptive. IUDs are recommended for women who are in a monogamous relationship, at low risk for acquiring STIs, and have no current pelvic inflammatory disease (PID). Contraindications to the use of progestin-containing LARC products include (a) known or suspected pregnancy, (b) hepatic tumors or active liver disease, (c) undiagnosed abnormal genital bleeding, (d) known or suspected carcinoma of the breast or personal history of breast cancer, (e) history of thrombosis or thromboembolic disorders, and (f) hypersensitivity to any components of the products. There are also multiple additional contraindications to IUD use. Evaluation of the patient is essential because IUDs cannot be used in the following situations: (a) anatomically abnormal or distorted uterine cavity, (b) acute PID, (c) postpartum endometritis or infected abortion in the past 3 months, (d) known or suspected uterine or cervical malignancy, (e) untreated acute cervicitis, (f) previously inserted IUD still in place, (g) increased susceptibility to pelvic infections, and (h) Wilson disease (Paragard only).

The most common adverse effects are abdominal/pelvic cramping, abnormal uterine bleeding, and expulsion of the device. Other side effects seen are ectopic pregnancy, sepsis, PID, embedment of the device, uterine or cervical perforation, and ovarian cysts.

Nonpharmacologic Contraceptive Methods

▶ *Barrier Contraceptives*

In addition to or as an alternative to hormonal contraceptives, several barrier contraceptive options are available for the prevention of pregnancy. Although barrier contraceptives are associated with far fewer adverse effects compared with hormonal contraceptives, their efficacy is highly user-dependent. Overall, compared with both hormonal contraceptives and IUDs, barrier contraceptives are associated with much higher unintended pregnancy rates[7] (see Table 49–1).

Diaphragms and Cervical Caps Diaphragms and cervical caps are dome-shaped rubber caps that are placed over the cervix to provide barrier protection during intercourse. Both diaphragms and cervical caps require fitting by a healthcare professional, and they must be refitted in the event of weight gain or weight loss. Diaphragms or cervical caps typically can be placed over the cervix as much as 6 hours prior to intercourse. FemCap should be placed 15 to 40 minutes before intercourse. Diaphragms and cervical caps must be left in place for at least 6 hours after intercourse before they can be removed. Diaphragms should not be left in place longer than 24 hours, and smaller cervical caps should not be left in place longer than 48 hours owing to the risk of toxic shock syndrome (TSS). Diaphragms and cervical caps are used along with spermicides to prevent pregnancy. When sexual intercourse is repeated with the diaphragm, reapplication of the spermicide is necessary. However, when sexual intercourse is repeated with a cervical cap, reapplication of the spermicide typically is not necessary.[7] Whether or not diaphragms or cervical caps provide adequate protection against STIs remains unclear.[39]

Spermicides Nonoxynol-9, a surfactant that destroys the cell membranes of sperm, is the only chemical spermicide in the United States.[4,7] Nonoxynol-9 is available in a variety of forms, including a cream, foam, film, gel, suppository, and tablet. Spermicides may be used alone, with a barrier method, or adjunctively with other forms of contraceptives to provide additional protection against unwanted pregnancy.[4] To be used most effectively, spermicides must be placed in the vagina not more than 1 hour prior to sexual intercourse, and they must come in contact with the cervix.[7] Additionally, film, suppositories, and tablets must dissolve to be effective. Although the efficacy of spermicides depends largely on how consistently and correctly they are used, their efficacy is enhanced when they are used in combination with a barrier contraceptive device.[39] Clinical trials assessing the ability of spermicides to protect against STIs have failed to produce positive results.[4] Furthermore, there exists some evidence to suggest that frequent use of spermicides actually may increase risk for acquisition of human immunodeficiency virus (HIV) secondary to vaginal mucosal tissue breakdown, which may allow a portal of entry for the virus.[7] The FDA requires manufacturers of nonoxynol-9 products to include a warning on the product label indicating that the spermicide does not provide protection against infection from HIV or other STIs. Patients should be encouraged not to use spermicides alone. They are recommended with a barrier method.

Condoms Condoms, which are available for both male and female use, act as physical barriers to prevent sperm from coming into contact with ova.[4] Condoms may be easy to use, are available without a prescription, and may be relatively inexpensive. Most condoms are made of latex. When used correctly, condoms can be very effective in prevention of unwanted pregnancy.[40] Condoms should be stored in a cool, dry place, away from exposure to direct sunlight. When stored improperly or when used with oil-based lubricants, however, latex condoms can break during intercourse, increasing the risk of pregnancy.[7] For latex-sensitive individuals, condoms made from lamb intestine ("natural membrane" condoms) and synthetic polyurethane condoms are available. Unlike latex condoms, condoms made from lamb intestine contain small pores that may permit the passage of viruses and therefore do not provide adequate protection against STIs.[4] As well, synthetic polyurethane condoms may be more likely to break than latex condoms. **KEY CONCEPT** Both latex and synthetic condoms can provide some protection against many STIs. Data from one meta-analysis suggested that HIV transmission can be reduced by as much as 90% when condoms are consistently used.[41] This is in contrast to hormonal contraceptives (oral, transdermal, or vaginal), IUDs, and most other barrier contraceptives, which do not protect against STIs. Relative to male condoms, female condoms may offer even better protection against STIs because they provide more extensive barrier coverage of external genitalia, including the labia and the base of the penis.[4] Female condoms are generally less effective than male condoms at preventing pregnancy, however. It is important to note that the male and female condoms are not recommended to be used together because they may adhere to one another, causing displacement of one or both condoms.[4]

Sponge The Today Sponge is a small, pillow-shaped polyurethane sponge impregnated with nonoxynol-9.[40] It is an over-the-counter barrier contraceptive that has been shown to be generally less effective at preventing pregnancy than diaphragms.[41] The sponge is moistened with water and then is inserted and placed over the cervix up to 6 hours prior to sexual intercourse. The sponge then is left in place for at least 6 hours following intercourse.[4] Although the sponge maintains efficacy for 24 hours (even if intercourse is repeated), as with diaphragms, the sponge should be removed after 24 hours owing to the risk of TSS.[7]

Table 49–7

Emergency Contraception

Product	Availability	Ingredient	Dose	When Recommended[a]
Levonorgestrel, Aftera, EContra EZ, EContra One-Step, Fallback Solo, My Choice, My Way, Opcicon One-Step, Option 2, Plan B One-Step, Preventeza, React, Take Action	All ages with no identification required	Levonorgestrel	1.5 mg	Within 72 hours of unprotected sex
ella	Only as a prescription	Ulipristal acetate	30 mg	Within 120 hours of unprotected sex

▶ *Fertility Awareness–Based Methods*

Fertility awareness–based methods (natural methods) represent another nonpharmacologic means of pregnancy prevention. Although failure rates of such methods can be high, some couples still prefer these types of approaches. Fertility awareness–based methods depend on the ability of the couple to identify the woman's "fertile window," or the period of time in which pregnancy is most likely to occur as a result of sexual intercourse.[4] During the fertile window, the couple practices abstinence, or avoidance of intercourse, to prevent pregnancy. In general, fertility awareness–based methods are not recommended for women who have irregular menstrual cycles or who have difficulty interpreting their fertility signs correctly.[4] More recently, the FDA has approved a fertility awareness mobile app that incorporates information about a woman's menstrual cycle and basal body temperature to provide a recommendation on whether to use a barrier contraceptive or abstinence based on predicted fertility windows.

Emergency Contraception

Emergency contraception (EC) is used to prevent pregnancy after known or suspected unprotected sexual intercourse. Ideally it should be used as soon as possible after unprotected sexual intercourse and within 72 hours (120 hours with ella), but it can still remain effective beyond this time frame. If a woman is already pregnant, EC cannot stop the pregnancy or harm the fetus. All oral EC products suppress LH and therefore delay or block ovulation. It is not proven, but evidence suggests EC will only work before ovulation, so it would not prevent implantation of a fertilized egg.[42] It is not recommended that EC be used as a regular form of birth control.

There are currently 14 FDA-approved oral agents available for use as EC. Thirteen of these agents have the active ingredient of levonorgestrel and are over the counter and available to all ages with no identification required. Common side effects of levonorgestrel containing EC are headache, nausea, abdominal pain, fatigue, dizziness, vomiting, and breast tenderness. Of note, there is some evidence that efficacy of levonorgestrel containing EC may be decreased in women weighing more than 75 kg or those with a BMI greater than 26 kg/m^2.[42]

The product known as ella (ulipristal acetate), a progesterone-receptor agonist/antagonist, is only available with a prescription. It can delay follicular rupture if taken just before ovulation and may cause endometrial changes to interfere with implantation. Common side effects include headache, nausea, abdominal pain, fatigue, dizziness, dysmenorrhea, upper abdominal pain, back pain, and can delay menses up to approximately 2 days. A pharmacokinetic study of ulipristal acetate showed similar serum levels in patients with a BMI greater than 30 kg/m^2 compared to those with a lower BMI, so it may be a preferred oral EC option in this population.[42]

The available products are listed in Table 49–7[43] along with information on availability and dosage. It is important to note that EC is more effective the earlier it is used after unprotected intercourse. If severe abdominal pain occurs, patients should be referred to their healthcare provider for evaluation of risk of an ectopic pregnancy. Patients should also contact their healthcare provider if their menstrual cycle is more than 1 week late after taking EC.

Patient Encounter Part 3: Missed Doses

The patient calls your clinic in a panic today because she forgot to take her oral contraceptive for the past 2 days, beginning the third week of active pills. Two days have elapsed since she took her last active pill, and she reports having had sexual intercourse last night. She states that her male partner used a condom. The patient is very concerned about her risk of pregnancy and interested to learn more about emergency contraception and her options.

Given this patient's reported imperfect use of her oral contraceptive, what information can you provide to the patient regarding her risk of pregnancy?

What additional education should be provided to the patient regarding her risk of STIs?

Provide appropriate patient education regarding the use of various forms of emergency contraception, in the event she decides to use EC.

OUTCOME EVALUATION

Schedule follow-up visits as needed and at the discretion of the provider. At each follow-up visit, assess blood pressure, headache frequency, and menstrual bleeding patterns, as well as compliance with the prescribed regimen. Strict adherence to the prescribed hormonal contraceptive regimen is essential for effective prevention of unintended pregnancy. **KEY CONCEPT** When a contraceptive dose is missed, the risk of accidental pregnancy may be increased. Depending on how many doses were missed, the contraceptive formulation being used, and the phase of the cycle during which doses were missed, counseling regarding the use of additional methods of contraception may be warranted. For further information, patients can be referred to https://www.cdc.gov/reproductivehealth/unintendedpregnancy/pdf/248124_fig_2_3_4_final_tag508.pdf.

Patient Care Process

Collect Information:

- Determine goals related to contraceptive use (pregnancy prevention, menstrual regulation, control of acne).
- Based on medical, social (ie, smoking), and family history, determine if patient qualifies for hormonal contraceptives. Rule out pregnancy and evaluate patient's risk for STIs.
- Conduct thorough medication history to identify potential for drug interactions.

Assess the Information:

- At follow-up visits, assess blood pressure, weight, and menstrual patterns for changes from baseline.
- Assess tolerability of and adherence to the prescribed contraceptive method.
- Assess safety of hormonal contraceptives by using the mnemonic "ACHES"[4]:

A = Abdominal pain
C = Chest pain
H = Headaches (especially if associated with focal neurologic symptoms)
E = Eye problems (blurred vision, ocular pain, visual changes)
S = Severe leg pain

- Also monitor for missed periods, signs of pregnancy, appearance of jaundice, and/or severe mood changes.
- Assess safety of IUDS by using the mnemonic "PAINS"[4]:

P = Period late
A = Abdominal pain, pain with intercourse
I = Infection, abnormal/odorous vaginal discharge
N = Not feeling well, fever, chills
S = String (missing, shorter, longer)

Develop a Care Plan:

- Select a contraceptive option that the patient is comfortable with, that is likely to achieve the patient's desired goal(s), and is not contraindicated.
- Educate regarding the potential for side effects, safety risks, drug interactions, and any noncontraceptive benefits that may result for the chosen method.
- Determine the patient's sexual behavior and evaluate whether the contraceptive method will impact the risk for STIs.
- Evaluate insurance coverage/cost factors.

Implement the Care Plan:

- Instruct the patient to consult a healthcare professional upon noticing or experiencing any warning signs.
- Stress the importance of adherence (especially if prevention of pregnancy is desired).
- Educate on what to do in the event of missed doses.

Follow-up: Monitor and Evaluate:

- Schedule a follow-up visit 3 to 6 months after initiating a new contraceptive.
- Assess blood pressure, headache frequency, and menstrual bleeding patterns.
- Assess patient tolerance and evaluate for the occurrence of side effects specific to the regimen prescribed.
- Assess adherence to the prescribed regimen.

Abbreviations Introduced in This Chapter

BMD	Bone mineral density
CHC	Combination hormonal contraceptive
CYP450	Cytochrome P450
EC	Emergency contraception
EE	Ethinyl estradiol
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
IUD	Intrauterine device
LARC	Long-acting reversible contraception
LH	Luteinizing hormone
MEC	Medical eligibility criteria
PID	Pelvic inflammatory disease
PMDD	Premenstrual dysphoric disorder
STI	Sexually transmitted infection
TSS	Toxic shock syndrome
WHO	World Health Organization

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50 Menopause and Menstruation-Related Disorders

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the underlying etiology of dysmenorrhea, amenorrhea, anovulatory bleeding, heavy menstrual bleeding, and menopause.
2. Explain the physiologic changes associated with dysmenorrhea, amenorrhea, anovulatory bleeding, heavy menstrual bleeding, and menopause.
3. Identify the signs and symptoms associated with dysmenorrhea, amenorrhea, anovulatory bleeding, heavy menstrual bleeding, and menopause.
4. Determine the desired therapeutic outcomes for patients with dysmenorrhea, amenorrhea, anovulatory bleeding, heavy menstrual bleeding, and patients taking menopausal hormone therapy (MHT).
5. Explain how to evaluate a patient for the appropriate use of MHT.
6. Recommend appropriate nonpharmacologic and pharmacologic interventions for dysmenorrhea, amenorrhea, anovulatory bleeding, heavy menstrual bleeding, and menopausal symptoms.
7. Design a monitoring plan to assess the safety and effectiveness of pharmacotherapy for dysmenorrhea, amenorrhea, anovulatory bleeding, heavy menstrual bleeding, and a patient taking MHT.

INTRODUCTION

Menstrual cycle disorders are common amongst women of reproductive age. The most common include dysmenorrhea, amenorrhea, anovulatory bleeding, and heavy menstrual bleeding. Menstruation-related disorders can negatively affect quality of life (QOL), reproductive health, and productivity and may also lead to long-term health consequences. As menstruation begins to cease, the perimenopause and menopause phases begin. During this time, irregular menses, vaginal dryness, dyspareunia, hot flashes, and mood swings may occur. This chapter explores the most common menstruation-related disorders women face and symptoms associated with menopause.

DYSMENORRHEA

Dysmenorrhea is pelvic pain, generally described as painful cramping, occurring during or just prior to menstruation. Primary dysmenorrhea occurs with normal pelvic anatomy and physiology, whereas secondary dysmenorrhea is associated with underlying pelvic pathology.[1]

Epidemiology and Etiology

Dysmenorrhea is the most commonly reported menstrual complaint, with over 50% of menstruating women reporting pain for at least 1 or 2 days each month.[2] Of adolescents with dysmenorrhea, up to 12% report missing work or school each month due to pain.[3] Risk factors include irregular or heavy menses, age less than 30, menarche prior to age 12, body mass index less than 20 kg/m^2, history of sterilization or sexual abuse, and smoking.[1,4] Causes of secondary dysmenorrhea may include endometriosis, pelvic inflammatory disease (PID), uterine or cervical polyps, and uterine fibroids.[3,4]

Pathophysiology

In primary dysmenorrhea, elevated arachidonic acid levels in the menstrual fluid lead to increased concentrations of prostaglandins and leukotrienes in the uterus. This induces uterine contractions, stimulates pain fibers, reduces uterine blood flow, and causes uterine hypoxia.[4]

Treatment

▶ *Desired Outcomes*

Desired treatment outcomes (Figure 50–1) are reduction of pelvic pain, improved QOL, and fewer missed days from school and work.

▶ *Nonpharmacologic Therapy*

Dysmenorrhea intensity has shown to be decreased by exercise, applying topical heat therapy, acupuncture, and consuming a low-fat vegetarian diet.[1,5,6] Exercise may reduce dysmenorrhea by increasing pelvic blood flow and stimulating the release of beta-endorphins which act as analgesics.[1,7] Heat applied as an abdominal patch has shown to be as effective as 400 mg of ibuprofen dosed three times daily.[5,6,8] In addition, a low-fat vegetarian diet may lessen the duration of dysmenorrhea. A variety of dietary supplements have been evaluated for dysmenorrhea, including fenugreek, fish oil, vitamin B1, ginger, valerian, and zinc oxide; however, none should be recommended at this time due to lack of quality evidence for efficacy.[9] Additionally, evidence supporting

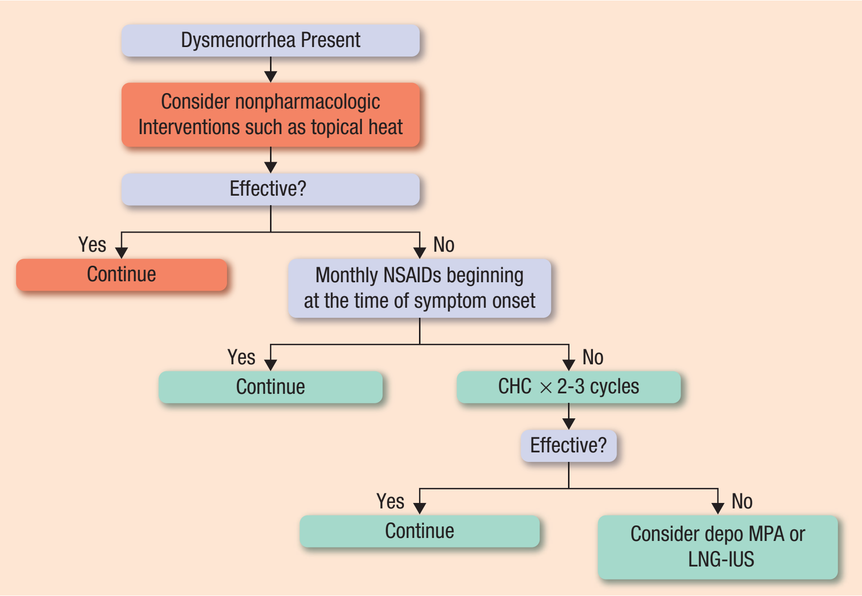
Dysmenorrhea Present
Consider nonpharmacologic Interventions such as topical heat
Effective?
Yes
No
Continue
Monthly NSAIDs beginning at the time of symptom onset
Yes
No
Continue
CHC × 2-3 cycles
Effective?
Yes
No
Continue
Consider depo MPA or LNG-IUS

FIGURE 50–1. Treatment algorithm for dysmenorrhea. (CHC, combination hormonal contraceptive; IUD, intrauterine device; MPA, medroxyprogesterone acetate; NSAID, nonsteroidal anti-inflammatory drug.) Reproduced with permission from DiPiro JT, Yee GC, Posey lM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach. 11th ed. New York City: McGraw-Hill; 2020.

acupuncture and acupressure is low and both are not currently recommended as standards of care.[6]

▶ *Pharmacologic Therapy*

Medication management options are summarized in Table 50–1.

Nonsteroidal Anti-inflammatory Drugs

KEY CONCEPT Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line therapy for dysmenorrhea and are effective in up to 80% of patients.[10] NSAIDs inhibit prostaglandin production, exert analgesic properties, decrease uterine contractions, and reduce menstrual blood flow. Choice of agent is based on effectiveness, tolerability, and patient preference, with the most commonly utilized agents being naproxen and ibuprofen.[1,4] Of note, aspirin is not recommended as it is not potent enough in usual dosages.

NSAID treatment should begin 1 to 2 days prior to menses, or at dysmenorrhea onset, and continued for 2 to 3 days or until pain resolves.[1,4] A loading dose (twice the usual single dose) is recommended, followed by the usual recommended dose.[1,3] For patients with limited response or with contraindications to NSAID therapy, combination hormonal contraceptives (CHCs) should be considered.[4]

Combination Hormonal Contraceptives

CHCs improve dysmenorrhea by decreasing endometrial lining and inhibiting ovulation, which decreases the formation of prostaglandins and leukotrienes contributing to menstrual pain.[3,4] Precisely, 2 to 3 months of therapy are often required to achieve full effects, and can take up to 6 months.[4] Both cyclic

Clinical Presentation and Diagnosis of Dysmenorrhea

General

- May be in acute distress depending on the severity of pain.

Symptoms

- Recurrent, crampy pelvic pain (lasting 2–3 days) beginning shortly before or during menses. Pain may radiate into lower back or thighs. Associated symptoms generally begin in adolescence and include nausea, vomiting, diarrhea, headache, dizziness, bloating, and fatigue.

Laboratory Tests

- Gonorrhea, chlamydia cultures, or polymerase chain reactions test, wet mount

Other Diagnostic Tests

- Pelvic examination for sexually active females, females reporting severe pain or limitation of activity, or who have not responded to first- and second-line treatments.
- Pelvic ultrasound may identify anatomic abnormalities (eg, masses/lesions), ovarian cysts, or endometriomas.

Patient Encounter 1, Part 1

A 14-year-old woman presents reporting crampy pelvic pain that radiates to her thighs during menses causing her to miss school a few days each month. Her last menses started 21 days ago, and her first menstrual cycle occurred at age 12. She has a history of sexual abuse when she was 6 to 8 years of age, which included penetration. She has been removed from the abuse situation, and reports she is not currently sexually active. She has been taking ibuprofen 800 mg three times a day for 4 days during menses for the last six cycles, which has provided some relief. She plays volleyball for her school, is 5′10″ (178 cm) tall, and weighs 146 pounds (66.2 kg).

What risk factors does the patient have for primary dysmenorrhea?

Table 50–1

Therapeutic Agents for Selected Menstrual Disorders

Specific Menstrual Disorder(s)	Agent(s)	Dose Recommended	Common Adverse Effects
Amenorrhea (primary or secondary)	CEE[a]	0.625–1.25 mg by mouth daily on cycle days 1–26[9]	Thromboembolism, breast enlargement, breast tenderness, bloating, nausea, GI upset, headache, peripheral edema
	Ethinyl estradiol patch[a]	50–100 mcg/24 hours[11]	
	Oral CHC[a]	30–40 mcg ethinyl estradiol formulations	
Amenorrhea (secondary)	Oral medroxyprogesterone acetate[a]	10 mg by mouth on cycle days 14–26[11]	Edema, anorexia, depression, insomnia, weight gain or loss, elevated total and LDL cholesterol may reduce HDL cholesterol
Amenorrhea (hyperprolactinemia)	Bromocriptine	2.5 mg by mouth two to three times daily[15]	Hypotension, nausea, constipation, anorexia, Raynaud phenomenon
	Cabergoline	0.25 mg by mouth twice weekly[15]	
Anovulatory bleeding	Oral CHC[a]	Optimal dose unknown[19] For acute or severe bleeding, product containing 35-mcg ethinyl estradiol; take one tablet by mouth three times daily × 1 week; then one tablet by mouth daily × 3 weeks.[19] Therapy continuation may be necessary to prevent future occurrences	As noted above for CEE, ethinyl estradiol, and oral CHC (progesterone side effects with the CHC depend on agent chosen)
	Oral medroxyprogesterone acetate[a]	For acute bleeding, 20 mg by mouth three times daily × 1 week; then 20 mg by mouth once daily × 3 weeks[19]	As noted above for oral medroxyprogesterone acetate
Dysmenorrhea	Oral CHC[38,a]	< 35-mcg ethinyl estradiol formulations + norgestrel or levonorgestrel[39]; use of extended-cycle formulations is beneficial for this indication	As noted above for CEE, ethinyl estradiol, and oral CHC (progesterone side effects with the CHC depend on agent chosen)
	Depot medroxyprogesterone acetate[a]	104 mg subcutaneously every 3 months (12–14 weeks) 150 mg intramuscularly every 3 months (13 weeks)	Irregular menses, amenorrhea
	Levonorgestrel IUD[10,a]	20 mcg released daily	Irregular menses, amenorrhea
	NSAIDs—any are acceptable except aspirin or salicylates; the most commonly studied/cited are included in this table.[1,3-5,38] Treatment should begin 1–2 days prior to the expected onset of menses	Ibuprofen 800 mg by mouth three times daily[a] Naproxen 550-mg loading dose by mouth started 1–2 days prior to menses, followed by 275 mg by mouth every 6–12 hours as needed[c] Mefenamic acid 500 mg by mouth as a loading dose, then 250 mg by mouth up to four times daily as needed[b] Diclofenac 50 mg by mouth three times daily[b]	GI upset, stomach ulcer, nausea, vomiting, heartburn, indigestion, rash, dizziness
Abnormal uterine bleeding	Oral CHC[a]	Optimal dose unknown	As noted above
	Levonorgestrel IUD[a]	20 mcg released daily	As noted above
	Medroxyprogesterone acetate (oral)[a]	5–10 mg by mouth on days 5–26 of the cycle *or* during the luteal phase[32]	As noted above
	NSAIDs	Doses as recommended for above; therapy should be initiated with the onset of menses[32]	As noted above
	Tranexamic acid	1300 mg (650 mg × 2) by mouth three times days × 5 days[35–37]	Fatigue, abdominal, back, or muscle pain

(Continued)

Table 50–1

Therapeutic Agents for Selected Menstrual Disorders (*Continued*)

Specific Menstrual Disorder(s)	Agent(s)	Dose Recommended	Common Adverse Effects
PCOS-related amenorrhea and/or anovulatory bleeding	If pregnancy is not an immediate goal:		
	Metformin	Metformin dosing: 1500-2000 mg by mouth daily in two to three divided doses.	Metformin: Anorexia, nausea, vomiting, diarrhea, flatulence, lactic acidosis
	Oral CHC	35 mcg or less ethinyl estradiol and progesterone with antiandrogenic effects (eg, drospirenone)	
	Levonorgestrel IUD	20 mcg released daily	
	Women with side effects or contraindications to estrogen:		
	Medroxyprogesterone acetate (oral)[a]	10 mg by mouth × 10 days[17]	As noted above
	Depot medroxyprogesterone acetate[a]	150 mg intramuscularly every 12 weeks	

[a] Use is contraindicated in patients with severe hepatic impairment.

[b] Not recommended in patients with severe renal impairment.

[c] Use is contraindicated with creatinine clearance < 30 mL/min (0.5 mL/s).

CEE, conjugated equine estrogen; CHC, combination hormonal contraceptive; GI, gastrointestinal; HDL, high-density lipoprotein; IUD, intrauterine device; LDL, low-density lipoprotein; NSAIDs, nonsteroidal anti-inflammatory drugs; PCOS, polycystic ovary syndrome.

(28-day) and extended cycle (91-day) therapies have been used effectively.[1,4] Continuous CHC may provide more rapid pain relief when compared to cyclic therapy; however, both effects are similar when evaluated at 6 months.[1,4] For dysmenorrhea secondary to endometriosis, CHCs, specifically extended cycle regimens, are considered first-line.[1,4] If no response with any agent occurs after 3 to 6 months, the patient should be reevaluated.[3]

Progestin-Only Hormonal Contraceptives

Long-acting progestins are often utilized for dysmenorrhea treatment and work by reducing or eliminating menses over 6 to 12 months of use, thus eliminating prostaglandin release. Three long-acting reversible contraceptive agents are available: depot medroxyprogesterone acetate (MPA), etonogestrel implant, and levonorgestrel-releasing intrauterine device (IUD). Observational data showed that women with active dysmenorrhea symptoms

Patient Encounter 1, Part 2

Additional workup reveals:

PMH: exercise-induced asthma

PSH: Tonsillectomy at age 7

FH: Mother and father alive and well; two siblings (ages 11 and 21), both alive and well

SH: (–) tobacco use; (–) illicit drug use; (–) alcohol use

Medication: albuterol inhaler 1 to 2 puffs prior to exercise as needed

Past Gynecologic History: Menarche at age 12; never pregnant; (–) sexual activity; (+) history of painful menses beginning at age 13; (–) heavy menstrual flow; menstrual cycle 27 to 28 days

ROS: (+) fatigue with menses; (–) headaches; (–) mild acne on face, chest, and upper back; (+) moderate-to-severe pelvic pain radiating to thighs with menses

PE:

General: Thin, athletic woman, in no acute distress

VS: BP 110/68, P 72, RR 14, Wt 146 lbs (66.2 kg), Ht 5′10″ (178 cm), Body mass index: 20.9 kg/m^2

HEENT: (–) hirsutism

Breasts: (–) galactorrhea

Pelvic examination: Normal appearance of external genitalia and vagina, cervix without lesions, uterus midposition without masses

Labs: (–) hCG

Given this information, what is your assessment of this patient's condition?

What nonpharmacologic therapies are recommended for this patient?

Is the patient's self-treatment with ibuprofen appropriate? Why or why not?

What pharmacologic therapies are recommended for this patient?

who used a levonorgestrel-releasing IUD saw a reduction in their symptoms from 60% to 29% after 3 years of therapy.[7]

Dysmenorrhea in Adolescents

Dysmenorrhea is the most common gynecologic complaint amongst female adolescents, reported in 60% to 90%, and the most common reason for missed school or work.[7] NSAIDs are the preferred initial treatment in adolescents, followed by hormonal treatment. **KEY CONCEPT** Adolescents with symptoms unresponsive to NSAID therapy for three menstrual periods should be offered CHC, which can also provide effective contraception if desired.[3] If symptoms do not improve within 3 to 6 months of NSAIDs and CHC, it is important to assess for medication adherence. If adherence is confirmed and patient still not experiencing symptom relief, further evaluation through laparoscopy is indicated. Since adolescence is a critical period for bone mineral density (BMD) accrual, and prolonged use of depot MPA may lead to significant loss of BMD that may not be completely reversible, other agents are considered first line.

AMENORRHEA

Amenorrhea is the absence of menses over a 90-day period and can be primary or secondary. **Primary amenorrhea** is the failure to reach menarche by age 15, in women who have never menstruated. **Secondary amenorrhea** is the cessation of menses for 3 months in a previously regular menstruating woman or 6 months in a previously irregular menstruating woman.[11]

Epidemiology and Etiology

KEY CONCEPT Unrecognized pregnancy can be a common cause of amenorrhea; therefore, a urine pregnancy test should be one of the first steps in evaluating amenorrhea. There are three main causes of amenorrhea: anatomical causes including pregnancy and uterine structural abnormalities, endocrine or hormone imbalances leading to chronic amenorrhea, and ovarian insufficiency or failure. Primary amenorrhea is often caused by chromosomal irregularities resulting in primary ovarian insufficiency or anatomic abnormalities.[11] Causes of secondary amenorrhea include **polycystic ovary syndrome** (PCOS), hypothalamic suppression, thyroid disorders, hyperprolactinemia, or primary ovarian insufficiency.[11] Additional causes include undernutrition, anorexia, and excessive exercise.

Pathophysiology

Normal menstrual cycle physiology depends on hormonal interactions involving the hypothalamus, anterior pituitary gland, ovary, and endometrium (Figure 50–2).[11] Table 50–2 shows causative condition(s) and the organ system(s) involved in the pathophysiology of amenorrhea. Amenorrhea is a potential side effect from using low-dose or extended oral CHCs, MPA, or levonorgestrel-releasing IUD.[11] Many women experience delayed return of menses after discontinuing hormonal contraception. If resolution of amenorrhea does not occur within 3 to 6 months after discontinuing contraception, evaluation for other conditions should be considered (eg, PCOS).

Treatment

▶ *Desired Outcomes*

Treatment goals include ensuring normal puberty is occurring, restoring the normal menstrual cycle, preserving bone density, preventing bone loss, improving QOL, reduction of associated symptoms, and restoring ovulation, thus improving fertility.[11]

▶ *Nonpharmacologic Therapy*

Nonpharmacologic therapy depends on the underlying cause. Amenorrhea secondary to undernutrition or anorexia may respond to weight gain and psychotherapy.[11] If excessive exercise is the cause, exercise reduction is recommended.[11] Women with functional hypothalamic amenorrhea should undergo a reasonable trial of psychological (such as cognitive behavior therapy), nutritional, and/or exercise intervention prior to starting pharmacologic therapy.

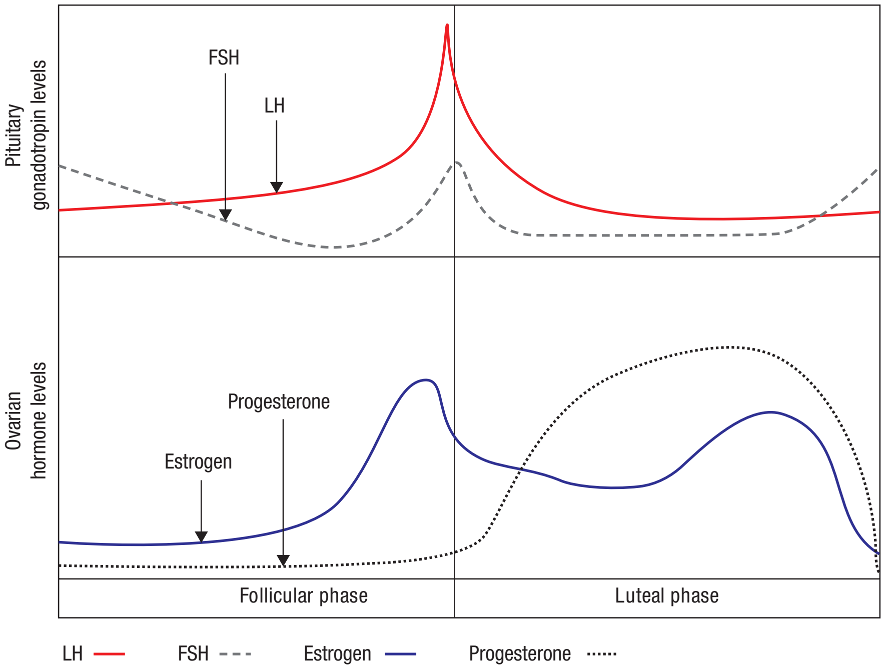

FIGURE 50–2. Hormonal fluctuations with the normal menstrual cycle. (FSH, follicle-stimulating hormone; GnRH, gonadotropin releasing hormone; LH, luteinizing hormone.) Reproduced with permission from DiPiro JT, Yee GC, Posey IM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach. 11th ed. New York City: McGraw-Hill; 2020.

Table 50–2

Expected Outcome Measures for Selected Menstrual Bleeding Disorders[10,12,19,25,28]

Menstruation-Related Disorder	Expected Outcome Measures
Dysmenorrhea	*Efficacy:* Reduction in menses-related pelvic pain; reduction in time lost from work/school; improved quality of life. *Time to relief/effect:* Improvement in pain may be observed within hours of NSAID therapy; improvement with other options such as oral CHCs may be observed after a full 1–3 cycles of use.
Amenorrhea	*Efficacy:* Normal breast development (especially primary amenorrhea in adolescents); BMD preservation/ improvement; return of menses. *Time to relief/effect:* Menses should occur within 1–2 months of therapy.
Anovulatory Bleeding	*Efficacy:* Alleviation of acute bleeding when present; ovulation and subsequent pregnancy in women desiring this; reduced risk of developing the long-term complications of PCOS (eg, diabetes and cardiovascular disease); improved quality of life. *Time to relief/effect:* The acute treatment of heavy bleeding should reduce bleeding within 10 days of therapy onset; return of ovulation may require several months of therapy; when oral CHCs are used, abnormal bleeding control can be expected within one to two treatment cycles.
Heavy Menstrual Bleeding	*Efficacy:* Decline in amount of blood loss with menses (monitor a decline in the number of times feminine hygiene products such as pads and tampons require changing during menses); increase in hemoglobin/ hematocrit if anemia was present as because of abnormal uterine bleeding. *Time to relief/effect:* A decline in menstrual blood loss should be realized within one to two cycles of therapy initiation.

BMD, bone mineral density; CHCs, combination hormonal contraceptives; NSAID, nonsteroidal anti-inflammatory drug; PCOS, polycystic ovary syndrome

▶ *Pharmacologic Therapy*

Estrogen/Progestin Replacement Therapy For most conditions associated with primary or secondary amenorrhea, estrogen supplementation with either an oral contraceptive, conjugated equine estrogen (CEE), or estradiol patch has historically been recommended. However, CHC and synthetic estrogen are no longer recommended as first-line agents for patients with functional hypothalamic amenorrhea. The 2017 Endocrine Society Clinical Practice Guideline for functional hypothalamic amenorrhea recommends patients trial nonpharmacological therapy first (with psychological and nutritional interventions), and then start a short-term transdermal estrogen with cyclic oral progestins.[13] Table 50–1 lists the types and doses of estrogen and progestin therapy for amenorrhea.

Dopamine Agonists When hyperprolactinemia is the cause of amenorrhea, dopamine agonists are preferred. Dopamine agonists restore normal prolactin levels, resolve amenorrhea, and restore ovulation in 80% to 90% of women.[14] Bromocriptine and cabergoline are the most commonly studied agents, with cabergoline being more effective in resolving amenorrhea.[14,15]

Progestins Progestins induce withdrawal bleeding in women with secondary amenorrhea. Withdrawal bleeding occurs with intramuscularly injected progesterone and oral MPA in 70% and 95% of patients, respectively.[16] The usual dose of oral MPA is 10 mg orally once daily for 7 to 10 days.[11]

Insulin-Sensitizing Agents PCOS-induced amenorrhea may respond well to insulin sensitizing agents.[17] Using metformin for this purpose is discussed in the anovulatory bleeding section.

All patients experiencing amenorrhea should follow a diet rich in calcium and vitamin D to support bone health. Supplemental calcium and vitamin D (1200 mg/800 IU/day) should be recommended for patients with inadequate dietary consumption.[11] Figure 50–3 illustrates treatment recommendations for amenorrhea.[11]

Amenorrhea in Adolescents

Optimal treatment of adolescents diagnosed with amenorrhea, especially primary ovarian insufficiency, includes careful consideration to both the physical and emotional needs of a young patient receiving this diagnosis. It may be difficult to process the emotions to understand the immediate and long-term impacts of amenorrhea diagnosis on long-term fertility. Patients may need higher doses of estrogen than menopausal women in order to ensure adequate replacement and optimal bone health. For patients with absent or incomplete breast development, estrogen therapy should be started and increased slowly before adding progesterone in order to allow for breast development and prevent tubular breast development. Once puberty is complete, the goal becomes maintaining normal ovarian functioning levels of estradiol. Estradiol 100 mcg daily is recommended, either by transdermal, oral, or occasionally transvaginal administration may be considered. Cyclic progesterone should be added for 10 to 12 days each month to help protect against endometrial hyperplasia and endometrial cancer. Oral contraceptives often contain higher doses of estrogen than what is needed and are no longer recommended as first-line therapy.[12]

ANOVULATORY BLEEDING

Anovulatory uterine bleeding is irregular menstrual bleeding from the endometrium ranging from light spotting to heavy blood flow.[18] It includes menstrual bleeding that occurs outside of the normal cyclic bleeding. This bleeding occurs due to the effects of unopposed estrogen. Of note, it does not include bleeding due to uterine anatomic lesions.[18] Many women pursue medical care to regulate menstrual cycles or improve fertility.

Epidemiology and Etiology

Anovulatory uterine bleeding is the most common form of noncyclic uterine bleeding. PCOS is the most common cause, occurring in 8% to 13% of women.[19] Anovulation results from dysfunction at any level of the hypothalamic–pituitary–ovarian axis which can be due to physiologic life stages such as adolescence, perimenopause, pregnancy, and lactation or pathologic causes (see Table 50–2).[18] Anovulation may also occur at any time during the reproductive years due to a pathologic cause. The most common causes of nonphysiologic ovulatory dysfunction are PCOS, hypothalamic amenorrhea, hyperprolactinemia, and premature ovarian failure.

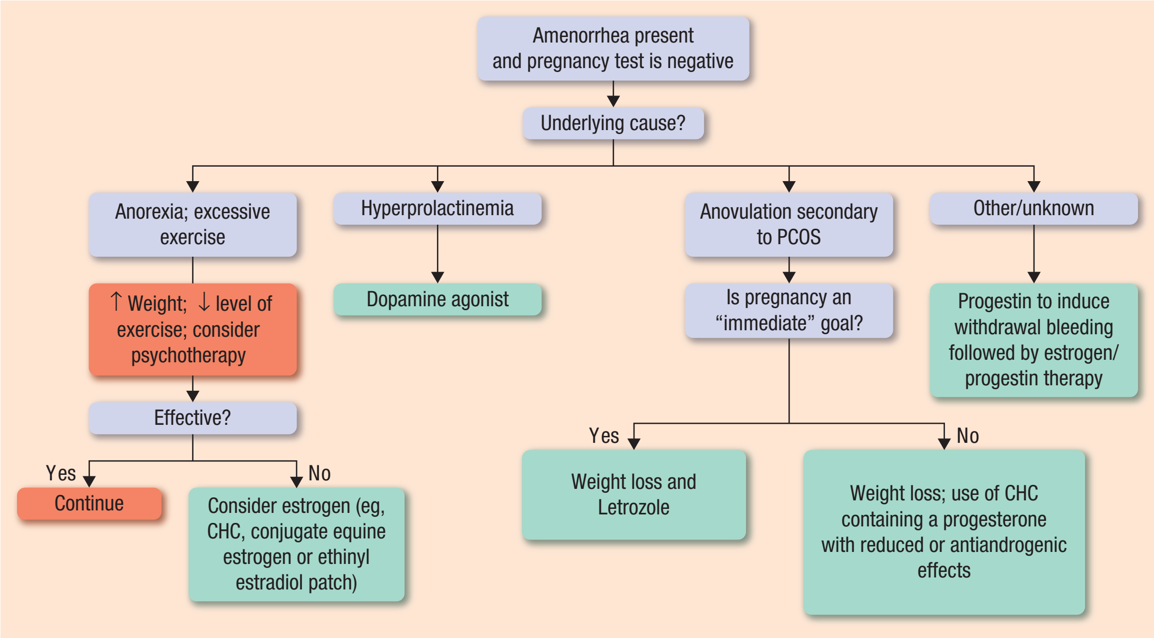
Amenorrhea present and pregnancy test is negative
Underlying cause?
Anorexia; excessive exercise
Hyperprolactinemia
Anovulation secondary to PCOS
Other/unknown
↑ Weight; ↓ level of exercise; consider psychotherapy
Dopamine agonist
Is pregnancy an "immediate" goal?
Progestin to induce withdrawal bleeding followed by estrogen/progestin therapy
Effective?
Yes
No
Continue
Consider estrogen (eg, CHC, conjugate equine estrogen or ethinyl estradiol patch)
Yes
No
Weight loss and Letrozole
Weight loss; use of CHC containing a progesterone with reduced or antiandrogenic effects

FIGURE 50–3. Treatment algorithm for amenorrhea. (CHC, combination hormonal contraceptive; IUD, intrauterine device; PCOS, polycystic ovary syndrome.) Reproduced with permission from DiPiro JT, Yee GC, Posey IM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach. 11th ed. New York City: McGraw-Hill; 2020.

Pathophysiology

In anovulation, a corpus luteum does not develop, and the ovary fails to secrete progesterone. This causes the endometrium to continue proliferation under the influence of unopposed estrogen, and eventually it becomes thick, vascular, and fragile. The clinical result is unpredictable, heavy, noncyclic bleeding, as sporadic sloughing of the endometrium begins to occur[18] (see Table 50–2).

Treatment

▶ *Desired Outcomes*

The desired outcomes are to stop acute bleeding, restore natural cycle of endometrial growth and shedding, decrease long-term complications of anovulation (eg, osteopenia and infertility), and improve QOL.[18]

▶ *Nonpharmacologic Therapy*

Nonpharmacologic treatment options depend on the underlying cause. For women with PCOS, weight loss of 5% to 10% may help improve menstrual regularity, decrease hirsutism, improve insulin sensitivity, and increase response to fertility treatments.[20] In women who have completed childbearing or who have failed medical management, endometrial ablation or resection, and hysterectomy are considered surgical options.

Clinical Presentation and Diagnosis of Amenorrhea

General

- Concerns about cessation of menses and fertility implications
- Generally no acute distress

Symptoms

- Cessation of menses
- Possible reports of infertility, vaginal dryness, decreased libido

Signs

- The absence of menses by age 15 in the presence of normal secondary sexual development or within 5 years of **thelarche** (if occurs before age 10)
- Recent significant weight loss or gain
- The presence of acne, hirsutism, hair loss, or **acanthosis nigricans** suggests androgen excess

Laboratory Tests

- Pregnancy test
- Thyroid-stimulating hormone (TSH)
- Prolactin
- If PCOS is suspected, consider free or total testosterone, 17-hydroxyprogesterone, fasting glucose, and fasting lipid panel.
- If premature ovarian failure is suspected, consider follicle-stimulating hormone (FSH) and luteinizing hormone (LH) measurements.

Other Diagnostic Tests

- Pelvic ultrasound to evaluate for polycystic ovaries
- May consider progesterone challenge, by administering either progesterone 100- to 200-mg intramuscular injection or oral MPA 10 mg daily for 5 to 10 days to see if it induces a menstrual period. If bleeding occurs beyond spotting within 2 weeks after progesterone is given, the amenorrhea is due to anovulation. If no withdrawal bleeding occurs, amenorrhea is due to other causes.

Patient Encounter 2

A 43-year-old woman presents for a gynecologic examination with complaints of galactorrhea and amenorrhea for the last year. All previous Pap smears have been normal, and she denies a history of sexually transmitted infections. She reports history of one sexual partner, her husband, of 10 years. Currently sexually active, she is not on any form of contraception and does not desire any more children. PMH significant for hypertension, type 2 diabetes mellitus, and hirsutism. Current medications include hydrochlorothiazide 25 mg once daily, lisinopril 20 mg once daily, and metformin 1000 mg twice daily. On examination, patient is overweight with mild acne and hirsutism.

Labs: (–) human chorionic gonadotropin (hCG); free testosterone 103 ng/dL (3.6 nmol/L; elevated); TSH 2.7 µIU/mL (mIU/L; WNL); fasting glucose 136 mg/dL (7.5 mmol/L); total cholesterol 198 mg/dL (5.12 mmol/L); LDL cholesterol 115 mg/dL (2.97 mmol/L), HDL cholesterol 60 mg/dL (1.55 mmol/L); triglycerides 68 mg/dL (0.77 mmol/L), prolactin 145 ng/mL (mcg/L; 6300 pmol/L)

Pelvic ultrasound: normal findings

What anovulatory disorder is this patient most likely experiencing?

What pharmacologic therapies are recommended for this patient?

▶ *Pharmacologic Therapy*

Estrogen Table 50–1 summarizes therapeutic agents and doses. Estrogen is the recommended treatment for managing acute bleeding episodes because it promotes endometrial growth and stabilization.[18] CHCs are useful for cycle regulation, helping to provide a more predictable menstrual cycle. For women with PCOS, CHCs also suppress ovarian hormones and adrenal androgen production, and oral agents also indirectly increase sex hormone-binding globulin. This, in turn, binds and reduces circulating androgen.[17,18] Women with high androgen levels or signs of hyperandrogenism (eg, hirsutism, acne) are recommended to start low-dose CHCs (35 mcg or less ethinyl estradiol) and a progesterone with minimal androgenic side effects (eg, norgestimate and desogestrel) or antiandrogenic effects (eg, drospirenone).[20]

Clinical Presentation and Diagnosis of Anovulatory Bleeding

General

- Acute distress may or may not be present.

Symptoms

- Irregular, heavy, or prolonged vaginal bleeding, perimenopausal symptoms (hot flashes, night sweats, vaginal dryness, dyspareunia)

Signs

- Acne, hirsutism, obesity

Laboratory Tests

- If suspect PCOS: free or total testosterone, fasting glucose, fasting lipid panel
- If suspect perimenopause: TSH and FSH

Other Diagnostic Tests

- Pelvic ultrasound to evaluate for polycystic ovaries

Progestins Women who experience side effects or have contraindication(s) to estrogen, or who have abnormal uterine bleeding due to anovulatory bleeding, should consider progesterone-only products. For women with PCOS, depot and intermittent oral MPA suppress pituitary gonadotropins and circulating androgens, leading to endometrial shedding.[19] If contraception is desired, placement of a levonorgestrel-releasing IUD is an option.

Estrogen Modulators Women with anovulatory bleeding from PCOS who are pursuing pregnancy should be seen by a fertility specialist. Women may be treated with letrozole or clomiphene citrate for ovulation induction under specialist care.

Insulin-Sensitizing Agents Metformin improves insulin sensitivity, reduces circulating androgen concentrations, and improves ovulation rates and should be considered for women with PCOS for management of metabolic features.[20] Notably, metformin may increase spontaneous ovulation, and contraception should be used in women with PCOS who do not desire pregnancy.

Anovulatory Bleeding in Adolescents

Anovulation is the most common cause of non-cyclic uterine bleeding in adolescents. Anovulatory bleeding in teenagers can become excessive, persistent, and require medications to treat. The differential diagnosis is similar to adults and should include evaluation for blood dyscrasias.[18,22] Patients should also be evaluated for PCOS by assessing for signs of hyperandrogenism, including acne and hirsutism.[18]

HEAVY MENSTRUAL BLEEDING

Heavy menstrual bleeding describes prolonged menstrual bleeding (lasting > 7 days) or cyclic, heavy menstrual bleeding (> 80 mL per cycle).[23] It can be difficult to quantify menstrual blood loss in clinical practice. Women will often seek medical attention with concerns of containment flow problems, unpredictable heavy flow, reduced QOL, anemia, and other dysmenorrhea symptoms. These women may have blood loss of less than 80 mL but still warrant treatment based on the heavy bleeding's impact on QOL, and social, professional, familial, and sexual aspects of life.

Epidemiology and Etiology

Heavy menstrual bleeding accounts for 18% to 30% of gynecological visits.[24] KEY CONCEPT Causes of heavy menstrual bleeding are divided into systemic disorders and reproductive tract abnormalities. KEY CONCEPT Women presenting with heavy menses should be examined to rule out intrauterine pregnancy, ectopic pregnancy, and miscarriage. Additionally, genital tract malignancies and infections may present with abnormal bleeding.[16] Systemic disorders include coagulation dysfunction such as von Willebrand disease, hemophilia, and platelet function disorders, in addition to hypothyroidism.[16,21,22] Specific reproductive tract causes of abnormal uterine bleeding are more common in older childbearing women, and include fibroids, adenomyosis, endometrial polyps, PID, and gynecologic malignancies.[25,26]

Clinical Presentation and Diagnosis of Heavy Menstrual Bleeding

General

- Acute distress may or may not be present.

Symptoms

- Reports of heavy/prolonged menstrual flow. Associated symptoms may include dysmenorrhea, fatigue, or lightheadedness in the case of severe blood loss.

Signs

- Orthostasis, tachycardia, and pallor may be noted, especially with significant acute blood loss.

Laboratory Tests

- Complete blood count (CBC) and ferritin levels; hemoglobin and hematocrit results may be low.
- TSH to rule out thyroid deficiencies
- If the history dictates, testing may be done to identify coagulation disorder(s) as a cause.

Other Diagnostic Tests

- Pelvic ultrasound
- Pelvic magnetic resonance imaging
- Papanicolaou smear
- Endometrial biopsy
- Hysteroscopy
- Sonohysterogram

Pathophysiology

Table 50–2 describes the pathophysiology of heavy menstrual bleeding and specific conditions resulting in abnormal uterine bleeding.

Treatment

▶ *Desired Outcomes*

Goals of therapy include reducing menstrual blood flow, preventing or correcting iron-deficiency anemia, improving QOL, and deferring the need for surgical intervention. Treatment recommendations are outlined in Table 50–1 and Figure 50–4.

▶ *Nonpharmacologic Therapy*

Surgical interventions may be considered and are based on the clinical stability of the patient, severity of bleeding, contraindications to medical management, and patient response to medical management. Interventions range from endometrial ablation to hysterectomy and are often guided based on the patient's choice to maintain fertility.[16]

▶ *Pharmacologic Therapy*

NSAIDs are beneficial for patients desiring therapy only during menses, and without the need for contraception. They are associated with a 10% to 51% reduction in blood loss and are also beneficial for dysmenorrhea symptoms.[24]

Combination Hormonal Contraceptives CHCs are beneficial to women with heavy menstrual bleeding who do not desire pregnancy and are associated with a 30% to 60% reduction in blood loss.[24] Although many CHCs have been used for heavy menstrual bleeding and it is assumed all will lower menstrual blood loss,

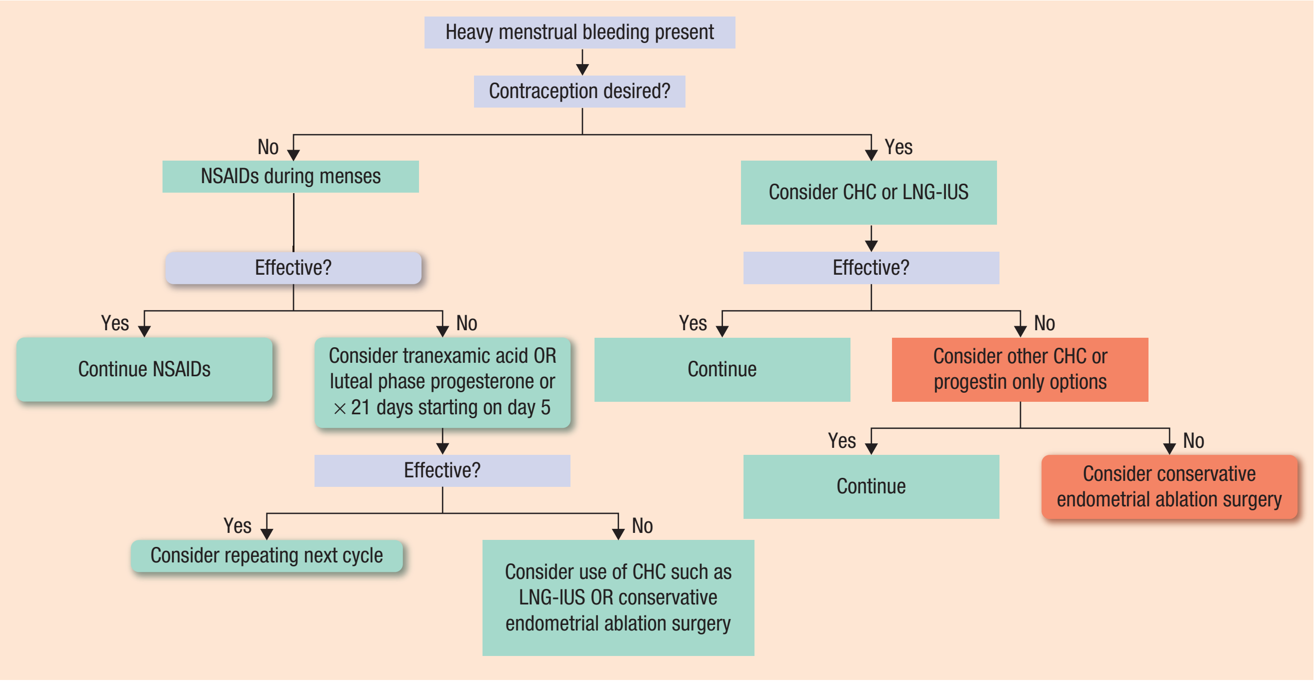
Heavy menstrual bleeding present
Contraception desired?
No
Yes
NSAIDs during menses
Consider CHC or LNG-IUS
Effective?
Effective?
Yes
No
Yes
No
Continue NSAIDs
Consider tranexamic acid OR luteal phase progesterone or × 21 days starting on day 5
Continue
Consider other CHC or progestin only options
Yes
No
Effective?
Continue
Consider conservative endometrial ablation surgery
Yes
No
Consider repeating next cycle
Consider use of CHC such as LNG-IUS OR conservative endometrial ablation surgery

FIGURE 50–4. Treatment algorithm for heavy menstrual bleeding. (CHC, combination hormonal contraceptive; IUD, intrauterine device; NSAID, nonsteroidal anti-inflammatory drug.) Reproduced with permission from DiPiro JT, Yee GC, Posey LM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach. 11th ed. New York City: McGraw-Hill; 2020.

Patient Encounter 3

An 18-year-old female presents for a follow-up for heavy menstrual bleeding. She reports she has been taking naproxen 550-mg loading dose 1 to 2 days prior to menses, followed by 275 mg every 6 to 12 hours during her period each month for the last 18 months. She notes the naproxen seems to have helped with the bleeding; however, her periods are heavy and require a change in supersize tampon every 3 to 4 hours despite continuing NSAID therapy. She reports issues with flow containment and associated embarrassment. She has noticed over the last few months, she feels tired and her hair has thinned. Her last menstrual cycle was 12 days ago, and she entered menarche at age 12. She is not sexually active and she does not take any medications. She is generally very active. Pelvic ultrasound completed and unremarkable.

What diagnostic tests should be considered for the patient?

What nonpharmacologic and pharmacologic therapies are recommended for this patient?

the only agent approved by the Food and Drug Administration (FDA) for heavy menstrual bleeding is the four-phasic formulation containing estradiol valerate and dienogest.[24]

Progestins Heavy menstrual bleeding may also be treated with progestin-only contraceptives. The levonorgestrel IUD reduces menstrual flow by up to 70% to 96% and is considered the most effective treatment to reduce menstrual flow.[24] In a small open-label study, the levonorgestrel 54-mg IUD resulted in a greater blood loss reduction and number of days missed at work or school when compared to oral CHCs.[28] When compared to endometrial ablation, the levonorgestrel IUD causes similar reductions in menstrual blood loss and improved QOL after up to 2 years following treatment. Its use may also help postpone or cancel the need for endometrial ablation or hysterectomy.

Cyclic progestin therapy as oral norethindrone acetate or MPA, either during the luteal phase only or for 21 days of the menstrual cycle, leads to regulation of the menstrual cycle in 50% of women.[26]

Progestin-related side effects are typically greater in women using the levonorgestrel IUD when compared with oral progestin and often include intermenstrual bleeding and breast tenderness.

Patient Care Process

Collect Information:

- Review medical history and physical assessment findings and complete physical examination and review of systems, including gynecological history (eg, start of menarche, presence of galactorrhea, symptoms of androgen excess, review of typical menstrual cycle including frequency, duration, and associated symptoms, sexual history, and history of gynecological infections). Additional workup may be necessary depending on a patient's presenting problem(s) (eg, amenorrhea, abnormal uterine bleeding, anovulatory bleeding, or PCOS), including a pregnancy test or pelvic examination.
- Perform medication history for the use of prescription, nonprescription, and dietary supplements. Determine if any treatments have previously helped with chief complaint(s). Identify allergies to medications or other substances.
- Review current and future desire for children and contraception beliefs and preferences with the patient.

Assess the Information:

- Based on medical history and presenting symptoms, determine which menstruation-related disorder the patient currently has.
- Review available diagnostic data to determine hormonal, reproductive, and pregnancy status.
- Document presenting symptoms and medical history, including pertinent family medical history.
- Based on physical examination, review of symptoms, and patient history, determine if patient is experiencing signs or symptoms of complications from menstruation-related disorder, such as symptoms of anemia in women presenting with abnormal uterine bleeding, or difficulty conceiving in women with amenorrhea or anovulatory bleeding.
- Assess the appropriateness, efficacy, safety, and adherence of current therapy.

Develop a Care Plan:

- Educate patient on lifestyle modifications and nonpharmacological therapy recommendations.
- Select pharmacotherapy, if indicated, that is effective and safe.
- Determine whether long-term maintenance treatment is necessary.
- Discuss the importance of adherence to medication management and lifestyle modifications.

Implement the Care Plan:

- Educate the patient about changes in drug therapy, medication administration, potential adverse effects, and how to manage and report adverse effects that occur.
- Address any patient concerns about their menstruation-related disorder and its management.
- Address any secondary concerns the patient may be experiencing (eg, infertility, anemia, decline in QOL).
- Determine whether the patient has insurance coverage or whether recommended agents are included on the patient's insurance formulary.

Follow-up: Monitor and Evaluate:

- Follow up in 3 to 6 month intervals, or more frequently if needed, to assess efficacy and safety of therapy until goals are met, or symptoms resolved.
- Assess improvement in QOL.
- Review medical history, physical examination findings, and laboratory and diagnostic tests to assess changes in clinical status and continued need for pharmacological therapy.
- Evaluate for adverse drug reactions, drug allergies, and drug interactions.

Tranexamic Acid Tranexamic acid works by preventing fibrin degradation and is effective for patients with chronic abnormal uterine bleeding.[16] Evidence shows it reduces bleeding in patients with chronic issues by 34% to 56%.[4]

Abnormal Uterine Bleeding in Adolescents

An estimated 50% of adolescents with heavy menstrual bleeding have a bleeding disorder, most commonly von Willebrand disease or platelet dysfunction.[22] The incidence of von Willebrand disease is 1% to 2% in the general population; however, an estimated 5% to 36% of adolescents presenting with heavy menses have von Willebrand disease.[22] It is important to assess adolescent women presenting with heavy menstrual bleeding for a potential bleeding disorder.

OUTCOME EVALUATION

Treatment success for menstruation-related disorders is measured by how well the treatment (a) relieves or reverses symptoms, (b) prevents or alleviates complications (eg, osteoporosis, anemia, and infertility), and (c) causes minimal adverse effects. A regular menstrual cycle should resume, with minimal premenstrual or dysmenorrhea symptoms. Depending on the desire for conception and related therapy, these cycles may be ovulatory or anovulatory.

Assess treatment effectiveness in restoring normal menstrual cycles with minimal adverse effects after an appropriate treatment interval (2–3 months). Assess improvement in well-being and QOL (eg, physical, psychological, and social functioning). Evaluate the patient for adverse drug reactions (see Table 50–1), drug allergies, and drug interactions. Table 50–3 lists the expected outcome measures for each discussed menstruation-related disorder.

MENOPAUSE

Epidemiology and Etiology

Menopause is marked by the final menstrual period (FMP) resulting from loss of follicular activity and confirmed by 12 months of amenorrhea.[27] The average age for women to experience menopause is 52 years; however, women who undergo a hysterectomy with bilateral salpingo-oophorectomy experience menopause earlier compared with women who experience natural menopause, due to the removal of the ovarian tissue. Other factors associated with early menopause include low body weight, increased menstrual cycle length, nulliparity, and smoking.

Perimenopause is the transitional period prior to menopause when hormonal and biologic changes begin. It begins with the onset of menstrual cycle irregularities, and/or other menopausal symptoms.[27] Women may still intermittently ovulate during this time.

Physiology

The physiologic changes that occur during the perimenopausal and menopausal periods are caused by the decrease and eventual loss of ovarian follicular activity.[28] As women age, the number of ovarian follicles decrease, and the remaining follicles require higher levels of follicle-stimulating hormone (FSH) for maturation and ovulation. During perimenopause, anovulatory cycles are more likely as the lack of progesterone production leads to irregular and unpredictable menses. During menopause, FSH concentrations may increase 10- to 15-fold, luteinizing hormone (LH) concentrations increase fivefold, and levels of circulating estradiol decrease more than 90%. Due to fluctuations in this increase, FSH and LH levels are not required for diagnosis.[28]

Clinical Presentation and Diagnosis of Menopause

Menopausal Symptoms

- Vasomotor symptoms (hot flashes, night sweats)
- Sleep disturbances
- Mood changes
- Genitourinary syndrome of menopause (genital symptoms such as dryness, burning, or irritation [sometimes described as vulvovaginal atrophy], urinary symptoms such as dysuria, urgency and recurrent urinary tract symptoms; and sexual symptoms of dryness and dyspareunia)
- New-onset depression
- Problems with concentration and memory

Diagnosis

- Amenorrhea for 12 months
- FSH greater than 40 IU/L (mIU/mL)
- Fivefold increase in LH *not required to make diagnosis

KEY CONCEPT Common symptoms of menopause include vasomotor symptoms, and genitourinary syndrome of menopause.[27,29] Additional symptoms may include mood changes, sleep disturbances, new-onset depression, problems with concentration memory, and arthralgias. Menopausal symptoms are often more severe in women with surgically induced menopause compared with natural menopause due to a more rapid decline in estrogen concentrations.[27] Women should undergo laboratory evaluation to rule out other causes, such as abnormal thyroid function or pituitary adenoma, before menopausal hormone therapy (MHT) may be considered.

Treatment

▶ *Desired Outcomes*

MHT is the most effective treatment for moderate-to-severe menopausal symptoms. Treatment goals include alleviating or reducing menopausal symptoms and improving QOL while minimizing adverse effects of therapy. Lowest effective dose, shortest

Patient Encounter 4

A 51-year-old African American woman with a history of hypothyroidism, obesity, and poorly controlled hypertension presents to the clinic complaining of hot flashes, vaginal dryness, dyspareunia, and insomnia. She states that she experiences approximately seven to eight hot flashes per day and is awakened from sleep at least three times per week requiring her to change her bed clothes. Her symptoms began about 6 months ago and have worsened to the point where they are significantly impacting her QOL. Upon questioning, she states she has no past surgical history.

Which of the patient's symptoms and past medical history are consistent with menopause?

What additional information do you need to know in order to make an appropriate therapeutic plan for this patient?

Table 50–3

Hormone Formulations and Dosages[11,15,16]

Product	Available Strengths	Common Dosages
Oral estrogens		
Conjugated estrogens (Premarin)	0.3–1.25 mg	0.3–0.625 mg/day
Esterified estrogens (Menest)	0.3–1.25 mg	0.3–1.25 mg/day
Estradiol (Estrace[a])	0.5–2 mg	1–2 mg/day
Estropipate[a]	0.75–3 mg	0.75–6 mg/day
Transdermal estrogens		
Estradiol patch (Alora, Minivelle, Vivelle-Dot)	0.025–0.1 mg/24 hour	0.025–0.1 mg, changed twice weekly
(Climara,	0.025–0.1 mg/24 hour	0.025–0.1 mg, changed weekly
(Menostar[b])	0.014 mg/24 hour	0.014 mg/ changed weekly
Topical estrogens		
Vaginal creams		
Conjugated estrogens (Premarin)	0.625 mg/g	0.5–2 g/day
Estradiol (Estrace)	0.01%	1 g one to three times/week
Gel		
Estradiol gel		
(Elestrin)	0.06%	1–2 actuations of pump once daily
(EstroGel)	0.06%	1 actuation of pump once daily
(Divigel)	0.1%	0.25 g/day packet once daily
Spray		
Estradiol spray (Evamist)	1.53 mg/actuation	1–3 sprays daily
Vaginal inserts		
Vaginal ring		
Estradiol (Estring)	2 mg	1 ring every 3 months
Estradiol acetate (Femring)	0.05–0.1 mg/24 hour	1 ring every 3 months
Vaginal tablet		
Estradiol (Vagifem)	10-mcg estradiol	One tablet twice weekly
(Yuvafem)	10-mcg estradiol	One tablet twice weekly
Vaginal insert		
Estradiol (Imvexxy)	4–10-mcg estradiol	One insert twice weekly
(Yuvafem)	10-mcg estradiol	One insert twice weekly
Progestogens[c,d]		
Medroxyprogesterone acetate (Provera)	2.5–10 mg	5–10 mg once daily for 12–14 days sequentially per 28-day cycle
Micronized progesterone (Prometrium)	100–200 mg	100 mg once daily for 12–14 days sequentially per 28-day cycle
Norethindrone acetate (Aygestin)	2.5–5 mg	5 mg once daily for 12–14 days sequentially per 28-day cycle
Combination products[d]		
Oral		
Conjugated estrogens + medroxyprogesterone (Prempro; Premphase)	0.3/1.5 mg–0.625/5 mg	One tablet daily
Conjugated estrogens + bazedoxifene (Duavee)	0.45 mg/20 mg	One tablet daily
Estradiol + norethindrone (Activella; Amabelz, Mimvey; Lopreeza)	0.5 mg/0.1 mg–1 mg/0.5 mg	One tablet daily
Estradiol + drospirenone (Angeliq)	0.5 mg/0.25 mg–1mg/0.5 mg	One tablet daily
Ethinyl estradiol + norethindrone acetate (Femhrt low dose, Fyavolv)	2.5 mcg/0.5 mg–5 mcg/1 mg	One tablet daily
Estradiol + norgestimate (Prefest)	1 mg/0.09 mg	One tablet daily
Estradiol + progesterone (Bijuva)	1 mg/100 mg	One capsule daily in evening
Transdermal		
Estradiol + norethindrone acetate (CombiPatch)	0.05/0.14–0.05/0.25 mg/24 hour	Apply one patch twice weekly
Estradiol + levonorgestrel (Climara Pro)	0.045/0.015 mg/24 hour	Apply one patch once weekly

[a] FDA-approved commercially available bioidentical product.

[b] Indicated for the prevention of postmenopausal osteoporosis only

[c] May be administered cyclically or continuously.

[d] Dose varies based on daily or cyclic administration.

CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate.

duration possible, and appropriate regimen and route of administration should be used to minimize risk.

▶ *General Approach to Treatment*

There are a number of national and international guidelines and consensus statements available on the management of menopause.[28-37] Women who seek medical treatment usually have symptoms that diminish their QOL. An assessment confirming that vasomotor symptoms (VMS) are adversely affecting sleep, daytime functioning, or QOL should be completed prior to initiating prescription hormone therapy.[34] **KEY CONCEPT** Women should undergo a risk factor assessment for absolute contraindications including breast or endometrial cancer; cardiovascular disease including coronary heart disease (CHD), stroke, or transient ischemic attack; active liver disease; and undiagnosed vaginal bleeding before MHT is considered and shared decision-making should be utilized to select appropriate therapy (Figure 50–5). Nonhormonal options are available for women who have contraindications or are unwilling to take MHT, but these options may have limited evidence for efficacy and safety.

▶ *Nonpharmacologic Therapy*

Evidence for efficacy and safety of nonpharmacologic therapy is limited. Group- and individual-based cognitive-behavioral therapy, clinical hypnosis, and yoga have limited evidence showing benefit for VMS.[27,28,38,39] Mindfulness-based stress reduction and weight loss may also be recommended. Due to the minimal adverse effects of these interventions, patients should try behavioral modifications prior and in addition to pharmacologic therapy. Cooling techniques, avoidance of triggers, exercise, and relaxation are not recommended for relief of VMS, as there are negative, insufficient, or inconclusive data supporting their use. First-line therapies to alleviate symptoms of mild genitourinary syndrome of menopause (GSM) include nonhormonal vaginal lubricants and moisturizers; however, evidence supporting the efficacy of these products is limited.[29]

▶ *Pharmacotherapy: Hormonal Therapy*

After assessment for appropriate indications and performance of a risk factor assessment, systemic MHT may be recommended for patients less than 60 years of age, with menopause onset within 10 years, and at a low risk of breast cancer or cardiovascular disease.[34] MHT can be considered with caution in those greater than 60, with menopause onset greater than 10 years prior; or with moderate risk of breast cancer or cardiovascular disease. MHT should be avoided in those with a high risk of breast cancer; or a high risk of cardiovascular disease; or those greater than 60, greater than 10 years since menopause onset, and at a moderate risk.

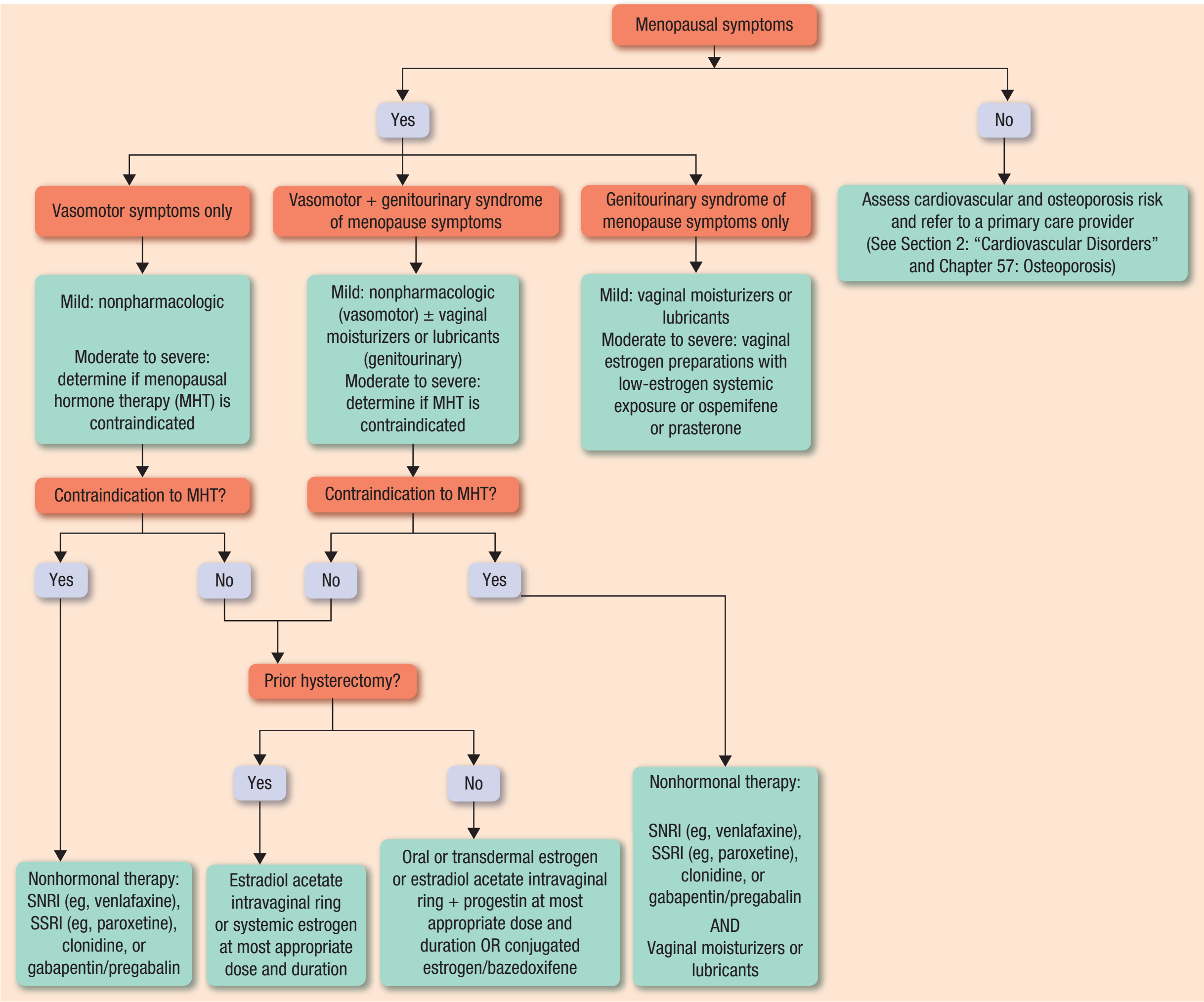
Menopausal symptoms
Yes
No
Vasomotor symptoms only
Vasomotor + genitourinary syndrome of menopause symptoms
Genitourinary syndrome of menopause symptoms only
Assess cardiovascular and osteoporosis risk and refer to a primary care provider (See Section 2: "Cardiovascular Disorders" and Chapter 57: Osteoporosis)
Mild: nonpharmacologic
Moderate to severe: determine if menopausal hormone therapy (MHT) is contraindicated
Mild: nonpharmacologic (vasomotor) ± vaginal moisturizers or lubricants (genitourinary)
Moderate to severe: determine if MHT is contraindicated
Mild: vaginal moisturizers or lubricants
Moderate to severe: vaginal estrogen preparations with low-estrogen systemic exposure or ospemifene or prasterone
Contraindication to MHT?
Contraindication to MHT?
Yes
No
No
Yes
Prior hysterectomy?
Yes
No
Nonhormonal therapy:
SNRI (eg, venlafaxine), SSRI (eg, paroxetine), clonidine, or gabapentin/pregabalin
AND
Vaginal moisturizers or lubricants
Nonhormonal therapy: SNRI (eg, venlafaxine), SSRI (eg, paroxetine), clonidine, or gabapentin/pregabalin
Estradiol acetate intravaginal ring or systemic estrogen at most appropriate dose and duration
Oral or transdermal estrogen or estradiol acetate intravaginal ring + progestin at most appropriate dose and duration OR conjugated estrogen/bazedoxifene

FIGURE 50–5. Treatment algorithm for postmenopausal women. (MHT, menopausal hormone therapy; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor) Reproduced with permission from DiPiro JT, Yee GC, Posey LM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach. 11th ed. New York City: McGraw-Hill; 2020.

Patient Encounter 5: Medical History, Physical Examination, and Diagnostic Tests

The workup reveals the following additional information:

PMH: Hypertension since age 45, currently poorly controlled; hypothyroidism since age 25; obesity

FH: Father: Deceased due to MI at age 54. Mother: Alive with hypothyroidism, HTN, and diabetes. Siblings: Two, noncontributory history

SH: Occupation: civil engineer; nonsmoker; drinks one glass of red wine with dinner on the weekends; smokes marijuana two times per month

Meds: lisinopril 5 mg by mouth once daily; levothyroxine 0.1 mg by mouth once daily; takes all medications 30 minutes before breakfast. Occasionally forgets to take lisinopril.

ROS: (+) hot flashes (+) dyspareunia; (+) vaginal dryness; (+) insomnia, (–) bowel changes, 5-lb (2.3 kg) weight gain since last visit 6 months ago.

PE:

Gen: WDWN woman in NAD

VS: BP 140/78, P 78, RR 16, T 37.0°C (98.6°F), Ht 5′6″ (168 cm), Wt 83.4 kg (184 lbs)

HEENT: WNL

Neck: Supple; no bruits, no adenopathy, no thyromegaly

Breasts: Supple; no masses

CV: RRR, normal S_1 and S_2; no MRG

Abd: Soft, nontender, nondistended; (+) BS, no masses

Genitourinary: Pelvic examination normal except (+) mucosal atrophy; stool guaiac (–)

Ext: (–) CCE; pulses intact

Neuro: normal sensory and motor

Labs:

FSH: 105 mIU/mL (IU/L)

TSH: 2.46 μIU/mL (mIU/L)

Chem-7 (fasting): Na 136 mEq/L (mmol/L), K 4.2 mEq/L (mmol/L), Cl 104 mEq/L (mmol/L), CO_2 25 mEq/L (mmol/L), BUN 9 mg/dL (3.2 mmol/L), SCr 0.9 mg/dL (80 μmol/L), Glucose 90 mg/dL (5.0 mmol/L)

CBC: Hgb 13 g/dL (130 g/L or 8.07 mmol/L), Hct 39% (0.39 volume fraction), WBC 4.5 × 10^3/mm^3 (5.5 × 10^9/L), platelets 250 × 10^3/mm^3 (250 × 10^9/L)

Fasting lipid levels: Total cholesterol (TC) 200 mg/dL (5.17 mmol/L), low-density LDL 128 mg/dL (3.31 mmol/L), HDL 48 mg/dL (1.24 mmol/L), triglycerides 120 mg/dL (1.36 mmol/L)

Assess the patient's condition based on this additional information.

What are the goals of treatment for this patient?

Conduct a risk factor assessment for this patient.

Recommend nonpharmacologic and pharmacologic treatment for this patient. Justify your recommendations.

Estrogens Estrogen is indicated for moderate-to-severe VMS with or without GSM. It is also indicated for the prevention of postmenopausal osteoporosis in women with significant risk; however, it is recommended that nonestrogen medications be used first line if the sole indication is osteoporosis.[34] Appropriate dose, duration, regimen, and route of administration should be utilized at the lowest effective dose of MHT. Topical vaginal products in the form of creams, tablets, or certain rings should only be prescribed for women experiencing GSM without VMS.

The transdermal route of administration bypasses the liver and has shown to have less risk of venous thromboembolism (VTE) and gallbladder disease.[28,33,39] Transdermal estrogen preparations are usually prescribed for patients who experience adverse effects, elevated triglycerides, or liver function abnormalities while taking an oral product. Low-dose vaginal estrogens are available in several forms and comparative analysis have found similar efficacy in the alleviation of GSM.[29]

Progestogens KEY CONCEPT Women who have an intact uterus should be prescribed a progestogen in addition to estrogen due to the increased risk of endometrial hyperplasia and endometrial cancer with estrogen monotherapy (unopposed estrogen).[27] Women with an intact uterus and on estrogen therapy must always be prescribed a progestogen or selective estrogen receptor modulator (SERM), bazedoxifene, for endometrial protection. Progestogens should be prescribed for at least 12 to 14 days of the month and often are prescribed continuously. Table 50–3 lists estrogen and progestogen preparations and dosages.

Adverse Effects

Estrogen therapy with or without a progestogen should be initiated at the lowest dose in order to minimize adverse effects. Changing preparations, particularly the progestogen, or changing the method of administration may alleviate adverse effects. Table 50–4 lists the adverse effects that may be associated with estrogen and progestogen preparations. Adverse effects associated with the use of vaginal estrogen include vaginal discharge, vulvovaginal candidiasis, vaginal bleeding, and breast pain.[29] Trials have not demonstrated an increase in risk of endometrial or breast cancer, VTE, or cardiovascular outcomes with vaginal estrogen therapy.

Contraindications

Systemic MHT is contraindicated in women with unexplained vaginal bleeding, severe active liver disease, prior estrogen-sensitive breast or endometrial cancer, coronary heart disease (CHD), stroke, dementia, personal history or inherited high risk of thromboembolic disease, porphyria cutanea tarda, or hypertriglyceridemia.[28]

Methods of Administration

▶ *Continuous Estrogen and Cyclic Progestogen*

Estrogen is administered daily, and progestogen is administered for 12 to 14 days of the month. Menses returns in approximately 90% of women 1 to 2 days following the last progestogen dose. Women may view this scheduled bleeding as an advantage as it limits spotting.

Table 50–4

Adverse Effects of Systemic Estrogens and Progestogens[5,11,15,16]

Estrogens
Common adverse effects
- Nausea
- Headache
- Bloating
- Breast tenderness
- Breakthrough uterine bleeding

Serious adverse effects
- Coronary heart disease
- Stroke
- Venous thromboembolism
- Breast cancer
- Gallbladder disease

Progestogens
Common adverse effects
- Nausea
- Headache
- Weight gain
- Bleeding
- Irritability
- Depression

Serious adverse effects
- Venous thromboembolism (in combination with estrogen)
- Breast cancer (in combination with estrogen)
- Decreased bone mineral density (effect of injectable medroxyprogesterone acetate)

▶ *Continuous Combined Estrogen and Progestogen*

Estrogen and progestogen are administered daily and result in endometrial atrophy; therefore, women do not experience withdrawal bleeding but may experience unanticipated breakthrough bleeding or spotting. Continuous combined regimens offer the best protection against endometrial hyperplasia and cancer. If bleeding persists beyond 6 to 12 months, women should seek medical attention to rule out endometrial hyperplasia or cancer.

Benefits of HT

▶ *Vasomotor Symptoms*

If after VMS severity assessment and risk factor assessment is conducted, it is decided to initiate MHT, pharmacotherapy should be individualized and reassessed every 6 to 12 months. During reassessment visits, discontinuation of therapy should be considered if severity becomes mild or contraindications arise. Extended treatment duration may be warranted for relief of persistent VMS and prevention of bone loss when unable to tolerate therapy primarily indicated for osteoporosis.[28]

▶ *Genitourinary Symptoms of Menopause*

Topical vaginal preparations should be prescribed for women with moderate-to-severe GSM who do not respond to lubricants and moisturizers. If VMS are also present, systemic MHT is warranted. Vaginal estrogen does not require supplementation with a progestogen in women using low doses; however, women with an increased risk of endometrial cancer may warrant endometrial surveillance.[40] Intermittent progestogen therapy may be considered for women at high risk for endometrial cancer. A vaginal estrogen product may also be considered in women with VMS and GSM receiving systemic MHT with adequate VMS relief but lacking adequate GSM relief in an effort to reduce additional systemic exposure. Estradiol in the form of a vaginal tablet or ring is not significantly absorbed systemically, with the exception of the estradiol vaginal ring 0.05 to 0.1 mg/24 hour which is the only vaginal ring indicated for VMS.

Risks of MHT

The Women's Health Initiative (WHI) was a large, randomized, double-blind, placebo-controlled trial conducted to evaluate the effect of MHT on several outcomes including cardiovascular disease, osteoporosis/fracture risk, and certain cancers.[41,42] The two arms of the WHI included a CEE plus MPA in women with an intact uterus and CEE monotherapy in women without. Both arms were terminated early due to a significant increase in risk (stroke, VTE, and breast cancer in estrogen plus progestogen and stroke in the estrogen monotherapy).

▶ *Cardiovascular Disease*

There is an increased risk of CHD and stroke with daily MHT compared with placebo in women with an intact uterus without established CHD.[43,44] Women who initiate MHT greater than 10 years after menopause have an increased cardiovascular risk.[28,45] MHT should not be prescribed for the prevention of CHD or in patients with preexisting CHD.

▶ *Breast Cancer*

There may be an increased risk of breast cancer with the use of MHT in older women and in those who initiate therapy within 5 years of menopause.[41,46] A significant increased risk of breast cancer was not noted in women using CEE monotherapy in the WHI.[42] In a long-term follow-up study from the WHI, the use of CEE alone compared to placebo was associated with a significantly lower risk of breast cancer incidence and breast cancer mortality.[47] In contract, women in the CEE + MPA arm had a significantly higher risk of breast cancer incidence compared to placebo and no difference was found in breast cancer mortality. Whether MHT is associated with an increased risk for breast cancer recurrence is still questionable. Women with a history of breast cancer, and possibly even a strong family history of breast cancer, should avoid the use of MHT and consider nonhormonal therapies for the treatment of VMS. In the management of GSM for women with a high risk of breast cancer, the use of local MHT may be an option for some women who fail nonpharmacologic and nonhormone treatments. This decision should include a discussion of risks and benefits and review by the patient's oncologist. Increased risk of breast cancer with local MHT is highly unlikely.[29]

▶ *Venous Thromboembolism*

There is an increased risk for VTE with MHT, which may be dose related.[41] MHT administered orally is associated with a higher risk compared with the transdermal route.[39]

Discontinuation of MHT

KEY CONCEPT When treating moderate-to-severe postmenopausal symptoms, the benefit-to-risk ratio appears to be best when MHT is started close to the time of menopause. MHT therapy should be tapered at discontinuation to limit the recurrence of hot flashes. Although VMS subside for most women within 4 years, approximately 10% will continue to experience symptoms. Literature suggests that one of every four women needs to be reinitiated on MHT due to persistent and bothersome symptoms. There are few studies to guide the optimal method of discontinuation, but slowly discontinuing MHT over 3 to 6 months after 4 to 5 years of therapy is considered reasonable and associated with less risk of recurrent symptoms while mitigating the increase in breast cancer risk that occurs at this time.[28,40] Women experiencing menopause prior to age 45 should be encouraged to use MHT until the natural average age of menopause onset.

Alternative Hormonal Treatments

▶ *Selective Estrogen Receptor Modulators (SERMs)*

Although estrogen +/– progestogen remains first-line therapy for the relief of moderate-to-severe VMS with or without GSM, additional hormone options utilizing SERMs are available.

Ospemifene is approved for the treatment of vaginal dryness and moderate-to-severe dyspareunia. Ospemifene acts as an estrogen agonist in some tissues (vaginal and endometrial) and antagonist in other tissues. Ospemifene's action on the endometrium resulted in a black-boxed warning for caution in women with an intact uterus due to a potential for increased risk of endometrial cancer in a woman with an intact uterus who takes unopposed estrogen therapy. Although labeling states that ospemifene should not be used in patients with known or suspected breast cancer, some studies have found a decreased risk.[28,29]

CEEs 0.45 mg/bazedoxifene (BZA) 20 mg (Duavee), the first tissue-selective estrogen complex, is approved for the treatment of postmenopausal osteoporosis and moderate-to-severe VMS in women with an intact uterus.[28] CEE/BZA acts as an agonist in bone tissue and an antagonist in breast and uterine tissue. Adverse effects with CEE/BZA are minimal with musculoskeletal symptoms reported most commonly. Efficacy appears to be similar to CEE/MPA, with potentially less occurrence of estrogen-like adverse effects with CEE/BZA. An advantage of the formulation may be for women intolerant to progestogen adverse effects or when progestogen is contraindicated; however, because no long-term data are available, the same precautions and contraindications as estrogen products should be assumed.

▶ *Dehydroepiandrosterone (DHEA)*

Dehydroepiandrosterone (DHEA) is a precursor hormone for the synthesis of estrone, estradiol, and testosterone and was recently approved for intravaginal administration as prasterone for the treatment of moderate-to-severe dyspareunia.[48] Prasterone is not recommended in women with a history or suspected breast cancer and in women with abnormal uterine bleeding. The most common adverse effects are vaginal discharge and abnormal Pap smear. Unlike other estrogen products, prasterone is not contraindicated in women with a history of VTE or endometrial hyperplasia.

▶ *Bioidentical MHT*

The term bioidentical hormones refers to exogenous hormones that are identical to those produced in a woman's body (eg, estradiol, estrone, estriol, and progesterone) that are either commercially manufactured (such as micronized progesterone and estradiol) or custom-compounded into formulations such as topical creams, gels, and suppositories. Custom-compounded formulations utilizing bioidentical hormones may be subject to higher out-of-pocket costs and are not subject to the same US FDA regulations as commercially manufactured prescription products; therefore, the efficacy and safety data are lacking.[28,49-51] A recent publication from the National Academies of Sciences, Engineering, and Medicine makes the following recommendations regarding compounded bioidentical hormone therapy (cBHT): restrict use to allergy and not patient preference alone; review cBHT as candidates for the FDA Difficult to Compound List; improve education for prescribers and pharmacists marketing, prescribing, compounding, and dispensing cBHT preparations; additional federal- and state-level oversight to address safety and effectiveness concerns; collect and disclose conflicts of interest; and strengthen and expand on evidence base for safety and effectiveness of cBHT.[52]

Patient Encounter 6

The patient has been in good health for the past 9 years and is now 60. She reports adherence with her medications, a healthy diet and exercise routine, and her medical conditions are controlled. However, 2 months ago, she had a heart attack. She is concerned that her hormone therapy may have caused this.

Educate the patient regarding the risk of CHD and MHT.

▶ *Perimenopausal Contraception*

During the perimenopausal period, women may experience hot flashes despite continued menstrual cycles. CHCs can provide relief of VMS while also providing contraception and decreasing risk of ovarian and endometrial cancer. In perimenopausal women who may have contraindications for CHC, a progestin-only IUD may be used.

Nonhormonal and Alternative Treatments

Nonhormonal and alternative therapies (Table 50–5) have been studied for symptomatic management of VMS.[38] **KEY CONCEPT** The limited, and often conflicting, evidence demonstrates that these agents are only modestly effective compared to MHT and have adverse effects.

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) reduce the frequency of hot flashes by increasing serotonin in the central nervous system. Of the SSRIs, paroxetine mesylate is the only one approved to treat VMS and has the most published data demonstrating a reduction in hot flashes.[37] Other SSRIs and SNRIs such as escitalopram, citalopram, fluoxetine, sertraline, venlafaxine, and desvenlafaxine may also be effective. SSRIs and SNRIs should be considered for women who are unwilling or unable to take MHT, particularly those who suffer from depression or anxiety.

Gabapentin, pregabalin, and clonidine have also been studied for the management of menopausal symptoms and have demonstrated reductions in severity and frequency of hot flashes.[53] Clonidine has demonstrated reductions in hot flashes but to a lesser extent than gabapentin.[37]

Phytoestrogens are plant sterols that are structurally similar to human and animal estrogen. There are differences among classes

Patient Encounter 7

It has been 6 months since this patient discontinued taking MHT secondary to her heart attack. She presents to her PCP for follow-up with a chief complaint of occasional mild hot flashes and recurrent severe vaginal dryness and dyspareunia.

Recommend the most appropriate therapy for her recurrent mild hot flashes and GSM.

Table 50–5

Nonhormonal Therapies for Menopause[13,39,40,42]

Product	Initial Dose	Common Dosages	Potential Adverse Effects
Venlafaxine[a,b] (Effexor, Effexor XR	37.5 mg	37.5–150 mg/day	Nausea, HA, somnolence, dizziness, insomnia, hypertension, xerostomia constipation, diaphoresis, weakness
Desvenlafaxine[a,b] (Pristiq)	25–50 mg/day	100–150 mg/day	Nausea, xerostomia, constipation, vomiting, anorexia, dizziness, drowsiness, and insomnia
Paroxetine mesylate[c] (Brisdelle)	7.5 mg	7.5 mg/day	Nausea, somnolence, insomnia, HA, dizziness, xerostomia, constipation, diarrhea, weakness, diaphoresis
Paroxetine CR (Paxil CR)	12.5 mg CR	12.5 mg–25 mg CR/day	
Paroxetine HCl (Paxil)	10–20 mg	10–20 mg/day	
Citalopram (Celexa)	10 mg/day	10–20 mg/day	Xerostomia, nausea, drowsiness, and insomnia
Escitalopram (Lexapro)	10 mg/day	10–20 mg/day	Nausea, insomnia, drowsiness, and headache
Clonidine (Catapres, Catapres TTS)	0.1 mg/day	0.1–0.4 mg/day	Drowsiness, dizziness, hypotension, dry mouth
Gabapentin[a] (Neurontin)	300 mg at bedtime	900 mg/day, divided in three daily doses (up to 2400 mg/day)	Somnolence and dizziness (can decrease with gradual increase in dosing)
Pregabalin[a] (Lyrica)	75 mg twice daily	150–300 mg/day	Peripheral edema, dizziness, drowsiness, ataxia, headache, fatigue, weight gain, infection, diplopia, and tremor

[a] Dosage adjustments recommended in patients with renal impairment.

[b] Dosage adjustment recommended in patients with hepatic impairment.

[c] FDA approved for the treatment of moderate to severe hot flashes associated with menopause.

HA, headache.

of phytoestrogens and biologic potencies vary, making it difficult to recommend specific dosing. The most commonly studied phytoestrogen is the isoflavone class. These products should not be considered in women with a history of estrogen-dependent cancers due to unknown effects. Isoflavones are modestly effective in relieving menopausal symptoms.[37,54]

Black cohosh may be used as an alternative therapy for VMS.[37] The mechanism of action, safety profile, drug–drug interactions, and adverse effects of black cohosh remain unknown. However, there have been case reports of hepatotoxicity with its use. It is not recommended for more than a 6-month period of time. Other alternative treatments that have been utilized but are not effective include dong quai, red clover leaf, kava, and evening primrose oil.

OUTCOME EVALUATION

Evaluating the outcomes of any therapy for menopausal symptoms focuses primarily on the woman's report of symptom resolution. Monitor for breakthrough bleeding or spotting and refer to a primary care provider if abnormal or heavy bleeding occurs.[27] Monitor subjective parameters such as adverse effect occurrence, contraindication occurrence, and adherence. Objective parameters, including blood pressure, should also be monitored. Encourage yearly clinical breast examinations, mammograms, lipid panel, and thyroid-stimulating hormone (TSH) determination, particularly for women with hypothyroidism on thyroid therapy, and conduct a BMD test as indicated. Also perform endometrial studies, as necessary, in women with undiagnosed vaginal bleeding. Frequent follow up, proper monitoring, and education will help to ensure that the woman achieves optimal results from any therapy chosen to treat menopausal symptoms.

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Patient Care Process

Collect Information:

- Obtain the chief complaint and history of present illness regarding symptomatology of VMS and GSM.
- Obtain patient health and functional goals for the treatment of VMS and GSM.
- Obtain a medical history that includes past medical history, social history, family history, surgical history, allergies, and information from a hot flash diary if the patient keeps one.
- Obtain a thorough medication history, including the use of over-the-counter and herbal products.

Assess the Information:

- Evaluate for the presence of VMS and GSM.
- Rule out other medical conditions that could be contributing to symptoms and manage those conditions prior to initiating therapy for symptoms.

(Continued)

Patient Care Process (*Continued*)

- If the patient is experiencing bothersome VMS with or without GSM, consider the use of MHT only after risk factor and contraindication assessment.
- If the patient has a contraindication or does not wish to use MHT, consider alternative, nonhormonal treatments for VMS.
- Consider appropriate nonpharmacologic interventions.

Develop a Care Plan:

- Create a patient-centered pharmacologic plan in conjunction with the health care provider.
- Create a patient-centered nonpharmacologic plan.

Implement the Care Plan:

- Recommend the appropriate dose of a pharmacologic agent and duration, regimen, and route of administration that are patient-specific and aim to utilize the lowest effective dose of MHT.
- Document findings and recommendations.
- Discuss the importance of adhering to the medication regimen.
- Discuss methods of administration, potential adverse effects, and expectations of therapy.
- Discuss lifestyle or behavioral interventions that may help to alleviate VMS and GSM.

Follow-up: Monitor and Evaluate:

- Efficacy: monitor for reduction in VMS, GSM, improvements in sleep, and QOL.
- Safety: monitor for breakthrough bleeding and spotting, adverse effects of MHT, blood pressure at every outpatient visit, yearly mammograms, yearly TSH, and endometrial studies in women with undiagnosed vaginal bleeding.
- Assess symptoms every 6 to 12 months, and consider tapering the MHT dose and discontinuing treatment after 4 to 5 years. If VMS return, determine whether a longer tapering schedule is warranted or if long-term treatment is necessary. If treatment beyond 5 years is necessary, consider switching to a nonhormonal product.

Abbreviations Introduced in This Chapter

BMD	Bone mineral density
cBHT	Compounded bioidentical hormone therapy
CEE	Conjugated equine estrogens
CHC	Combination hormonal contraceptive
CHD	Coronary heart disease
DHEA	Dehydroepiandrosterone
FMP	Final menstrual period
FSH	Follicle-stimulating hormone
GSM	Genitourinary syndrome of menopause
hCG	Human chorionic gonadotropin
IUD	Intrauterine device
LH	Luteinizing hormone
MHT	Menopausal hormone therapy
MPA	Medroxyprogesterone acetate
NSAID	Nonsteroidal anti-inflammatory drug
PCOS	Polycystic ovary syndrome
PID	Pelvic inflammatory disease
QOL	Quality of life
SERMs	Selective estrogen receptor modulators
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TSH	Thyroid-stimulating hormone
VMS	Vasomotor symptoms
VTE	Venous thromboembolism
WHI	Women's Health Initiative

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51

Erectile Dysfunction

Cara Liday

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the pathophysiology of erectile dysfunction (ED).
2. Recognize risk factors and medications associated with the development of ED.
3. List the goals of therapy when treating ED.
4. Describe current nonpharmacologic and pharmacologic options for treating ED, and determine appropriate first- and second-line therapies for a specific patient.
5. Identify patients with significant cardiovascular risk and recommend an appropriate treatment approach for their ED.
6. Identify contraindications for the use of phosphodiesterase type 5 (PDE5) inhibitors.
7. Compare and contrast the benefits and risks for current PDE5 inhibitors.
8. Assess reasons for PDE5 failure and determine an optimal approach to improve treatment efficacy.

INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent inability to achieve or maintain an erection sufficient for sexual intercourse.[1] ED is the most prominent sexual disorder in men and can lead to lower quality of life and self-esteem.[2] Other male sexual complaints include libido and ejaculatory disorders, but these are not considered ED.

EPIDEMIOLOGY AND ETIOLOGY

The incidence of ED increases with age. Few men report erection problems before age 40, but one study reported rates as high as 61% in men aged 40 to 69 years and 77% in men older than 70 years.[3] The increase in incidence could be due to physiologic changes that occur with aging, the onset of chronic disease states associated with ED, increased medication use, lifestyle factors, or a combination of the above.

PATHOPHYSIOLOGY

The penis consists of three components, two dorsolateral corpora cavernosa and a ventral corpus spongiosum that surrounds the penile urethra and distally forms the glans penis. The corpora are composed of sinusoidal spaces that are encased in a fibrous sheath called the tunica albuginea.

In the flaccid state, a balance exists between blood flow into and out of the corpora cavernosa. Sexual stimulation triggers a reduction in sympathetic tone and an increase in parasympathetic activity. This stimulates the release of nitric oxide (NO), which in turn enhances the production of cyclic guanosine monophosphate (cGMP). The enzyme phosphodiesterase type 5 (PDE5) is responsible for the catabolism of cGMP within the cavernosal tissue. Prostaglandins, E_1 and E_2, stimulate increased production of cyclic adenosine monophosphate (cAMP). Increased cAMP and cGMP concentrations ultimately lead to smooth muscle relaxation and increased blood flow into the cavernosal spaces. As the spaces become engorged, pressure increases, subtunical venules (very small veins) are compressed by the tunica albuginea, and the penis becomes rigid and elongated (Figure 51–1).

Detumescence, or return of the penis to a flaccid state, occurs with an increase in norepinephrine. This results in smooth muscle contraction, a reduction in blood inflow, decompression of the sinusoidal spaces, and enhanced outflow.

Testosterone also plays a significant albeit complex role in erectile function. In addition to stabilization of intracavernosal levels of NO synthase, the enzyme responsible for triggering the NO cascade, testosterone, is responsible for much of a man's libido. While low testosterone has been associated with ED[5], normal or low serum testosterone levels are not a strong indicator of ED.

Normal penile erections are complex events that require the full function of the vascular, neurologic, hormonal, and psychological systems. Anything that affects the function of these systems may lead to ED. **KEY CONCEPT** ED can be classified as organic, psychogenic, or a mixture of these. Organic dysfunction includes abnormalities in the vascular, hormonal, or neurologic systems or may be medication-induced (Tables 51–1 and 51–2). It is estimated that 10% to 25% of ED cases are due to medications. Note that many of the risk factors for ED are the same as those for cardiovascular (CV) disease, including hypertension, diabetes, dyslipidemia, smoking, obesity, metabolic syndrome, and sedentary behavior. In many patients, ED is the first indication of the endothelial dysfunction associated with CV, with a time between onset of ED and a CV event of 2 to 5 years.[7] The presence of ED risk factors leads to the assumption that the patient has organic dysfunction. Most commonly, medical conditions that impair arterial flow into or out of the erectile tissue or affect the innervation will be strongly associated with ED. Patients with diabetes mellitus have exceptionally high rates of ED as a result

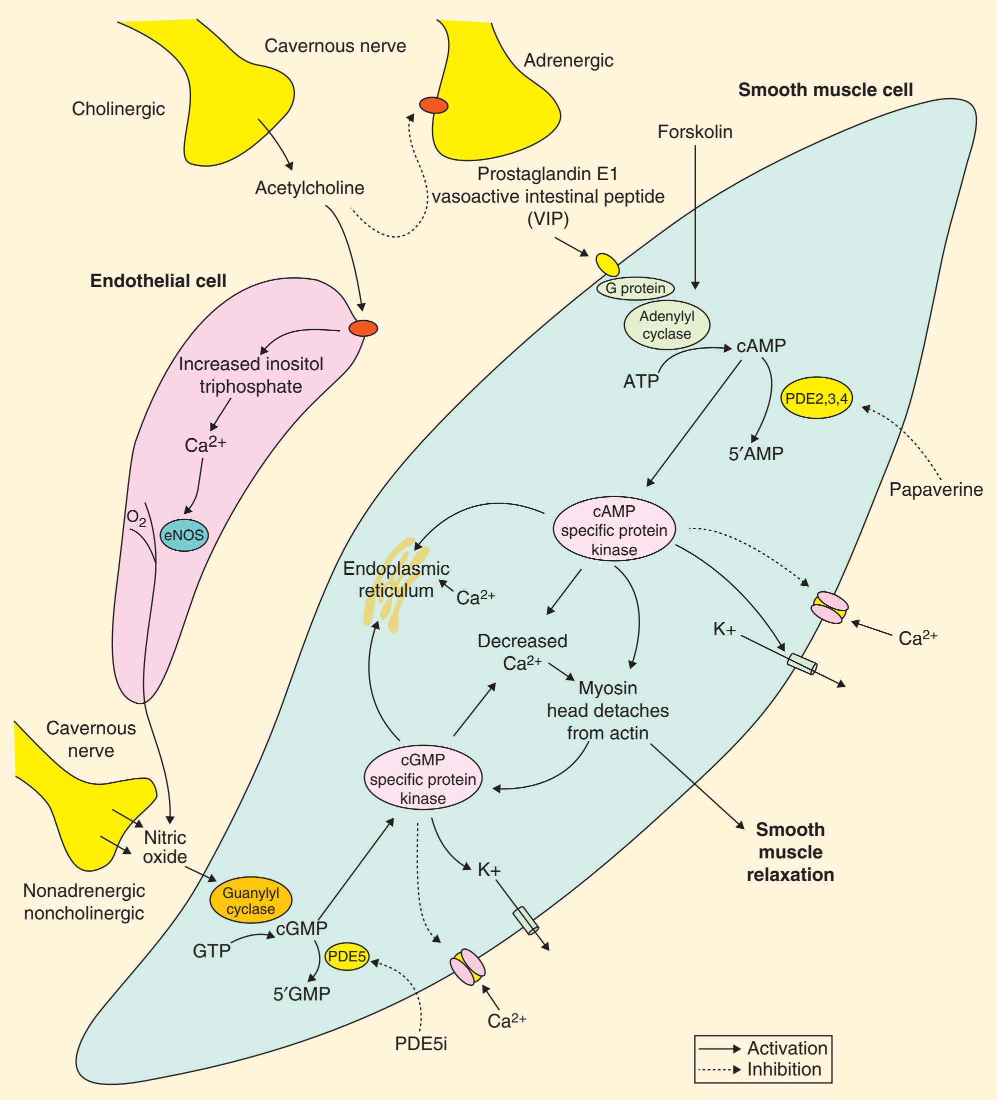

Cavernous nerve
Cholinergic
Adrenergic
Smooth muscle cell
Forskolin
Acetylcholine
Prostaglandin E1
vasoactive intestinal peptide
(VIP)
Endothelial cell
G protein
Adenylyl cyclase
cAMP
ATP
PDE2,3,4
Increased inositol
triphosphate
Ca^{2+}
5′AMP
Papaverine
O_2
eNOS
cAMP specific protein kinase
Endoplasmic reticulum
Ca^{2+}
K+
Ca^{2+}
Decreased Ca^{2+}
Myosin head detaches from actin
Cavernous nerve
cGMP specific protein kinase
Smooth muscle relaxation
Nitric oxide
K+
Nonadrenergic noncholinergic
Guanylyl cyclase
cGMP
GTP
PDE5
5′GMP
Ca^{2+}
PDE5i
Activation
Inhibition

FIGURE 51–1. Molecular mechanism of penile smooth muscle relaxation. Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) activate their specific protein kinases, which leads to sequestration of intracellular calcium by the endoplasmic reticulum. The resultant decrease in intracellular calcium leads to smooth muscle relaxation. Sildenafil inhibits the action of phosphodiesterase (PDE) type 5 and increases the intracellular concentration of cGMP. Papaverine is a nonspecific (PDE) inhibitor. (ATP, adenosine triphosphate; eNOS, endothelial nitric oxide synthase; GTP, guanosine triphosphate.) (Reproduced, with permission, from Shindel AW, Lue T. Physiology of penile erection and pathophysiology of erectile dysfunction. In: Partin AW, Dmochowski RR, Kavoussi LR, et al., eds. Campbell-Walsh-Wein Urology, 12th ed. Philadelphia, PA: Elsevier; 2021:1497.)

of vascular disease and neuropathy. Additionally, a relationship has been found between low testosterone levels and an increased incidence of metabolic syndrome and type 2 diabetes.[8]

Psychogenic dysfunction occurs if a patient does not respond to psychological arousal. Common causes include performance anxiety, strained relationships, lack of sexual arousability, and overt psychiatric disorders such as depression and schizophrenia. KEY CONCEPT Many patients may initially have organic dysfunction but develop a psychogenic component as they try to cope with their inability to achieve an erection.[2]

CLINICAL PRESENTATION AND DIAGNOSIS OF ED

The introduction of oral medications and direct-to-consumer advertising has made patients feel more comfortable approaching practitioners for treatment advice. Despite this, some patients may only discuss their dysfunction when questioned directly by their provider or if their partner initiates the interaction.

TREATMENT

Desired Outcomes

ED is not a life-threatening condition, but if left untreated, it can be associated with depression, loss of self-esteem, poor self-image, and marital discord.[10] The primary goal of therapy is achievement of erections suitable for intercourse and improvement in patient and partner quality of life. Additionally, the ideal therapy should have minimal side effects, be convenient to administer, have a quick onset of action, and have few or no drug interactions.

General Approach to Treatment

KEY CONCEPT Before initiating treatment for ED, a physical examination and thorough medical, social, and medication histories with

Table 51–1

Factors Associated with ED[1,4,6]

Chronic Medical Conditions
Hypertension
Diabetes mellitus
Benign prostatic hyperplasia
Coronary and peripheral vascular disease
Neurologic disorders (eg, Parkinson disease and multiple sclerosis)
Endocrine disorders (hypogonadism, pituitary, adrenal, and thyroid disorders)
Psychiatric disorders
Dyslipidemia
Renal failure
Liver disease
Penile disease (Peyronie's disease or anatomic abnormalities)
Surgical Procedures
Perineal or vascular surgeries
Radical prostatectomy
Lifestyle
Smoking
Excessive alcohol consumption
Obesity
Poor overall health and reduced physical activity
Trauma
Pelvic fractures or surgeries
Spinal cord or brain injuries

Table 51–2

Medication Classes Associated With ED[4,6]

Antihypertensives
β-Blockers (excluding nebivolol)
Thiazide diuretics
Centrally acting agents (clonidine, methyldopa, and reserpine)
Spironolactone
α-Blockers
CNS Depressants
Opioid analgesics
Benzodiazepines
Hypnotics
Lipid Medications
Gemfibrozil
HMG-CoA reductase inhibitors
Antidepressants/Antipsychotics
Tricyclic antidepressants
Monoamine oxidase inhibitors
Selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors
Lithium
Anticonvulsants
Carbamazepine
Phenytoin
Gastrointestinal Agents
Histamine 2-receptor antagonists
Proton pump inhibitors
Antiandrogens and Hormones
5α-Reductase inhibitors
Progesterone and estrogen
Corticosteroids
Recreational Drugs
Ethanol
Cocaine
Marijuana
Opiates

Clinical Presentation and Diagnosis

Possible Signs and Symptoms

- Marital difficulties
- Low self-confidence or morale; depression
- Full or partial inability to achieve erections
- Erections sufficient for intercourse, but early detumescence
- The problem may have a slow or acute onset, or may wax and wane

Diagnosis

- ED may be the presenting symptom of other chronic disease states
- The following should be performed to determine factors that can cause or exacerbate ED and to assess the patient's ability to safely perform intercourse:
  - Medical history with emphasis on cardiovascular and psychiatric disorders, diabetes, trauma, and surgical procedures
  - Social history including nutrition and a history of smoking, recreational drug use, exercise, and alcohol consumption
  - Medication history including prescription, nonprescription, and herbal or dietary supplements

Physical Examination

- Review for **hypogonadism** (gynecomastia, testicular atrophy, reduced body hair, increase in body fat)
- Digital rectal examination to determine whether prostate is enlarged
- Vital signs
- Abnormalities of the penis; impaired vasculature or nerve function to the penis

Labs

- Fasting glucose or HbA_{1c}
- Serum testosterone if signs of hypogonadism
- Fasting lipid panel
- Further cardiac testing if warranted

Determine Severity

- Use an abridged, five-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool.[9]
- How do you rate your confidence that you could get and keep an erection?
- When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
- During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
- During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
- When you attempted sexual intercourse, how often was it satisfactory for you?
- Questions scored 1 to 5, very low to very high, respectively. Score of 21 or less indicates ED likely.

Table 51–3

The Princeton III Consensus Recommendations for Cardiovascular Risk Assessment and the Management of Erectile Dysfunction[7,11]

Risk	Risk Description	Treatment Recommendation
Low	Able to perform exercise of moderate activity without symptoms Successful revascularization (CABG, stent, angioplasty) Asymptomatic, well-controlled hypertension Mild valvular heart disease Left ventricular dysfunction/heart failure (NYHA classes I and II) Uncomplicated previous MI	May initiate or resume sexual activity and begin ED treatment without further evaluation
Intermediate	Has three or more risk factors for CV disease Mild or moderate, stable angina Had a recent MI within the past 2–8 weeks Moderate heart failure (NYHA Class III) Noncardiac sequelae of atherosclerotic disease (PAD, stroke, TIA)	Further evaluation using exercise stress testing is required before resuming sexual activity. After completion, will be reassigned to low- or high-risk category
High	Moderately or severely symptomatic Unstable or refractory angina, despite treatment Uncontrolled hypertension Severe heart failure (NYHA Class IV) Recent MI without intervention (< 2 weeks) High-risk cardiac arrhythmia Obstructive hypertrophic cardiomyopathy with severe symptoms Moderate or severe valvular heart disease	Sexual activity should be deferred until cardiac condition stabilized

CABG, coronary artery bypass grafting; CV, cardiovascular; NYHA, New York Heart Association; PAD, peripheral arterial disease; PDE, phosphodiesterase; TIA, transient ischemic attack; MI, myocardial infarction.

emphasis on cardiac disease must be taken to assess for the ability to safely resume sexual activity and to assess for possible drug interactions. The Princeton Consensus was developed to estimate risk associated with sexual activity and determine the safety of ED treatment.[7,11] In patients with intermediate or high CV risk, additional testing should occur to determine whether sexual activity is safe (Table 51–3).

KEY CONCEPT Treatment options for ED include lifestyle modifications, medical devices, pharmacologic treatments, surgery, and psychotherapy. Reversible causes of ED should be identified first and treated appropriately. Additionally, combining different treatment modalities, that is, devices and pharmacologic options, may increase efficacy.

KEY CONCEPT When determining the best treatment for an individual, the role of the clinician is to inform the patient and their partner of all available options while understanding their medical history, desires, and goals. KEY CONCEPT After addressing risk factors and lifestyle modifications, oral PDE5 inhibitors are considered first line with vacuum erection devices (VEDs) as another noninvasive option, but the choice of treatment is primarily left up to the couple. Ultimately, the choice of therapy should be individualized, taking into account patient and partner preferences, concomitant disease states, response, administration route, cost, tolerability, and safety. Common drug treatment regimens for ED are listed in Table 51–4.

▸ *Nonpharmacologic Therapy*

Lifestyle Modifications Control of risk factors and general lifestyle modifications should always be addressed first in the management of ED. A healthy diet, increase in regular physical activity, and weight loss are associated with higher International Index of Erectile Function (IIEF) scores and an improvement in erectile function.[12] The clinician should also recommend smoking cessation, reduction in excessive alcohol intake, and the discontinuation of illicit drug use.

Psychotherapy Psychotherapy is an appropriate treatment approach for patients with psychogenic or mixed dysfunction. Counseling may include simple sex education and improved partner communication in addition to cognitive and behavioral therapy. Psychotherapy may help relieve anxiety and eliminate unrealistic expectations while enhancing pharmacologic efficacy.[10,13] Patients with psychogenic dysfunction may benefit from the addition of other therapies, whether nonpharmacologic or pharmacologic.

Vacuum Erection Devices VEDs induce erections by creating a vacuum around the penis; the negative pressure draws blood into the penis by passively dilating arteries and engorging the corpora. The erection is maintained with a constriction band placed at the base of the penis to reduce venous outflow (Figure 51–2). VEDs may be used as often as desired, but it is recommended that the constriction band not be left in place longer than 30 minutes at a time.

Onset of action can be slow until the user is experienced, which limits spontaneity. In addition, patients and partners may complain of a cold, lifeless, discolored penis that has a hinge-like feel. Painful ejaculation or the inability to ejaculate are additional adverse effects. VEDs are contraindicated in persons with sickle cell disease and a history of priapism. They should be used with caution in those on oral anticoagulants or who have bleeding disorders.

VEDs are highly effective treatment modalities for ED and are considered a first- or second-line therapy. They are generally more acceptable to older patients in stable relationships and with infrequent sexual encounters. Efficacy rates are as high as 90% in obtaining an erection sufficient for intercourse, and although satisfaction rates are as high as 94%, the discontinuation rate after 2 years is close to 40%.[14] A double pumping technique in which the vacuum is applied for 1 to 2 minutes, removed, then reapplied for another 3 to 4 minutes may improve comfort levels and rigidity. Higher efficacy rates can also be achieved by combining VEDs with other therapies.

Table 51–4

Common Drug Treatment Regimens for ED

Route of Administration	Generic Name	Brand Name	Typical Dosing Range[a]	Maximum Dosing Frequency
Oral	Sildenafil	Viagra	25–100 mg 1 hour prior to intercourse	Once daily
	Tadalafil	Cialis	5–20 mg 30 minutes prior to intercourse or daily dose of 5–20 mg	Once daily
	Vardenafil	Levitra, Staxyn	10 mg 1 hour prior to intercourse	Once daily
	Avanafil	Stendra	100–200 mg 15 minutes prior to intercourse	Once daily
	Testosterone undecanoate	Jatenzo[b]	158–396 mg twice daily	Twice daily
Intracavernosal	Alprostadil	Caverject, Caverject Impulse, Edex	1.25–60 mcg 5–20 minutes prior to intercourse[c]	Three times weekly, 24 hours between injections
Intraurethral	Alprostadil	MUSE	125–1000 mcg 5–10 minutes prior to intercourse[c]	Two times daily
Intramuscular	Testosterone cypionate	Depo-Testosterone	50–400 mg every 2–4 weeks	Once weekly
	Testosterone enanthate	Delatestryl, Xyosted	50–400 mg every 2–4 weeks	Once weekly
			50–100 mg once weekly by autoinjector	Once weekly
	Testosterone undecanoate	Aveed	750 mg on day 1 and week 4; then every 10 weeks	After titration once every 10 weeks
Topical	Testosterone patch	Androderm	2–6 mg/day applied at night to back, abdomen, upper arms, or thighs	Once daily
	Testosterone gel	AndroGel 1%, Testim, Vogelxo	5–10 g gel per day (50–100 mg testosterone) in morning to shoulders, upper arms, abdomen (AndroGel 1% only)	Once daily
		AndroGel 1.62%	40.5–81 mg/day in morning to shoulders or upper arms	Once daily
		Natesto	11 mg intranasally three times daily; 6–8 hours apart (2 pump actuations, 1 per nostril)	Three times daily
		Fortesta	10–70 mg/day in morning to thigh (1–7 pumps)	Once daily
	Testosterone solution	Axiron	30–120 mg/day in morning to axilla (1–4 pumps)	Once daily
Buccal	Testosterone	Striant	30 mg every 12 hours to gum region above incisor; rotate to alternate sides with each dose	Two times daily
Subcutaneous implantable pellet	Testosterone	Testopel	150–450 mg (150 mg for every 25 mg testosterone propionate required weekly)	Every 3–6 months

[a] Use the lowest effective dose to limit adverse effects.

[b] Oral testosterone undecanoate has warnings about increased blood pressure and CV events and is not indicated for age-related low testosterone.

[c] Initial dose, to achieve erection lasting 1 hour, must be titrated in physician's office.

MUSE, medicated urethral system for erection.

Prostheses Penile prostheses are semirigid malleable or inflatable rods, which are inserted surgically into the corpus cavernosa (see Figure 51–3). The malleable rods are rigid at all times but may be bent into position by the patient when desired. The inflatable prostheses are preferred due to a more "natural" erection as they remain flaccid until the pump within the scrotum moves fluid from a reservoir to the cylinders within the penis. Detumescence is achieved when the fluid is then transferred back to the reservoir by activating a release button.

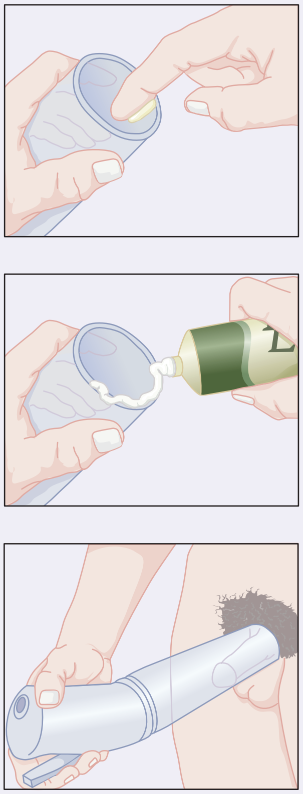
Patient satisfaction rates can be as high as 90%, with partner satisfaction rates slightly lower, but prostheses are costly and the most invasive treatment available so are considered last-line therapy.[15] Complications include mechanical failure and infection. Failure rates are less than 5% while infection occurs in 1% to 2% with primary implantation.[15]

▶ *Pharmacologic Therapy*

Phosphodiesterase Type 5 Inhibitors Avanafil, sildenafil, tadalafil, and vardenafil act by selectively inhibiting PDE5, which is responsible for degradation of cGMP. With prolonged cGMP activity, smooth muscle relaxation is induced, leading to an erection (see Figure 51–1). However, the PDE5 inhibitors are only effective in the presence of sexual stimulation to drive the NO/cGMP system, making them facilitators of an erection, not initiators.

KEY CONCEPT Effectiveness of the four available PDE5 inhibitors is essentially comparable, but differences exist in onset, duration of action, absorption with a fatty meal, and, to a small degree, incidence of side effects and drug interactions (Table 51–5). Review of available data for each individual agent shows a 60% to 75% response rate depending on the dose of agent used and the etiology of dysfunction.[2,6] Although efficacy rates appear to be similar between agents, there are some data to suggest that continuation rates are higher and patient preference greater with tadalafil due to its longer duration of efficacy (18 hours).[16] The PDE5 inhibitors are considered first-line therapies due to high efficacy rates, convenience of dosing, and minimal severe adverse effects.

All four PDE5 inhibitors are approved for as-needed dosing. Tadalafil has also been approved for use as a daily medication at a lower dose (2.5–5 mg) than the as-needed dose with similar



Assemble your system according to the two-step procedure.

Step 1

Apply Osbon Personal Lubricant to the following:

1. 2 in inside the open end of the cylinder;
2. the rim of the cylinder that meets the body to form the vacuum seal; and
3. the entire head of the penis.

Applying lubricant properly will help you achieve the best erection possible.

Tip: Trimming the pubic hair around the base of the penis with a pair of scissors may also prove helpful in creating an airtight seal.

Step 2

It is recommended that you stand for this step (the system can also be used when you are sitting or lying down).

Place the lubricated penis inside the cylinder with the label on the cylinder facing up. With one hand, hold the cylinder at a downward 45° angle with the open end snugly against the body.

Tip: Rotate cylinder slightly back and forth to make an airtight seal against the body, make sure the testicles are not drawn into the cylinder.

FIGURE 51–2. Technique for using a vacuum erection device. (From Lee M, Sharifi R. Erectile dysfunction. In: Dipiro JT, Yee GC, Posey LM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020:1394.)

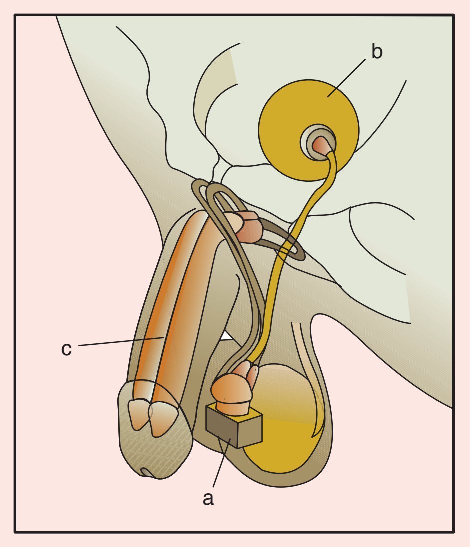


FIGURE 51–3. Example of a surgically implanted penile prosthesis. (a, activation mechanism; b, reservoir with fluid for inflating prosthesis; c, inflatable rods in corpora.) (From Lee M, Sharifi R. Erectile dysfunction. In: Dipiro JT, Yee GC, Posey LM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020:1406.)

efficacy. It also has an indication for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia.

PDE enzymes are also found in retinal, muscle, peripheral vascular, and tracheal smooth muscle tissue. Inhibition of PDE enzymes throughout the body leads to many of the most common adverse effects, including headache, facial flushing, nasal congestion, dyspepsia, myalgia, back pain, and, rarely, priapism. Vardenafil and sildenafil may also cause blurred vision, difficulty in discriminating blue from green, bluish tones in vision, or difficulty seeing in dim light due to cross-reactivity with PDE type 6 in the retina. Labeling for all PDE5 inhibitors includes a warning about rare nonarteritic ischemic optic neuropathy in which blood flow is blocked to the optic nerve. If patients experience sudden or decreased vision loss, they should call a health care provider immediately. PDE5 inhibitors have also been associated with acute hearing impairment although a causal relationship has not been established.[2]

Patient Encounter 1, Part 1

A 72-year-old man with type 2 diabetes, hypertension, dyslipidemia, BPH, and obesity comes into your clinic for routine follow-up with his spouse. When reviewing their history, they state they are only able to achieve partial erections that are insufficient for intercourse. They are quite emotional and state that the problem is distressing and has caused significant marital discord.

PMH: Type 2 diabetes for 20 years, uncontrolled. Hypertension for 8 years, currently controlled. Dyslipidemia for 15 years, controlled. BPH for 5 years uncontrolled.

SH: Retired; alcohol only occasionally; nonsmoker; No regular exercise; eats a healthy diet with orange or grapefruit juice daily.

Meds: Metformin 1000 mg orally twice daily; insulin glargine 60 U subcutaneously once daily; lisinopril/HCTZ 20/25 mg orally once daily; diltiazem ER 24 hour 120 mg orally once daily; rosuvastatin 40 mg orally once daily; tamsulosin 0.4 mg orally once daily.

ROS: (–) Morning, nocturnal, or spontaneous erections suitable for intercourse; (+) nocturia, urgency, dribbling; (–) symptoms of prostatitis; (–) chest pain, or anginal symptoms.

PE:

VS: BP 130/78, P 85, RR 18, Wt 249 lb (113 kg), Ht 70 in. (178 cm)

CV: Normal examination

Labs: Fasting glucose 189 mg/dL (10.5 mm/L); HbA_{1c} 9% (0.09; 74 mmol/mol Hgb), total testosterone 400 ng/dL (14 nmol/L); SCr 0.9 mg/dL (80 μmol/L), PSA 0.8 ng/mL (0.8 mcg/L)

What risk factors does this patient have for ED?

Identify treatment goals for this patient.

What pharmacologic and nonpharmacologic alternatives are available for this patient?

Based on the information available, which of the available options will be your treatments of choice based on concomitant disease states and medications, degree of invasiveness, side effects, ease of use, and side-effect profile?

What are the safety and efficacy monitoring parameters for the chosen treatment?

Table 51–5

Comparison of PDE Inhibitors

	Sildenafil (Viagra)	Tadalafil (Cialis)	Vardenafil (Levitra, Staxyn)	Avanafil (Stendra)
Available strengths	25-, 50-, 100-mg tabs	2.5-, 5-, 10-, 20-mg tabs	2.5-, 5-, 10-, 20-mg tabs	50-, 100-, 200-mg
Initial dosage in healthy adults	50 mg up to once daily taken 1 hour prior to sexual activity	10 mg up to once daily taken 30 minutes prior to sexual activity or 2.5 mg daily at the same time each day	10 mg up to once daily taken 1 hour prior to sexual activity	100 mg up to once daily taken 15 minutes prior to sexual activity
Dosing range for healthy adults	25–100 mg	5–20 mg	5- to 20-mg Levitra 10-mg Staxyn	50–200 mg
Dosage in the elderly	25 mg	10–20 mg	5 mg	50–200 mg
Dosage in renal impairment	25 mg (severe[b])	5–10 mg (moderate[a]) 5 mg (severe[b]) Daily use NR (severe[b])	5–20 mg	50–200 mg[c]
Dosage in hepatic impairment	25 mg	10 mg[c]	5 mg[c]	50–200 mg[c]
Time to onset	60 minutes	30–60 minutes	60 minutes	15 minutes
Onset delayed by high-fat meal?	Yes	No	Yes No—ODT	No
Duration of effect	Up to 4 hours	Up to 36 hours	Up to 6 hours	Up to 6 hours
Half-life	3–4 hours	18 hours	4–6 hours	5 hours
Metabolism	CYP3A4 (major) CYP2C9 (minor)	CYP3A4	CYP3A4 (major) CYP3A5 (minor) CYP2C (minor)	CYP3A4 (major) CYP2C9 (minor)
Clinically relevant drug interactions	Nitrates,[d] α_1-blockers,[e] protease inhibitors, azole antifungals, erythromycin, grapefruit	Nitrates,[d] α_1-blockers,[e] protease inhibitors, azole antifungals, erythromycin	Nitrates,[d] α_1-blockers,[e] antiarrhythmic agents,[f] grapefruit, erythromycin	Nitrates,[d] α_1-blockers,[e] protease inhibitors, azole antifungals, erythromycin, grapefruit

[a] Moderate renal impairment = creatinine clearance (CrCl) 31–50 mL/min (0.51–0.83 mL/s).

[b] Severe renal impairment = CrCl < 30 mL/min (0.50 mL/s).

[c] Mild to moderate only—contraindicated in severe disease.

[d] Oral, topical, sublingual, and injectable nitroglycerine products are all contraindicated.

[e] Selective α_1-blockers (such as alfuzosin, silodosin, and tamsulosin) are appropriate in combination. If nonselective, initiate with lowest dose possible.

[f] Vardenafil can cause QT-interval prolongation; this effect in combination with certain antiarrhythmic agents can lead to life-threatening arrhythmias.

CYP, cytochrome P-450 isoenzyme; NR, not recommended; ODT, oral disintegrating tablet

In addition to the inherent risk of renewing sexual activity, PDE5 inhibitors can lead to significant hypotension. Patients taking organic nitrates are at highest risk, as these drugs potentiate the drop in blood pressure. All four PDE5 inhibitors are absolutely contraindicated in patients taking any form of nitrate, whether scheduled or as needed for acute situations. Additionally, caution should be used when combining a PDE5 inhibitor with α-blockers. Vardenafil contains a precautionary statement about the possibility of QT prolongation. Drug interactions and cautions vary slightly between agents and are described in Table 51–5.

Up to a third of patients will not respond to therapy with PDE5 inhibitors. To achieve the greatest effect, patients must be fully informed of the onset and duration of effect, impact of high-fat meals, the need for sexual stimulation, and explanation that a single trial is not adequate. It is estimated that six to eight attempts with a medication and specific dose may be needed before successful intercourse.[6]

Alprostadil Alprostadil is a prostaglandin E_1 analog that induces an erection by stimulating adenyl cyclase, leading to increased cAMP, smooth muscle relaxation, rapid arterial inflow, and increased penile rigidity (see Figure 51–1). Alprostadil is available as an intracavernosal injection (Caverject or Edex) or an intraurethral suppository (MUSE, medicated urethral system for erection), with the injectable dose showing greater efficacy.[6,14] Both forms of alprostadil are considered more invasive than oral medications or VEDs and are, therefore, second-line therapies.

MUSE consists of a urethral pellet of alprostadil with an applicator (Figure 51–4). Onset of action is within 5 to 10 minutes and it is effective for 30 to 60 minutes. Success rates are between 30% and 66%, with higher doses showing the most consistent response.[15] The patient should void to moisten the urethra, insert the pellet, and then massage to distribute the medication. Aching in the penis, testicles, legs, and perineum; warmth or burning sensation in the urethra, minor urethral bleeding or spotting, priapism; and light-headedness are all possible adverse effects. In addition, partners may experience burning or itching, and use is contraindicated with a pregnant partner unless using a condom.

Intracavernous alprostadil injection is the more effective route and is the only Food and Drug Administration (FDA)-approved injection for ED. The onset of action is similar to intraurethral alprostadil, but duration varies with dose and must be titrated by a health care professional in a medical setting to achieve an

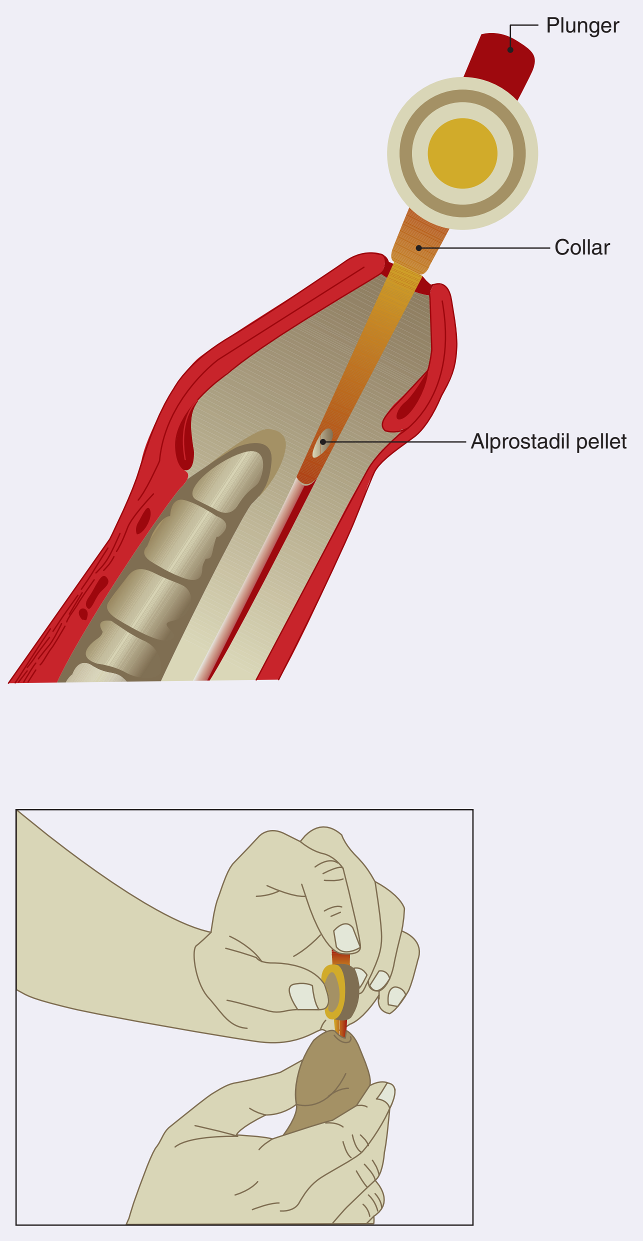


FIGURE 51–4. Technique for administration of intraurethral alprostadil with a mediated urethral system for erection applicator. (From Lee M, Sharifi R. Erectile dysfunction. In: Dipiro JT, Yee GC, Posey LM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020:1405.)

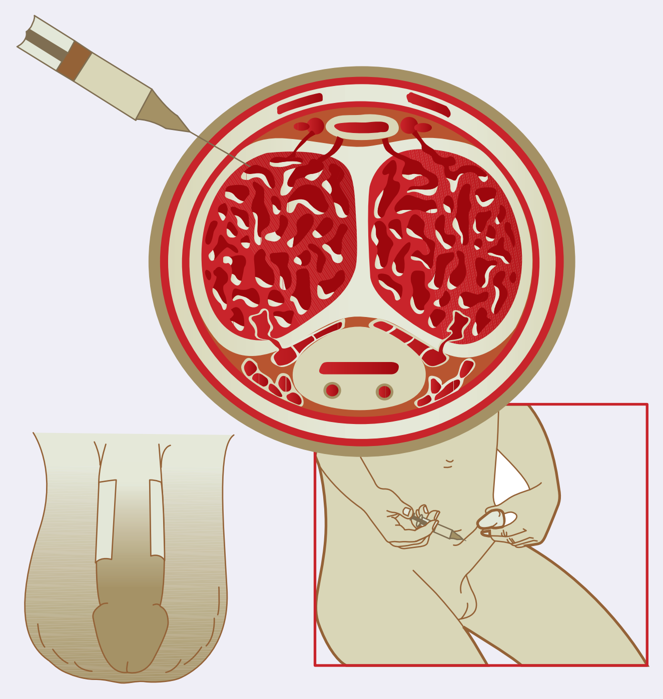


FIGURE 51–5. Technique for administration of intracavernosal injections. (From Lee M, Sharifi R. Erectile dysfunction. In: Dipiro JT, Yee GC, Posey LM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020:1404.)

erection lasting no more than 1 hour. Papaverine and phentolamine are nonapproved intracavernosal agents that are only used in combination. Injections should be performed into one side directly into the corpus cavernosum, and then the penis should be massaged to distribute the drug to both corpora (Figure 51–5). Education is extremely important with intracavernosal injections. Patients must be adequately informed of technique, expectations, side effects, and when to seek help. Intracavernosal injections are effective in 60% to 80% of patients, but side effects, lack of spontaneity, and fear of needles limit their widespread use and, therefore, this therapy is most appropriate for patients in long-term stable relationships.[2,6] Adverse effects include pain with injection, bleeding or bruising at the injection site, fibrosis, or priapism. Use with caution in patients with sickle cell disease, those on anticoagulants, or those who have bleeding disorders, due to an increased risk of priapism and bleeding.

Testosterone Supplementation KEY CONCEPT Androgens are important for general sexual function and libido, but testosterone supplementation is only indicated in patients with documented low serum testosterone levels. In patients with hypogonadism, testosterone replacement is the initial treatment of choice, as it corrects decreased libido, fatigue, muscle loss, sleep disturbances, and depressed mood. However, testosterone is contraindicated in patients with prostate cancer, erythrocytosis, uncontrolled heart failure, or sleep apnea.

Testosterone supplementation may improve ED symptoms but is not universally effective. Initial supplementation should occur for 3 months with reevaluation and the addition of another ED therapy if needed at that time. Dosage forms include intramuscular, an implanted pellet, topical patches or gel, nasal spray, and a buccal tablet.

Injectable testosterone, cypionate and enanthate, offer the most inexpensive replacement option. There are several drawbacks associated with parenteral testosterone, including the need to administer deep intramuscular injections every 2 to 4 weeks. Testosterone undecanoate offers the benefit of an extended dosing interval of 10 weeks but is a more expensive injectable option. Concentrations of hormone are well above physiologic values within the first few days, and then decline and eventually dip below physiologic levels prior to the next dose. These changes in concentration may lead to mood swings and a reduced sense of well-being.[17] Implantable subcutaneous testosterone pellets are a longer acting and convenient alternative that are placed every 3 to 6 months.

Patient Encounter 1, Part 2

The patient returns to the clinic a year later after having undergone a radical prostatectomy due to a new diagnosis of prostate cancer. Current medication list includes: metformin, glargine, lisinopril/HCTZ, amlodipine, rosuvastatin, and tadalafil. They describe continued distress with no erections suitable for intercourse. After his prostatectomy, they switched from daily tadalafil to an as-needed dose of 20 mg prior to sexual activity. They have attempted more than 10 times with this dose and are waiting 60 minutes after dosing to attempt intercourse.

What treatment options should be considered for this patient?

Patient Encounter 2

A 62-year-old man presents with a history of hypertension and dyslipidemia. They have had ED for the past year, but now complains of being tired all the time. The patient does not have much of a libido anymore, is struggling to sleep, and is gaining weight.

Meds: Losartan 50 mg orally once daily, atorvastatin 40 mg orally once daily, vardenafil 10 mg orally as needed.

Labs: Lipid panel and complete metabolic panel within normal limits; total testosterone 125 ng/dL (4 nmol/L)

Based on the information provided, what is your assessment of the patient?

What should be recommended as the next step in treatment of ED?

Treatment with topical products is attractive to patients due to convenience, but they tend to be more expensive than the injections. Testosterone patches and gels are administered daily and result in serum levels within the physiologic range during the 24-hour dosing period.[17] Care must be taken with the use of the gel to prevent transfer of testosterone to children and females by washing hands thoroughly, allowing the site to dry, and covering immediately. Newer formulations for the axilla, thigh, and nasal mucosa may reduce this risk. It is recommended to avoid swimming or showering for 2 to 3 hours after patch or gel application. The most common side effects of topical testosterone are dermatologic reactions.

Oral testosterone products are also available for supplementation but have poor oral bioavailability and undergo extensive first-pass metabolism. Alkylated derivatives such as methyltestosterone and fluoxymesterone have been formulated, but this modification makes them considerably more hepatotoxic and, therefore, undesirable. Oral testosterone undecanoate contains

Patient Care Process

Collect Information:

- Assess the patient's specific symptoms to determine the type of dysfunction.
- Ask specific questions related to onset and frequency of dysfunction and status of sexual relationships. Assess severity with the IIEF-5 questionnaire.
- Perform complete histories, physical examination, and laboratory tests (see Clinical Presentation and Diagnosis, Tables 51–1 and 51–2).
- Assess cardiovascular risk (see Table 51–3).
- Speak with the patient regarding available options of therapy and preference.

Assess the Information:

- Evaluate medications, concomitant disease states, and lifestyle factors that could exacerbate ED or indicate a need to defer sexual activity.
- Based on histories, determine whether the patient has either compelling indications for or contraindications to specific therapies.
- Review relevant laboratory and cardiac tests (eg, testosterone, HbA1c, complete metabolic panel, treadmill).
- Assess the efficacy, safety, and adverse effects of current treatment.

Develop a Care Plan:

- Treat underlying diseases, discontinue medications, and eliminate risk factors which can exacerbate ED.
- PDE5 inhibitors are first-line treatment unless contraindicated, not tolerated, or ineffective, but treatment should be individualized.
- Give supplementation if patient has low testosterone.

Implement the Care Plan:

- Initiate PDE5 inhibitor or patient treatment of choice and provide education regarding:
  - ED
  - Nonpharmacologic therapy: lifestyle changes such as weight loss, healthy diet, regular exercise, smoking cessation, and psychotherapy when warranted
  - Treatment of associated disease states
  - Drug therapy—mechanisms of action and adverse effects
  - Device technique

Follow-up: Monitor and Evaluate:

- Follow up in 4 to 6 weeks or more frequently to assess effectiveness and safety of therapy including specific warning signs for PDE5 inhibitors (eg, vision changes, fibrosis, pain, priapism, or hypotension).
- Reeducate on lifestyle, associated disease states, expectations, and methods for increasing efficacy with therapy.
- Increase dosage, switch to alternate therapy, or add alternate therapy if needed.

warnings for increased blood pressure and CV events and is not indicated for age-related low testosterone.

An alternative to the oral route is the buccal mucoadhesive system. This system adheres to the inside of the mouth and testosterone is absorbed through the oral mucosa and delivered to the systemic circulation with no first-pass effect. Side effects unique to this dosage form include oral irritation, bitter taste, and gum edema.

General side effects of testosterone include gynecomastia, dyslipidemia, polycythemia, and acne. Weight gain, hypertension, edema, and exacerbations of heart failure also occur due to sodium retention. The undecanoate formulation also carries a risk of serious pulmonary oil microembolism reactions and anaphylaxis after any dose; therefore, patients must be monitored for 30 minutes after the injection. Before initiating testosterone, the patient should undergo evaluation for benign prostatic hypertrophy and prostate cancer due to worsening of urinary symptoms and elevations in serum prostate specific antigen (PSA) with supplementation. Routine follow-up includes yearly PSA, digital rectal examination, hemoglobin, and liver function, in addition to assessment of response.

OUTCOME EVALUATION

Successful therapy for ED results in an increase in erections suitable for intercourse and, most importantly, in an improvement in the patient's quality of life. Ideally, the therapy chosen is free of significant adverse effects, discomfort, and inconvenience. Laboratory evaluation and a physical examination are not necessary for evaluation of effectiveness but may be necessary for adverse event monitoring.

Evaluate satisfaction and effectiveness after a 4-week trial. Some therapies will require multiple visits over the long term to determine the correct dose and to detect adverse effects. If the initial therapy is not effective, the patient must be further evaluated to determine whether the initial assessment of comorbid disease states, type of dysfunction, and patient goals were appropriate. After providing further education and determination of realistic goals, providers may then increase the dose of medication, switch to another therapy, or add a therapy if indicated.

Abbreviations Introduced in This Chapter

cAMP	cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
FDA	Food and Drug Administration
IIEF	International Index of Erectile Function
MUSE	Medicated urethral system for erection
NO	Nitric oxide
PDE5	Phosphodiesterase type 5
VED	Vacuum erection device

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52 Benign Prostatic Hyperplasia

Mary Lee and Roohollah Sharifi

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the pathophysiology of benign prostatic hypertrophy (BPH).
2. Recognize the symptoms and signs of BPH.
3. List the desired treatment outcomes for BPH.
4. Identify factors that guide selection of a particular α_1-adrenergic antagonist for an individual patient.
5. Compare and contrast α_1-adrenergic antagonists, 5α-reductase inhibitors, anticholinergic agents, tadalafil, and mirabegron in terms of mechanism of action, treatment outcomes, adverse effects, and interactions.
6. Describe the indications, advantages, and disadvantages of a combination drug regimen that includes an α_1-adrenergic antagonist and 5α-reductase inhibitor.
7. Describe the indications for surgical intervention.
8. Apply the patient care process to develop an individualized treatment plan.

INTRODUCTION

The prostate is an organ, which is the shape and size of a horse chestnut. It encircles the portion of the proximal posterior urethra that is located at the base of the urinary bladder. The prostate produces secretions, which are part of the ejaculate.

Benign prostatic hypertrophy (BPH) is the most common benign neoplasm in men who are at least 40 years of age. BPH can produce lower urinary tract symptoms (LUTS), a collection of obstructive and irritative voiding symptoms that are consistent with impaired emptying of urine from and defective storage of urine in the bladder, respectively. Medications are first-line treatment to reduce symptoms and/or delay complications of BPH.[1]

EPIDEMIOLOGY AND ETIOLOGY

BPH first presents as benign prostatic hyperplasia, a histologic disease in many elderly men which increases in prevalence with advancing patient age. Benign prostatic hyperplasia may progress to BPH, which is clinically evident, and then to benign prostatic obstruction, which produces LUTS. Of patients with histologic disease, only about 50% of patients develop an enlarged prostate on digital palpation and 25% of patients exhibit clinical voiding symptoms.[2,3] It is estimated that 8% of men 40 years of age, increasing to 35% of men 60 to 69 years of age, have voiding symptoms consistent with BPH, and 20% to 30% of all male patients who live to the age of 80 years will require a prostatectomy for severe voiding symptoms of BPH.[3]

Two chief etiologic factors for BPH include advanced patient age and the stimulatory effect of androgens.

- Prior to 40 years of age, the prostate in men is approximately 15 g (0.5 oz) to 20 g (0.7 oz). However, in men who have reached 40 years of age, the prostate undergoes a growth spurt, which continues as men advance in age. BPH can result in clinically symptomatic LUTS.[3,4]
- The testes and adrenal glands produce 90% and 10%, respectively, of circulating testosterone. Testosterone enters prostate cells, where predominantly Type II 5α-reductase converts testosterone to dihydrotestosterone, which combines with a cytoplasmic receptor. The complex enters the nucleus and induces changes in protein synthesis that promote glandular tissue growth of the prostate.

The prostate is composed of two types of tissue: (a) glandular or epithelial tissue, which produces prostatic secretions, including prostate-specific antigen (PSA), and (b) muscle or stromal tissue, which can contract around the urethra and bladder outlet when stimulated. In an enlarged prostate, the epithelial to stromal tissue ratio is 1:5.[5] Whereas androgens stimulate glandular tissue growth, they have no direct effect on stromal tissue. Stromal tissue growth may be stimulated by estrogen, which is derived from peripheral tissue conversion of testosterone. Stromal tissue is innervated by α_{1A}-adrenergic receptors. When stimulated, prostatic stroma contracts around the urethra, narrowing the urethra and causing obstructive voiding symptoms.

PATHOPHYSIOLOGY

KEY CONCEPT LUTS and signs of BPH are due to static, dynamic, and/or detrusor factors. The static factor refers to anatomic obstruction of the bladder neck caused by an enlarged prostate gland. As the gland grows around the urethra, the prostate occludes the urethral lumen. The dynamic factor refers to excessive stimulation of α_{1A}-adrenergic receptors in the smooth muscle of the prostate, urethra, and bladder neck, which results in smooth muscle contraction. This reduces the caliber of the urethral lumen and causes obstructive voiding symptoms. Stromal tissue is the

Clinical Presentation and Diagnosis of BPH

General

In early stages of disease, the patient may complain of obstructive voiding symptoms. If untreated, the disease may progress and the patient may complain of irritative voiding symptoms or acute urinary retention, which can be painful due to maximal distention of the urinary bladder. Also, the patient may be symptomatic of disease complications.

Symptoms

Patients may complain of any combination of three types of voiding symptoms:

- obstructive: urinary hesitancy, decreased force of urinary stream, straining to void, and intermittency
- irritative: urinary frequency, nocturia, and urgency with or without incontinence
- postmicturition: dribbling, incomplete bladder emptying

A patient with LUTS will seek medical care once voiding symptoms curb daily activities, are bothersome to the patient or his significant other, or cause embarrassment. Symptom severity is assessed by the patient using a standardized instrument (eg, the AUA Symptom Scoring Index; Table 52–1). However, a patient's perception of the bothersomeness of his voiding symptoms may not match with the AUA Symptom Score. In this case, after thorough evaluation of the signs and complications of BPH disease, the physician and patient should discuss the bothersomeness of the symptoms and decide together on the most appropriate course of treatment.[2,12,13]

It should be noted that LUTS is not specific for BPH. LUTS may be due to other urologic disorders including prostate cancer, prostatitis, or neurogenic bladder.

Signs

- Enlarged prostate on digital rectal exam (DRE); check for prostate nodules or induration, which suggests prostate cancer instead of BPH as the cause of the patient's voiding symptoms.
- Distended urinary bladder
- Rule out **meatal stenosis** or **urethral stricture**, which could cause voiding symptoms similar to LUTS.
- Check anal sphincter tone as an indirect assessment of peripheral innervation to the detrusor muscle of the bladder.

Complications of Untreated BPH

Upper and lower urinary tract infection, urosepsis, urinary incontinence, urinary retention, renal impairment, bladder diverticula, bladder stones, or recurrent gross hematuria.

Medical History

- Check the patient's general health, including previous surgery, presence of diabetes mellitus, or medications that may cause or worsen voiding symptoms.
- Have the patient provide a diary of his voiding pattern for the past week: date and time of each voiding, volume voided, and whether or not the patient had urinary leakage during the day.

Laboratory Tests

- Serum PSA: The combination of PSA and DRE of the prostate can be used to screen for prostate cancer, which could also cause an enlarged prostate. Also, PSA is a surrogate marker for an enlarged prostate due to BPH.[12]
- Urinalysis to rule out infection as a cause of the patient's voiding symptoms; also check urinalysis for microscopic hematuria, which typically accompanies BPH.
- Plasma BUN and serum creatinine may be increased as a result of long-standing bladder outlet obstruction. These tests are not routinely performed but rather are reserved for those patients in whom renal dysfunction is suspected.

Other Diagnostic Tests[12]

- Decreased peak and mean urinary flow rate (< 10–15 mL/s). A decreased urinary flow rate is not specific for BPH; it can also be due to other urologic disorders (eg, urethral stricture, meatal stenosis, or **bladder hypotonicity**).
- PVR measures urine left in the bladder after the patient voids. A normal PVR is 0 mL. A PVR greater than 50 mL is associated with recurrent urinary tract infection.
- DRE to check for an enlarged prostate (> 15–20 g [0.5–0.7 oz]). Nodules, induration, or asymmetry may be due to prostate cancer or some other disease.
- A focused neurological examination to check the integrity of innervation to the urinary bladder (that is responsible for bladder emptying).
- Transurethral cystoscopy reveals an enlarged prostate, which decreases urethral lumen caliber; information from this procedure helps the surgeon decide on the best surgical approach.
- Transrectal ultrasound of the prostate; a transrectal probe is inserted to evaluate prostate size and best surgical approach.
- Transrectal prostate needle biopsy is done if the patient has areas of nodularity or induration on DRE; tissue biopsy can document the presence of prostate cancer.
- Computerized tomography of the urinary tract (CT urogram) with contrast will show a thickened bladder wall, hydronephrosis, and retention of contrast in the bladder if the patient has chronic bladder outlet obstruction; this is only indicated in patients with recurrent hematuria, recurrent urinary tract infection, and urolithiasis.
- Filling cytometry provides information on bladder capacity, detrusor contractility, and the presence of uninhibited bladder contractions, which could also cause LUTS.

primary locus of α_1-adrenergic receptors in the prostate. An estimated 98% of α-adrenergic receptors in the prostate are found in prostatic stromal tissue. Of the α_1-receptors found in the prostate, 70% of them are of the α_{1A}-subtype and the remainder are of the α_{1B} and α_{1D} subtypes.[6] In some patients, excessive α_1-adrenergic stimulation of stromal tissue may cause significant LUTS even though the prostate is only slightly enlarged. The detrusor factor refers to bladder detrusor muscle hypertrophy in response to prolonged bladder outlet obstruction. To further explain, detrusor muscle fibers undergo hypertrophy so that the bladder can

Patient Encounter 1

A 75-year-old man with a BPH and an AUA Symptom Score of 7, urinary hesitancy, and a slow urinary stream presents to the clinic. He wakes up three times every night to void. A DRE reveals a prostate of 30 g (1.1 oz). His PSA is 3 ng/mL (3 mcg/L). A urinary flow rate is 10 mL/s and PVR is 0 mL. A serum creatinine is 1.5 mg/dL (132.6 mmol/L). The patient weighs 80 kg. He is otherwise healthy, takes no medications, and reports that he feels fine and really doesn't like to take any medications that are not necessary.

What stage of BPH does this patient have?

How should the patient be managed?

Table 52–1

Questions to Determine the AUA Symptom Score and Interpretation of Scores

Directions for the patient: The patient should be asked to respond to each question based on the absence or presence of symptoms over the past month. For each question, the patient can respond using a 1–5 scale, where 0 = not at all or none; 1 = less than 1 time in 5; 2 = less than half of the time; 3 = about half of the time; 4 = more than half of the time; and 5 = almost always

Directions for the clinician: After the patient completes the questionnaire, the scores for individual items should be tallied for a final score. Scores of 0–7 = mild symptoms; scores of 8–19 = moderate symptoms; scores more than 20 = severe symptoms. Score range 0-35.

Questions to Assess Obstructive Voiding Symptoms

1. How often have you had a sensation of not emptying your bladder completely after you finished urinating?
2. How often have you found you stopped and started again several times when you urinated?
3. How often have you had a weak urinary stream?
4. How often have you had to push or strain to begin urinating?

Questions to Assess Irritative Voiding Symptoms

5. How often have you found it difficult to postpone urination?
6. How often have you had to urinate again < 2 hours after you finished urinating?
7. How many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?

AUA, American Urological Association.

Data from AUA Practice Guidelines Committee. AUA guideline on the management of benign prostatic hyperplasia (2010, reaffirmed 2014). www.auanet.org/content/guidelines-and-quality care/clinical-guidelines.cfm?sub=bph. Last accessed August 31, 2020.

generate higher pressure to overcome bladder outlet obstruction. The hypertrophic detrusor muscle becomes irritable, contracting abnormally in response to small amounts of urine in the bladder. This causes storage voiding symptoms (urinary frequency, nocturia, urgency, or urinary incontinence). If obstruction is not treated, the bladder muscle will decompensate and be unable to empty completely; postvoid residual urine volume (PVR) will increase.

More recently, atherosclerosis of the pelvic vascular supply to the prostate and bladder has been linked to BPH. Specifically, atherosclerosis leads to hypoxia, which stimulates prostate stromal tissue to increase release of growth factors.[7] Also, in experimental models, chronic inflammation may also stimulate prostate gland growth.[7] Finally, many patients with BPH also have metabolic syndrome, which is characterized with insulin resistance and increased alpha-adrenergic tone.[4]

The natural history of untreated BPH is unclear in patients with mild symptoms. It is estimated that up to 38% of untreated men with mild symptoms will have symptom improvement over a 2.5- to 5-year period.[8] It may be that such patients attribute their symptoms to aging, grow tolerant of their symptoms, or adopt behavioral changes in their lifestyle that minimize their voiding symptoms. However, the majority of patients with mild symptoms will experience disease progression. Patients with moderate-to-severe symptoms can experience decreased quality of life as daily activities are reduced because of LUTS. Also, such patients may develop complications of BPH, which include urinary retention, recurrent urinary tract infection, renal impairment, urolithiasis, or persistent prostate bleeding.[1,9] Predictors of disease progression include an enlarged prostate of at least 40 g (1.4 oz) or PSA of 1.6 ng/mL (1.6 mcg/L) or greater.[10] Finally, erectile dysfunction commonly develops in patients with BPH. Effective treatment of BPH symptoms often improves sexual function without initiating specific treatment for erectile dysfunction.[11]

TREATMENT

Desired Outcomes[1,12,13]

KEY CONCEPT Drug treatment is expected to decrease the American Urological Association (AUA) Symptom Score (Table 52–1) by 30% to 50% (or at least by three or more points),[1,12] improve peak and mean urinary flow rate by at least 1 to 3 mL/s, and decrease PVR to normal (< 50 mL total) when compared with pretreatment baseline values.

- Slowing disease progression. When compared with baseline, symptoms and signs of BPH, serum blood urea nitrogen (BUN), and creatinine should improve, stabilize, or decrease to the normal range with treatment.
- Preventing disease complications and reducing the need for surgical intervention.
- Avoiding or minimizing adverse treatment effects.
- Providing economical therapy.
- Maintaining or improving quality of life.

General Approach to Treatment

Until recently, the principal approach to treatment focused on reducing BPH symptoms (Figure 52–1). However, treatment should also slow disease progression and decrease complications of BPH, particularly in patients at high risk.[9,11-14]

KEY CONCEPT For patients with mild symptoms (AUA Symptom Score of 7 or less) that the patient does not consider to be bothersome, watchful waiting is a reasonable approach to treatment. The patient is instructed to schedule return visits to the clinician every 6 to 12 months. At each visit, the patient's symptoms are reassessed using the AUA Symptom Scoring Index, and results are compared against the baseline (see Table 52–1). In addition, the patient is educated about implementing nonpharmacologic measures to reduce voiding symptoms (see section on Nonpharmacologic Therapy) and avoiding factors that

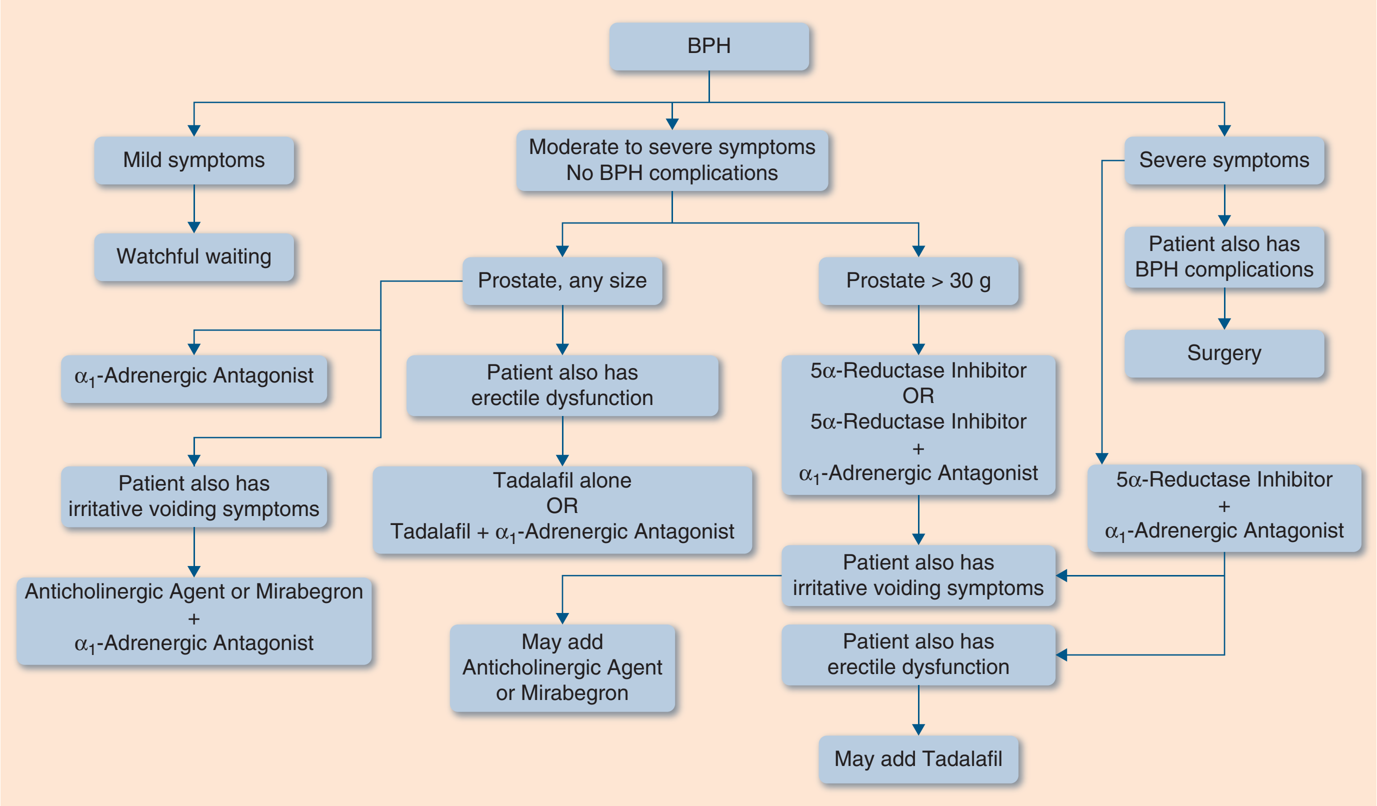
BPH
Mild symptoms
Moderate to severe symptoms No BPH complications
Severe symptoms
Watchful waiting
Prostate, any size
Prostate > 30 g
Patient also has BPH complications
Surgery
α_1-Adrenergic Antagonist
Patient also has erectile dysfunction
5α-Reductase Inhibitor OR 5α-Reductase Inhibitor + α_1-Adrenergic Antagonist
Patient also has irritative voiding symptoms
Tadalafil alone OR Tadalafil + α_1-Adrenergic Antagonist
5α-Reductase Inhibitor + α_1-Adrenergic Antagonist
Patient also has irritative voiding symptoms
Anticholinergic Agent or Mirabegron + α_1-Adrenergic Antagonist
May add Anticholinergic Agent or Mirabegron
Patient also has erectile dysfunction
May add Tadalafil

FIGURE 52–1. Algorithm for selection of treatment for BPH based on symptom severity and presence of disease complications.

worsen LUTS (Table 52–2). A digital rectal examination (DRE) is repeated annually. If the patient's symptoms are unchanged, watchful waiting is continued. If the patient's symptoms worsen, specific treatment is initiated.[12] Watchful waiting is effective in approximately 33% to 65% of patients with mild LUTS after 5 years.[1,12,13,17]

KEY CONCEPT For patients with moderate-to-severe symptoms and no complications of BPH, the patient is usually offered drug treatment first. α_1-Adrenergic antagonists are preferred over 5α-reductase inhibitors because the former have a faster onset of action (days to a few weeks) and improve symptoms independent of prostate size. 5α-reductase inhibitors have a delayed onset of peak clinical effect of 6 months and are most effective in patients with moderate-to-severe LUTS and larger size prostate glands (larger than 30 g or 1.1 oz). Because of the delay in clinical effect, a 5α-reductase inhibitor is often taken with an α_1-adrenergic antagonist. With either medication, treatment must be continued as long as the patient responds (Table 52–3).[1,12]

KEY CONCEPT Combinations of medications to treat moderate or severe symptoms of BPH are more expensive and can cause more adverse effects than single drug treatment. Therefore, combination medication regimens are reserved for patients who have voiding symptoms that do not respond to an adequate trial of single drug treatment or patients who are at high risk of developing complications of BPH. Refer to the section on Combination Therapy for a detailed description of various regimens and their advantages and disadvantages.

KEY CONCEPT Surgery is indicated for patients who are at risk of disease progression (ie, those with large prostates [larger than 40 g or 1.4 oz]) and PSA higher than 1.6 ng/mL (1.6 mcg/L), have moderate-to-severe symptoms and who are unresponsive to or intolerant of drug treatment, or have complications of BPH disease.[1,9,10] Although potentially curative, surgery can result in significant morbidity, including erectile dysfunction, retrograde ejaculation, urethral stricture, urinary incontinence, bleeding, or urinary tract infection. The gold standard is prostatectomy, which can be performed transurethrally using electrocautery or as an open surgical procedure. A transurethral prostatectomy is typically reserved for prostates of intermediate size (30 g [1.1 oz] to 80 g [2.8 oz]), whereas an open prostatectomy is used for very large prostates (larger than 80 g [2.8 oz]) or when the patient has additional urologic disorders, for example, large bladder stones or bladder diverticula, that can be surgically treated at the same time.[9] The newer bipolar technique for performing a TURP, which uses saline irrigating solution, has reduced the incidence of dilutional hyponatremia, a common adverse effect of the older monopolar technique, which uses glycine or sterile water irrigating solution.[9] The outcomes of prostatectomy include an almost immediate improvement of LUTS, an increase of peak urinary flow rate by 6 to 15 mL/s, and a PVR decrease of 30 to 80 mL. The need for reoperation is 5% to 10% at 10 years.[9]

To minimize complications of prostatectomy,[9,18] or in patients who are taking anticoagulants, minimally invasive surgical procedures, such as transurethral incision of the prostate, transurethral vaporization, transurethral microwave thermotherapy, transurethral laser ablation, or prostatic urethral lift are options.[9,18] A variety of laser energy sources are used to vaporize tissue: holmium, thulium, potassium-titanyl-phosphate (KTP or green light), or diode.[9,18] The choice of energy source is largely determined by the surgeon's level of training, the patient's anatomy, and potential risks for the patient. Prostatic urethral lift refers to transurethral implantation of a mechanical device that pins up the lateral lobes and reduces urethral obstruction.[1,9,18] The potential advantages of minimally invasive surgical procedures include less blood loss

Table 52–2

Drugs and Diseases That Can Cause Irritative or Obstructive Voiding Symptoms[15,16]

Pharmacologic Class	Example Drugs	Mechanism of Effect
Androgens	Testosterone	Stimulate prostate enlargement to cause obstructive voiding symptoms
α-Adrenergic agonists	Phenylephrine, pseudoephedrine	Stimulate contraction of prostatic and bladder neck smooth muscle to cause obstructive voiding symptoms
Anticholinergic agents	Antihistamines, phenothiazines, tricyclic antidepressants, antiparkinsonian agents Antiarrhythmics: disopyramide, procainamide, quinidine	Block detrusor muscle contraction, thereby impair bladder emptying and cause acute urinary retention
Caffeine	Caffeine	Acts like a diuretic to increase urine output
	Calcium Channel Blocker, Nifedipine, diltiazem	Block detrusor muscle contraction and thereby impairs bladder emptying
Anticonvulsants	Valproic acid	Causes sleepiness, which leads to functional incontinence
Diuretics	Thiazides diuretics, loop diuretics	Produce polyuria
Antidepressants, selective serotonin reuptake inhibitors	Escitalopram	Suppresses acetylcholine-mediated contraction of detrusor muscle; acute urinary retention may result
Opiates	Morphine, hydromorphone, meperidine	Decrease bladder motility
Sedatives	Benzodiazepines, ethanol	Can cause functional incontinence
Disease	**Example Diseases**	**Mechanism of Effect**
Diabetes mellitus		Results in glucosuria, which can cause urinary frequency; also can be associated with a neuropathy of the bladder which can produce irritative symptoms
Neurologic disorder	Parkinson disease, multiple sclerosis, brain tumors, spinal cord injury	Associated with neurogenic bladder which can produce irritative symptoms
Urethral stricture		Reduces urethral caliber which can cause obstructive symptoms
Meatal stenosis		Blocks urethral opening which can cause obstructive symptoms
Obesity		Causes stress urinary incontinence
Cigarette smoking		Unknown

and retrograde ejaculation, shorter periods of catheterization postoperatively, and no need for hospitalization. However, minimally invasive surgical procedures are associated with a shorter duration of effectiveness and higher reoperation rates than prostatectomy.[9]

Nonpharmacologic Therapy

To reduce nocturia, patients should be instructed to stop drinking fluids 3 or 4 hours before going to bed and then void before going to sleep. During the day, timed voiding every 2 to 3 hours, double voiding, toilet mapping (knowing the location of toilets on the way to and from various destinations), or voiding before a long trip may be helpful. Patients should avoid excessive intake of caffeine-containing beverages, sugar-sweetened drinks, and alcohol, which can cause urinary frequency. Patients should avoid taking nonprescription medications that can worsen obstructive voiding symptoms (eg, antihistamines or decongestants). Patients who take a diuretic should avoid taking it in the evening. Patients are also advised to stop smoking and lose excessive weight. An alteration in the testosterone: estrogen ratio occurs in overweight men because of testosterone conversion to estrogen in adipose tissue, which may contribute to the development of BPH. For patients with diseases known to worsen LUTS, optimal management of such disorders is key (see Table 52–2).[12,19]

Although a variety of herbal agents are used for symptomatic management, including pygeum (African plum), *Cucurbita pepo* (pumpkin seed), *Secale cereale* (rye pollen), *Serenoa repens*, and *Hypoxis rooperi* (South African star grass), objective evidence of efficacy is lacking.[20,21]

Pharmacologic Therapy

Table 52-3 compares five pharmacologic treatment approaches for BPH management.

▶ α_1-Adrenergic Antagonist Monotherapy[22]

KEY CONCEPT α_1-Adrenergic antagonists reduce the dynamic factor causing BPH symptoms. These drugs competitively antagonize α_1-adrenergic receptors, thereby causing relaxation of the bladder neck, prostatic urethra, and prostate smooth muscle.[12,22] A secondary mechanism of action may be that α_1-adrenergic antagonists induce prostatic apoptosis.[23]

All α_1-adrenergic antagonists are considered equally effective in relieving symptoms.[12,22] See Table 52–4. In various clinical trials, 30% to 80% of patients experience improvement in the AUA Symptom Score by 4 to 6 points, and 20% to 40% of patients experience urinary flow rate increases of 2 to 3 mL/s.[1] The onset of action is days to weeks, with peak clinical effects observed in several weeks. An adequate clinical trial is at least 2 to 4 weeks of continuous treatment at a full maintenance dose with any of these agents.[12,22] Durable responses have been demonstrated for many years with continued use. However, some patients will develop disease progression despite treatment. α_1-Adrenergic antagonists are hepatically metabolized. Therefore, in patients with significant hepatic dysfunction, these drugs should be used in the lowest possible dose. With the exception of silodosin, these drugs do not require dosage modification in patients with renal dysfunction.

Table 52–3

Comparison of α-Adrenergic Antagonists, 5α-Reductase Inhibitors, Anticholinergic Agents, Tadalafil, and Mirabegron for Treatment of BPH

Characteristic	α-Adrenergic Antagonists	5α-Reductase Inhibitors	Anticholinergic Agents	Tadalafil	Mirabegron
Relaxes prostatic smooth muscle	Yes	No	No	Yes	No
Reduces size of enlarged prostate	No	Yes	No	No	No
Useful in patients with enlarged prostates	Yes (works independent of the size of the prostate)	Yes	Yes	Yes	No[a]
Efficacy in relieving voiding symptoms and improving flow rate	++	+	+, irritative symptoms	+	+, irritative symptoms
Reduces the frequency of BPH-related complications	No	Yes	No	No	No
Reduces the frequency of BPH-related surgery	No	Yes	No	No	No
Frequency of daily dosing	Once or twice daily, depending on the agent and the dosage formulation	Once daily	Once or twice daily, depending on the agent	Once daily	Once daily
Requirement for up-titration of dose	Yes (for terazosin and doxazosin immediate-release); no (for alfuzosin or silodosin; possibly for doxazosin extended-release and tamsulosin)	No	Yes, depending on the agent	No	Yes, but minimal
Peak onset of action	Days to 6 weeks, depending on need for dose titration	6 months	Days	Days	2–8 weeks
Decreases PSA	No	Yes	No	No	No
Cardiovascular adverse effects	Yes, hypotension	No	Yes, tachycardia	Yes, hypotension	Yes, hypertension, tachycardia
Drug-induced sexual dysfunction	Ejaculation disorders	Decreased libido, erectile dysfunction, ejaculation disorders	Yes, erectile dysfunction	No	No
Significant drug interactions	Antihypertensives Calcium channel blockers β-adrenergic antagonists CYP 3A4 inhibitors CYP 3A4 inducers	CYP 3A4 inhibitors (dutasteride only)	Drugs with anticholinergic effects/side effects Drugs that prolong QT interval CYP 3A4 inhibitors CYP 3A4 inducers	Nitrates Drugs that prolong QT interval CYP 3A4 inhibitors CYP 3A4 inducers α-Adrenergic antagonists	CYP2D6 substrates Drugs that prolong the QT interval

[a] Mirabegron is not FDA-approved for BPH.

BPH, benign prostatic hyperplasia; CYP, cytochrome P-450; PSA, prostate-specific antigen.

α_1-Adrenergic antagonists are distinguished by several characteristics:

- *Uroselectivity*. Pharmacologic uroselectivity refers to preferential inhibition of α_{1A}-receptors, which comprise 70% of α_1 receptors in the prostatic stroma, prostatic urethra, and bladder neck.[22] Pharmacologically uroselective α_{1A}-adrenergic antagonists, tamsulosin and silodosin, have the potential to produce less hypotension than other α_1-adrenergic antagonists, because the former have a lower propensity to antagonize α_{1B}-adrenergic receptors in the peripheral vasculature. Silodosin has significantly greater α_{1A}-adrenergic selectivity than tamsulosin and is preferred when a patient has minimal tolerance for any blood pressure–lowering adverse effects.[6]

Although not a pharmacologically uroselective α_{1A}-adrenergic antagonist, alfuzosin is only available in an extended-release formulation and is prescribed as a fixed dose with no up-titration. As a result, alfuzosin is considered functionally uroselective.[22]

Uroselectivity is a dose-related phenomena. Large daily doses of tamsulosin, silodosin, or alfuzosin may cause loss of uroselectivity, with resultant hypotension and dizziness in some patients.[22,24]

Table 52–4

Comparison of Pharmacologic Properties of α1-Adrenergic Antagonists

	Terazosin	Doxazosin	Alfuzosin	Tamsulosin	Silodosin
Brand name	*	Cardura Cardura-XL	Uroxatral	Flomax	Rapaflo
Generation	Second	Second	Second	Third	Third
Uroselective	No	No	Functionally (Clinically)	Pharmacologically	Pharmacologically
Need for up-titration	Yes	Yes (with immediate-release); possibly (with extended-release)	No	Minimal	No
Daily oral dose (mg)	5–20	2–8, immediate-release; 4–8, extended-release	10	0.4–0.8; (0.8 mg/day dose has not consistently produced clinical improvement over 0.4 mg/day)	8
Recommended dose reduction in patients with renal dysfunction	None needed	None needed	Manufacturer recommends caution in patients with severe renal insufficiency. No specific dosing recommendations provided	If creatinine clearance > 10 mL/min (0.17 mL/s), no dose reduction needed. Tamsulosin has not been studied in patients with creatinine clearance < 10 mL/min (0.17 mL/s)	If creatinine clearance > 50 mL/min (>0.83 mL/s), no dosage adjustment is needed. If creatinine clearance 30–50 mL/min (0.50–0.83 mL/s), use 4 mg/day.Contraindicated in patients with creatinine clearance < 30 mL/min (0.50 mL/s)
Recommended dose reduction in patients with hepatic dysfunction	Manufacturer provides no specific recommendation. Terazosin should be used cautiously as it undergoes extensive hepatic metabolism	Manufacturer provides no specific recommendation in patients with mild/moderate impairment. Avoid use in patients with severe hepatic impairment	Contraindicated in patients with moderate/severe hepatic impairment. Alfuzosin should be used cautiously in patients with mild hepatic impairment	Patients with mild/moderate hepatic impairment require no dosage adjustment. Manufacturer provides no specific recommendation in patients with severe hepatic impairment	Patients with mild/moderate hepatic impairment require no dosage adjustment. Contraindicated in patients with severe hepatic impairment
Best time to take doses	At bedtime	Immediate-release: anytime during the day; however, it is typically given at bedtime Extended-release: anytime during the day	After meals for best oral absorption	On an empty stomach for best oral absorption. If taken 30 minutes after a meal, as recommended by the manufacturer, extent of absorption is reduced, thereby further reducing the potential for hypotensive adverse effects	Take with a meal, which decreases extent of absorption. Theoretically, this would help decrease hypotensive adverse effects
Special administration instructions	None	Do not crush, cut, or chew extended release tablet	Do not crush or chew tablet	Do not crush, chew, or open capsule	May open capsule and sprinkle on applesauce. Must swallow (not chew) applesauce within 5 minutes of preparation. Follow with a full cup of water.
Half-life (hours)	12	22	5	10	13
Formulation	Immediate-release	Immediate-release and extended-release	Extended-release	Modified-release	Modified-release
Cardiovascular adverse effects	++	++	+	0 to +	0 to +
Ejaculation disorders	+	+	+	++	++
Rhinitis	+	+	+	+	+
Malaise	+	+	+	+	+
Major substrate for CYP 3A4	No	Yes	Yes	Yes	Yes

+ minimal; ++ moderate; * terazosin is only available as a generic formulation.

Despite the blood pressure–lowering property of some α_1-adrenergic antagonists, they are not recommended to be used alone to treat patients with both BPH and essential hypertension. In the ALLHAT study,[25] doxazosin was associated with a higher incidence of congestive heart failure when compared to other antihypertensives. Therefore, in patients with both hypertension and moderate-to-severe LUTS, it is recommended that an appropriate antihypertensive be added to the α_1-adrenergic antagonist.

- *Need for up-titration of daily dose*. Up-titration is required for immediate-release terazosin and doxazosin. It is minimally required for extended-release doxazosin and tamsulosin. It is not required for extended-release alfuzosin or silodosin. The need for up-titration with a particular α_1-adrenergic antagonist delays its onset of peak action.[26]
- *Plasma half-life*. α_1-Adrenergic antagonists with short plasma half-lives (eg, prazosin, which is a first generation α_1-adrenergic antagonist) require multiple doses during the day. This is challenging for most patients, and thus, prazosin is not recommended for BPH.[12]
- *Dosage formulation*. Immediate-release formulations of terazosin and doxazosin are quickly absorbed and produce high peak plasma levels, which contributes to hypotensive adverse effects. Modified- or extended-release formulations of doxazosin, alfuzosin, tamsulosin, and silodosin produce lower peak levels, but more sustained therapeutic plasma levels, than immediate-release formulations. Modified- or extended-release formulations have less potential for producing hypotensive episodes, which allows for initiation of treatment with a therapeutic dose, a faster onset of peak clinical effects, and once daily dosing.[22,26]
- *Adverse effects*. Hypotensive adverse effects of α_1-adrenergic antagonists can range from asymptomatic blood pressure reductions to dizziness and syncope. This adverse effect occurs in approximately 2% to 14% of treated patients and is most commonly associated with immediate-release terazosin and doxazosin; is less commonly associated with extended-release alfuzosin and extended-release doxazosin; and least commonly associated with tamsulosin and silodosin.[22,26] To minimize first-dose syncope from terazosin and doxazosin immediate-release, a slow up-titration from a subtherapeutic dose of 1 mg/day to a therapeutic dose is essential. The first dose should be given at bedtime so that the patient can sleep through the peak serum concentration of the drug when the adverse effect is most likely to occur. A 3- to 7-day interval between each dosage increase should be allowed, and the patient should be maintained on the lowest effective dose of the α_1-adrenergic antagonist. If the patient is noncompliant with his regimen or he skips or interrupts treatment, the α_1-adrenergic antagonist should be restarted using the usual starting dose and then retitrated up. The patient should not be instructed to simply double up on missed doses or resume treatment with the currently prescribed daily dose, as this can lead to significant hypotension or syncope.

  Reversible delayed or absent ejaculation occur with all α_1-adrenergic antagonists. This is due to pharmacologic blockade of peripheral α_{1A}-adrenergic receptors in the vas deferens and seminal vesicles, which results in decreased antegrade flow of semen to the ejaculatory ducts, or at the bladder neck.[27] The incidence appears to be dose-related and highest with daily doses of tamsulosin 0.8 mg and silodosin 8 mg, occurring in up to 26% and 28% of treated patients, respectively.[27-29] Ejaculation disorders generally do not necessitate discontinuation of treatment as some elderly patients may not be sexually active. Although this adverse effect may decrease a patient's satisfaction with the quality of sexual intercourse, ejaculation disorders are not harmful to the patient.

  Nasal congestion and malaise occur more commonly with nonuroselective α_1-adrenergic antagonists and are an extension of the pharmacologic blockade of α_{1B}-adrenergic receptors in the vasculature of the nasal mucosa and in the central nervous system, respectively. Tolerance often develops to these adverse effects and they rarely require discontinuation of treatment. Avoid use of topical or oral decongestants, as these may exacerbate obstructive voiding symptoms. Cautious use of antihistamines with anticholinergic adverse effects is also recommended in patients with severe BPH and large PVRs, as these drugs may precipitate acute urinary retention.[15,16]

  Floppy iris or small pupil syndrome has been reported with α_1-adrenergic antagonists, most often with selective α_{1A} adrenergic antagonists.[30] In response to tamsulosin, the iris dilator muscle relaxes and the pupil constricts. Pupillary constriction interferes with the surgical procedure and increases the risk of intraoperative and postoperative complications. That is, the α_1-adrenergic antagonist can cause the iris to become flaccid, floppy, or billow out, and it can prolapse into the incision.[30] Individuals undergoing cataract surgery should discuss α_1-adrenergic antagonist use with the provider performing the surgery. Although the drug will not need to be held or discontinued, the provider can use certain surgical techniques to deal with the drug's effect on the iris dilator muscle.[30] Likewise, when initiating an α_1-adrenergic antagonist, an individual who needs cataract surgery should have this ophthalmologic procedure performed prior to starting the medication, if possible.[30]
- *Potential for drug interactions*. Hypotensive adverse effects of terazosin and doxazosin can be additive with those of diuretics, antihypertensives, and phosphodiesterase type 5 inhibitors (eg, sildenafil). In patients at greatest risk for hypotension, or in those patients who tolerate hypotension poorly, including those with poorly controlled coronary artery disease or severe orthostatic hypotension, tamsulosin, or silodosin may be safer options.[31] In patients who cannot tolerate adverse effects of any α_1-adrenergic antagonist, a 5α-reductase inhibitor or surgery could be considered, particularly if the prostate is enlarged and greater than 30 g (1.1 oz). When initiating a phosphodiesterase type 5 inhibitor, patients who are taking α_1-adrenergic antagonists should be stabilized first on a fixed dose of the α_1-adrenergic antagonist, and then patients should be started on the lowest effective dose of phosphodiesterase type 5 inhibitor to minimize the likelihood of hypotensive effects.[31]

▶ *5α-Reductase Inhibitor Monotherapy*

KEY CONCEPT 5α-reductase inhibitors reduce the static factor, which results in shrinkage of an enlarged prostate by approximately 15% to 25% after 6 months of continuous treatment. They inhibit 5α-reductase, which is responsible for intraprostatic conversion of testosterone to dihydrotestosterone (DHT), the active androgen that stimulates prostate tissue growth. Two subtypes

Table 52–5

Comparison of Pharmacologic Properties of 5α-Reductase Inhibitors

	Finasteride	Dutasteride
Brand name	Proscar	Avodart
Subtype inhibition of the 5α-reductase enzyme	Type II	Types I and II
Percentage decrease of serum dihydrotestosterone level	70–76	90–95
Time to peak onset of reduction in serum dihydrotestosterone level	6 months	1 month
Percentage decrease of intraprostatic dihydrotestosterone	85–90	> 95
Half-life	6.2 hours	5 weeks
Daily dosage (mg)	5	0.5
Dosage formulation	Tablet	Capsule
Instructions for drug administration	Take with or without meals	Take with or without food. Do not open or chew capsules. Swallow capsule whole
Recommended dose reduction in patients with renal dysfunction	None needed	None needed
Recommended dose reduction in patients with hepatic dysfunction	Manufacturer provides no specific recommendation. Finasteride should be used cautiously as it undergoes extensive hepatic metabolism	Manufacturer provides no specific recommendation. Dutasteride should be used cautiously as it undergoes extensive hepatic metabolism

of 5α-reductase, Type I and II, are present in the prostate; the majority is the Type II isoenzyme.[12,32] Finasteride is a selective Type II isoenzyme inhibitor, whereas dutasteride is a nonselective inhibitor of both isoenzymes. When compared with finasteride, dutasteride produces a faster and more complete inhibition of 5α-reductase in prostate cells. However, no difference in clinical efficacy has been demonstrated between these two agents.[12,33] Thus, finasteride and dutasteride are considered therapeutically equivalent (Table 52–5). It should be noted that 5α-reductase inhibitors may also cause apoptosis of prostate cells, which could contribute to a reduction in prostate gland size.[34]

Finasteride and dutasteride are considered equally effective in decreasing the AUA symptom score by 2.7 to 4.5 points in 30% to 70% of patients, increasing the urinary flow rate by 1.6 to 2.2 mL/s, and decreasing PVR by 18% to 28%, which is less improvement than that seen with α_1-adrenergic antagonists.[12,32] A minimum of 6 months is required to evaluate the full clinical effectiveness of treatment, which may be a disadvantage in patients with moderate-to-severe symptoms. Durable responses have been demonstrated in responding patients treated continuously for years. Unique to 5α-reductase inhibitors is that they prevent BPH-related complications and prevent disease progression. 5-α-reductase inhibitors have been shown to reduce both the incidence of acute urinary retention by 57% and the need for prostate surgery by 55% in patients with significantly enlarged prostate glands (larger than 40 g [1.4 oz]) when used continuously for at least 4 consecutive years.[35]

These agents are hepatically metabolized; however, no specific recommendations for dosage modification are available in patients with significant hepatic dysfunction. No dosage adjustment is needed in patients with renal impairment.

Sexual dysfunction, including decreased libido, erectile dysfunction, ejaculation disorders, and gynecomastia, occurs in 5% to 15% of treated patients.[36,37] The frequency of sexual dysfunction peaks generally 1 year after the start of treatment,[37] and the incidence of such adverse effects tends to be higher for dutasteride than for finasteride.[33] Proposed mechanisms for these adverse effects include: (a) by decreasing DHT, this decreases nitric oxide in the corpora cavernosa, which leads to erectile dysfunction; (b) by crossing the blood–brain barrier, they inhibit neurotransmitters responsible for sexual drive; (c) they inhibit blood flow to the genitalia, which results in ejaculatory disorders; and (d) unused testosterone is converted to estrogen peripherally, which contributes to gynecomastia.[37,38]

Recently, a syndrome of chronic fatigue, penile and scrotal shrinkage, persistent sexual dysfunction, and gynecomastia after discontinuation of finasteride has been described.[38] Some have suggested that these symptoms are simply related to the aging of the patient who coincidentally is taking finasteride. In addition, there have been reports of dementia, depression, and suicidal ideation.[38] Further study is needed to establish cause–effect relationships for these possible adverse effects.

These agents reduce the incidence of prostate cancer by 25% but are suspected to increase the risk of developing moderate-to-high grade cancer, if prostate cancer does develop, and are not recommended for the prevention of prostate cancer.[39]

Patient Encounter 2

A 60-year-old man is diagnosed with moderate LUTS secondary to BPH. After a urologic work up, the patient has an AUA symptom score of 16, a urinary flow rate of 8 mL/s, PVR 60 mL, and prostate size of 50 g (1.8 oz) on transrectal ultrasound, and a PSA of 8 ng/mL (8 mcg/L). He has essential hypertension, which is well controlled on hydrohlorothiazide, valsartan, and amlodipine. The patient is a house painter and uses ladders all the time. He is started on dutasteride for BPH. The patient is sexually active.

Why should an α_1-adrenergic antagonist be used cautiously in this patient?

To enhance adherence to dutasteride, what education should be provided to this patient?

Exposure to 5α-reductase inhibitors is contraindicated in pregnant women, as the drugs may cause feminization of a male fetus. Pregnant women should not handle these drugs unless they are wearing gloves.

During continuing treatment of BPH, the patient should undergo an annual repeat PSA and DRE. These agents decrease PSA by a mean of 50% after 6 months of continuous use. A rising PSA level suggests that the patient has worsening BPH, new-onset prostate cancer, or that the patient is noncompliant with his regimen of 5α-reductase inhibitor. An abnormal DRE suggestive of prostate cancer would reveal a nodule or area of induration on the prostate. In this case, a prostate biopsy is required to rule out prostate cancer.

▶ Tadalafil

Tadalafil is expensive and should be reserved for patients with both BPH and erectile dysfunction, or those patients with LUTS that is not responsive to α-adrenergic antagonists. Tadalafil may be prescribed alone, or along with an α_1-adrenergic antagonist or 5α-reductase inhibitor. Proposed mechanisms of action for tadalafil include: (a) relaxation of smooth muscle of the urethra, prostate, and bladder neck, mediated by increased production of cyclic guanosine monophosphate, relieves obstructive voiding symptoms; (b) relaxation of detrusor smooth muscle which reduces irritative bladder symptoms; and (c) relaxation of vascular smooth muscle, which increases blood flow and decreases inflammation of the prostate.[40] Tadalafil is comparable to α_1-adrenergic antagonists in relieving obstructive voiding symptoms, but also reduces irritative voiding symptoms.[41] However, tadalafil does not increase urinary flow rate or reduce PVR.[42] Although patients will experience symptom improvement in a week, full clinical effects may take 2 to 3 months.[12,43] The usual recommended dose is 5 mg by mouth daily; the dose should be reduced to 2.5 mg daily if the creatinine clearance is 30 to 50 mL/min (0.50–0.83 mL/s). Daily doses greater than 5 mg have not been shown to be beneficial for BPH. Tadalafil should be avoided if the creatinine clearance is less than 30 mL/min (0.50 mL/s). Tadalafil is contraindicated in patients on nitrates by any route of administration. If added to treatment with an α_1-adrenergic antagonist, the patient's blood pressure should be stabilized first. If the patient is sexually active, tadalafil should not be used in patients with unstable angina, uncontrolled or high-risk arrhythmias, persistent hypotension, poorly controlled hypertension, or New York Heart Association Classification IV congestive heart failure; or patients who have had a myocardial infarction or stroke within the past 2 weeks.[31]

Common adverse effects include headache, dizziness, flushing, dyspepsia, back pain, myalgia, and cyanopsia (Table 52–6).

Tadalafil should be used cautiously in patients who are at high risk for priapism. This includes patients with sickle cell disease, multiple myeloma, leukemia; or those taking other erectogenic agents.

Although other phosphodiesterase type 5 inhibitors share the same mechanism of action as tadalafil and can improve the AUA Symptom Score, tadalafil is preferred because of its longer plasma half-life, which is theoretically beneficial in the management of BPH, a chronic disease.

▶ Anticholinergic Agents

Approximately 45% to 50% of men with BPH have symptoms of overactive bladder.[40,44,45] These irritative voiding symptoms are due to involuntary detrusor muscle contraction in response to small volumes of urine in the bladder. The detrusor muscle is innervated with muscarinic receptors. M_2 receptors comprise 75% of all muscarinic receptors; however, their physiologic function, along with that of M_4 and M_5 receptors, is not well understood. M_3 receptor stimulation is associated with abnormal detrusor contractions, which can cause irritative voiding symptoms.[44]

Anticholinergic agents are indicated when a patient has bothersome irritative voiding symptoms despite treatment with an α_1-adrenergic antagonist. Typically, an anticholinergic agent is added sequentially to an established α_1-adrenergic antagonist regimen. The ideal patient for the combination has a urinary flow rate of at least 10 mL/s and a PVR less than 50 mL. A recent meta-analysis showed that the addition of an anticholinergic agent to an α_1-adrenergic antagonist improved irritative symptoms more than what was observed with the α_1-adrenergic antagonist alone.[12,45] No cases of urinary retention were reported.

Many anticholinergic agents are available. Darifenacin is the only M_3 uroselective anticholinergic agent. Because M_3 receptors are present in the gastrointestinal tract, and eye, darifenacin can cause constipation, xerostomia, and mydriasis. Refer to Chapter 53, Urinary Incontinence and Pediatric Enuresis, for a discussion of the properties of anticholinergic agents.

If irritative symptoms do not improve after starting an anticholinergic agent, up-titrating the dose or switching to another anticholinergic agent may be helpful. Patients at the highest risk of anticholinergic agent-induced acute urinary retention include those with a PVR of 200 mL or more, low urinary flow rate, or previous history of acute urinary retention.[12,44,45] Also, the medication profile of patients should be checked for overall anticholinergic burden, which increases the likelihood of anticholinergic adverse effects, including dry mouth, tachycardia, constipation, confusion, drowsiness, and acute urinary retention. Finally, elderly patients have a high risk of cognitive impairment from anticholinergic agents, especially those with a history of stroke, head trauma, Parkinson disease, and Alzheimer disease.[43-45]

▶ Mirabegron

In the urinary bladder, 95% of all β-adrenergic receptors are of the β_3 type. Receptor stimulation relaxes the detrusor muscle, decreases detrusor overactivity, and increases bladder capacity, but does not interfere with the bladder's contractility.[40]

Mirabegron is a β_3-adrenergic agonist. It causes release of norepinephrine which stimulates β_3-adrenergic receptors, thereby reducing irritative voiding symptoms.[46,47] Although not Food and Drug Administration (FDA)-approved for BPH, mirabegron is an alternative to an anticholinergic agent in patients who poorly tolerate or are at high risk of anticholinergic adverse effects, or when irritative voiding symptoms do not respond to an anticholinergic agent. Mirabegron is typically added to an α_1-adrenergic antagonist.[47] The usual dose is 50 mg by mouth daily. Larger daily doses have shown no greater efficacy than 50 mg.[46] If the creatinine clearance is 15 to 29 mL/min (0.25–0.48 mL/s), the dose should be reduced to 25 mg daily. Mirabegron should be avoided if the creatinine clearance is less than 15 mL/min (0.25 mL/s) or in patients with poorly controlled hypertension. Common adverse effects of mirabegron include headache, hypertension, tachycardia, constipation, and nasopharyngitis.

▶ Combination Therapy

KEY CONCEPT A combination of an α_1-adrenergic antagonist and 5α-reductase inhibitor may be considered in symptomatic patients who do not respond to an adequate trial of monotherapy or in symptomatic patients at high risk of BPH complications.[12] In such patients, combination therapy will relieve voiding symptoms

Table 52–6

Summary of Adverse Effects of α-Anticholinergic Agents, Tadalafil, and Mirabegron and Management Suggestions

Drug Class	Adverse Reaction	Management Suggestion
α-Adrenergic antagonist	Hypotension	Start with lowest effective dose, give doses at bedtime, and slowly up-titrate at 0.5- to 1-week intervals to a full therapeutic dose, if using immediate-release terazosin or doxazosin Use tamsulosin, silodosin, extended-release doxazosin, or alfuzosin, as alternatives to immediate-release products, particularly in patients with low blood pressure at baseline or in those taking other antihypertensives
	Malaise	Educate the patient that this is a common adverse effect; tolerance may develop to malaise. Usually does not require discontinuation of treatment
	Nasal congestion	Educate the patient that this is a common adverse effect; tolerance may develop to rhinitis. Usually does not require discontinuation of treatment. Avoid decongestants.
	Ejaculation disorders	Educate the patient that this is a common adverse effect and is not harmful.
	QT interval prolongation	This is a rare but potentially serious adverse effect of alfuzosin only. The patient will most likely have chest pain, dizziness, loss of energy, and pass out. The patient should discontinue the medication and seek immediate attention of the prescriber. At high risk are patients taking other medications that prolong QT interval.
5α-Reductase inhibitor	Gynecomastia	Educate the patient that this may be painful or bothersome but not harmful
	Decreased libido	If the patient is sexually active, sexual counseling may be helpful. May be reversible despite continued use of the 5α-reductase inhibitor.
	Erectile dysfunction	The addition of sildenafil or another erectogenic drug may be helpful. May be reversible despite continued use of the 5α-reductase inhibitor.
	Ejaculation disorders	Educate the patient that this may occur but it is not harmful. May be reversible despite continued use of the 5α-reductase inhibitor
Anticholinergic agent	Dry mouth	Educate the patient that this is a common adverse effect. If drinking fluids and sucking on sugarless hard candy are not effective, the healthcare provider may switch to another agent in the same class or possibly reduce the daily dose.
	Constipation	This is a common adverse effect. Educate the patient to drink plenty of fluids and eat a high-fiber diet.
	Confusion, drowsiness	If this occurs, consider switching to another agent in the same class with less potential to cross the blood–brain barrier, eg, trospium
	Acute urinary retention	Do not use anticholinergic agents in patients with a PVR > 200 mL as they are high risk of developing this adverse effect, which is a urologic emergency
	Increased risk of heat stroke	By decreasing perspiration, patients who are in hot climates and who do not have access to air conditioning, are at risk of heat stroke. Use of anticholinergic agents in elderly who are exposed to these conditions should be avoided
Tadalafil	Headache	Educate the patient that this is a common adverse effect. It is usually mild, temporary, and does not require treatment discontinuation. If necessary, acetaminophen is usually effective
	Dizziness	Educate the patient that this is a common adverse effect and does not require treatment. If the patient is taking other blood pressure–lowering medications, stabilize blood pressure on these medications before starting tadalafil
	Flushing	This is a reversible, dose-related adverse effect that does not require treatment discontinuation
	Nasal congestion	This is an extension of the vasodilatory effects of tadalafil. It is reversible, dose-related, and does not require treatment discontinuation
	Visual loss	This can occur any time after tadalafil is started. It is usually painless. The patient should discontinue tadalafil and seek immediate medical attention
	Back pain	If severe, the patient should report this to the clinician. It may require discontinuation of tadalafil
	Dyspepsia	Heartburn-like symptoms may occur. Usually, it is mild and does not require treatment
	Back pain or myalgia	This occurs more often with tadalafil than with the other phosphodiesterase inhibitors. It usually resolves once the drug is stopped. If not severe, tadalafil may be continued as the adverse effect may resolve with continued tadalafil use.
Mirabegron	Hypertension	May need to initiate or adjust existing antihypertensive medications. Educate patient to monitor blood pressure while taking this medication.
	Tachycardia	Educate the patient that this is a common adverse effect. However, if increased pulse rate or palpitations are associated with low blood pressure, chest pain, or difficulty breathing, the patient should seek medical attention.
	Headache	Educate the patient that this is a common adverse effect. It is usually mild, temporary, and does not require treatment discontinuation. If necessary, a low dose of acetaminophen is usually effective.
	Constipation	This is a common adverse effect. Educate the patient to drink plenty of fluids and eat a high-fiber diet.
	Dizziness	Educate the patient that this is a common adverse effect. The patient should monitor blood pressure and seek medical attention if dizziness is moderate or severe.
	Angioedema	In addition to swelling of the face, lips, tongue, and throat, the patient may have shortness of breath and wheezing. This is an allergic reaction that requires immediate discontinuation of the drug and notification of the prescriber. The patient should not continue taking mirabegron unless the prescriber approves doing so.
	QT interval prolongation	This is a rare but potentially serious adverse effect. The patient will most likely have chest pain, dizziness, loss of energy, and pass out. The patient should discontinue the medication and seek immediate attention of the prescriber.

and also may reduce the risk of developing BPH-related complications by 64% and reduce the need for prostatectomy by 67% after continued use for a minimum of 4 years.[40,48-50]

The benefit of combination therapy with any α_1-adrenergic antagonist and any 5α-reductase inhibitor is well established. A recent study suggests that initiating a combination regimen in patients with moderate LUTS due to BPH is more likely to produce persistent improvements in AUA Symptom Score and urinary flow rate and may reduce the risk of clinical progression after 1 year than treatment with an α_1-adrenergic antagonist alone.[50] Because combination therapy is also associated with low adherence, a commercially available combination formulation of dutasteride 0.5 mg and tamsulosin 0.4 mg is available. In summary, combination therapy generally requires long-term use of an α_1-adrenergic antagonist and 5α-reductase inhibitor, which is more expensive, and is associated with lower adherence and more adverse effects than a single drug regimen. Therefore, clinicians should discuss the advantages and disadvantages of such a combination regimen with the patient before a final decision is made (see Table 52–4).[12,49]

Several other combination therapy regimens have also been used for moderate-to-severe LUTS due to BPH. Unlike that of the previously described combination, the published evidence to support newer combinations is limited. One rationale for combined use is that drugs working by different mechanisms to reduce LUTS may provide additional benefit. Tadalafil has been combined with an α_1-adrenergic antagonist[47,45] or with a 5α-reductase inhibitor. To minimize an additive blood pressure–lowering effect, tamsulosin or silodosin are preferred α_{1A}-adrenergic antagonists when combined with tadalafil. Similarly, tadalafil can offset erectile dysfunction that commonly occurs with finasteride or dutasteride. As tadalafil is expensive, combination therapy with tadalafil is reserved for patients with both moderate or severe BPH and erectile dysfunction.

For patients with moderate or severe irritative voiding symptoms due to BPH that are not responsive to an α_1-adrenergic antagonist alone, an anticholinergic agent may be added. The combination increases urine storage in the bladder and decreases voiding frequency and urgency.[12] Patients at low risk of acute urinary retention should be carefully selected for such combination therapy. These include patients with PVRs less than 50 mL and those with a urinary flow rate of at least 10 mL/s.

For patients who poorly tolerate anticholinergic adverse effects, an alternative is mirabegron, which may be added to an α_1-adrenergic antagonist. A combination of tamsulosin and mirabegron has reduced urinary urgency and frequency and increased urine storage in the bladder when compared to tamsulosin alone.[40,46]

Patient Encounter 3

A 69-year-old man LUTS secondary to BPH presents to clinic. He complains of moderate to severe urinary urgency and nocturia, which has necessitated his use of adult diapers during the day, and interrupted sleep during the night. His AUA symptom score is 20, PVR is 150 mL. He is started on tamsulosin 0.4 mg by mouth daily. After 4 weeks, a repeat AUA symptom score is 18 and he patient still complains of urinary urgency and nocturia.

What additional treatment options could be considered?

If an anticholinergic agent is selected, would an M2 selective agent be recommended?

Let us presume that the prescriber is concerned that the patient may develop confusion during treatment with an anticholinergic. What measures could be taken to minimize this adverse effect?

OUTCOME EVALUATION

KEY CONCEPT Once the peak effects of drug treatment are expected to occur, monitor the drug for effectiveness. This is approximately 2 to 4 weeks after the start of an α_1-adrenergic antagonist, anticholinergic agent, tadalafil, or mirabegron; and 3 and 6 months after the start of a 5α-reductase inhibitor. Assess symptom improvement using the AUA Symptom Scoring Index. A reduction in symptom score by a minimum of three points is anticipated. However, it should be noted that the AUA Symptom Score may not match the patient's perception of the bothersomeness of his voiding symptoms. If the patient perceives his symptoms as bothersome, independent of the AUA Symptom Score, consideration should be given to modifying the patient's treatment regimen. Similarly, a patient may regard his symptoms as not bothersome even though the AUA Symptom Score is high. At baseline and during treatment, the clinician should objectively assess symptoms and check urinary flow rate, PVR, and the absence of complications of BPH. If the patient shows a response to treatment, instruct the patient to continue the drug regimen and have the patient return at 6-month intervals for monitoring. If the patient shows an inadequate response to treatment, the dose of α_1-adrenergic antagonist can be increased (except for alfuzosin and silodosin) or another drug can be added to reduce the patient's symptoms or until the patient experiences adverse drug effects.

For the α_1-adrenergic antagonists, the severity of hypotensive-related adverse effects, which may manifest as dizziness or syncope, may require a dosage reduction, slower up-titration of the dose, or drug discontinuation. Other adverse effects of α_1-adrenergic antagonists are nasal congestion, malaise, headache, and ejaculation disorders. None of these generally require discontinuation of treatment, and these often improve as treatment continues. For the 5α-reductase inhibitors, the most bothersome adverse effects are decreased libido, erectile dysfunction, ejaculation disorders, and gynecomastia. In sexually active men, erectile dysfunction may be improved with erectogenic drugs; however, this adverse effect may necessitate discontinuation of treatment. The adverse effects of anticholinergics are dose-related and may be poorly tolerated and require drug discontinuation. Whereas tadalafil is well tolerated, mirabegron may increase blood pressure, necessitating the initiation or modification of an existing antihypertensive regimen.

Initial failure to respond to α_1-adrenergic antagonists occurs in 20% to 70% of treated patients. It is likely in these patients that the static factor may predominate as the cause of symptoms in these patients. In these patients, adding a 5α-reductase inhibitor may be helpful to shrink the prostate. Initial failure to respond to 5α-reductase inhibitors occurs in 30% to 70% of treated patients. It is likely that the dynamic factor may predominate as the cause of symptoms in these patients. Switching to or adding an α_1-adrenergic antagonist may be helpful. In contrast, drug treatment failures after an initial good response to drug therapy will likely be an indication of progressive BPH disease. In such patients, modifying the drug regimen or surgical intervention may be indicated. Finally, nonadherence to prescribed medication regimens, particularly combination therapy regimens for BPH, occurs in up to 40% of patients.[26]

Table 52–6 summarizes the adverse effects of the agents used to treat BPH and includes management suggestions for these situations.

Patient Care Process

Collect Information:

- Review the medical history and physical examination.
- Conduct a medication history for medications or dietary supplements that could be contributing to his voiding symptoms (Table 52–2). Identify allergies to medications and other substances. List current medications that the patient may be taking for LUTS and identify dose, start date, response to treatment, and adverse effects of treatment (Tables 52–3 to 52–6).
- Speak with the patient to identify lifestyle habits, preferences and health beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Based on the medical history, determine whether the patient has compelling indications for specific medications for BPH, (eg, does the patient also have erectile dysfunction?).
- Based on medical history, signs and symptoms, AUA Symptom Score (Table 52–1), and presence of complications of BPH disease, classify BPH as mild, moderate, or severe.
- Review available laboratory tests, especially serum electrolytes, renal function, and urinalysis.
- Assess the patient's adherence to lifestyle modification measures.
- Assess the efficacy and safety of, and patient adherence to current pharmacotherapy.
- Identify any significant adverse drug effects or interactions from current pharmacotherapy.

Develop a Care Plan:

- If the patient's AUA Symptom Score is in the range of 8 to 35 despite existing pharmacotherapy for BPH, modify the existing regimen. Consider increasing the dose of the drug, if feasible, or adding a drug to the existing regimen.
- If the patient is not on current pharmacotherapy for BPH but has mild LUTS, initiate lifestyle modifications. If LUTS is moderate to severe, drug therapy is also indicated. Choose medications and doses that are optimal for the patient.

Implement the Care Plan:

- Review lifestyle modification measures that reduce LUTS and reinforce adherence.
- Educate the patient about new or changes to drug therapy, best time to take daily doses, potential adverse effects, and how to self-manage and report adverse effects that might occur.
- Address any patient concerns about BPH and its management.
- Determine whether the patient has insurance coverage or whether recommended agents are included on this patient's insurance formulary.
- Educate the patient on the importance of adherence to the prescribed drug regimen.

Follow-up: Monitor and Evaluate:

- After starting an α_1-adrenergic antagonist, tadalafil, an anticholinergic agent, or mirabegron, assess effectiveness and safety of therapy in 1 month, and then at 6 months. At each visit, repeat the AUA Symptom Scoring Index, check for disease progression, repeat urinary flow rate and PVR, and assess adverse effects of treatment. As long as the patient continues to respond and tolerates the medication well, repeat all assessments at yearly intervals thereafter.
- After starting a 5α-reductase inhibitor, assess effectiveness and safety of therapy at the end of the third and sixth month.

Abbreviations Introduced in This Chapter

AUA	American Urological Association
BPH	Benign prostatic hyperplasia
BUN	Blood urea nitrogen
DRE	Digital rectal examination
FDA	Food and Drug Administration
LUTS	Lower urinary tract symptoms
PSA	Prostate-specific antigen
PVR	Postvoid volume
TURP	Transurethral resection of the prostate

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Urinary Incontinence and Pediatric Enuresis

Sum Lam and Gladys El-Chaar

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the pathophysiology of the major types of urinary incontinence (UI): urgency, stress, overflow, and functional.
2. Recognize the signs and symptoms of the major types of UI in individual patients.
3. List the treatment goals for a patient with UI.
4. Compare and contrast available therapeutic agents for UI; identify factors that guide drug selection for an individual patient.
5. Formulate a monitoring plan and provide patient counseling for a patient on a given treatment regimen based on patient-specific information.
6. Explain the pathophysiology of pediatric enuresis.
7. List treatment goals; compare and contrast available management strategies for managing pediatric enuresis.
8. Formulate a patient-specific monitoring plan and implement patient counseling for a patient on a given treatment regimen.
9. Describe nonpharmacologic treatment approaches for pediatric enuresis.

INTRODUCTION

Urinary incontinence (UI) is defined as the complaint of involuntary leakage of urine.[1] It is often associated with other bothersome lower urinary tract symptoms such as **urgency**, increased daytime **frequency**, and **nocturia**. Despite its prevalence in both genders, UI remains an underreported health problem that can negatively impact an individual's quality of life. Patients with UI may sense a loss of self-control, independence, and self-esteem, and often modify their activities for fear of an "accident." Patients with UI may also suffer from other consequences, including perineal dermatitis and infections, pressure ulcers, urinary tract infections (UTIs), and falls. In the United States, the estimated national cost of urgency urinary incontinence (UUI) in 2007 was $66 billion, with projected costs of $83 billion in 2020.[2]

EPIDEMIOLOGY AND ETIOLOGY

The true prevalence of UI is unclear because of varying definitions of UI and reporting bias.[3]

- About 44% of noninstitutionalized persons aged 65 and older report UI[4]
- 7% to 37% of women aged 20 to 39 report some degree of UI
- 9% to 39% of women aged 60 and older report daily UI
- 11% to 34% of older men report some degree of UI
- 2% to 11% of older men report daily UI
- In the noninstitutionalized setting, more than 50% of elderly women and more than 25% of elderly men report UI
- 46% of short-term and 76% of long-term nursing home residents report UI[4]

UI can result from abnormalities within (intrinsic to) and outside of (extrinsic to) the urinary tract. Within the urinary tract, abnormalities may occur in the urethra (including the bladder outlet and urinary sphincters), the bladder, or a combination of both structures. Focusing on abnormalities in these two structures, a simple classification scheme emerges for all but the rarest intrinsic causes of UI. **KEY CONCEPT** Accurate diagnosis and classification of UI type is critical to the selection of appropriate drug therapy.

PATHOPHYSIOLOGY

Stress Urinary Incontinence[5]

Stress urinary incontinence (SUI) occurs most frequently in women and is related to the underactivity of urethra and/or urethral sphincters, leading to inadequate resistance to impede urine flow from the bladder. SUI occurs when intra-abdominal pressure is elevated by exertional activities like exercise, running, lifting, coughing, and sneezing. SUI is usually episodic, associated with small volume leakage and rarely causes nocturia or **enuresis**. The etiology for urethral underactivity is not completely understood, although it is thought be related to the loss of the trophic effects of estrogen on the uroepithelium at menopause. The peak of SUI prevalence in the perimenopausal years supports this hypothesis. Clearly established risk factors for SUI include the following:

- Pregnancy (increased risk with increased parity)
- Childbirth (vaginal delivery)

Patient Encounter 1, Part 1

A 60-year-old woman presents to the clinic complaining of urinary symptoms that are mentioned by "the lady on a television commercial for a drug for overactive bladder." She often experiences a strong, sudden urge to urinate during the daytime. She has not leaked urine during the last 3 months. She is afraid "it might happen someday when she could not get to the toilet fast enough." On average she takes about 10 trips per day to bathroom during the daytime and gets up at least once at night to urinate. She is especially bothered by her urinary symptoms when she needs to attend consecutive sessions of work meetings that last more than 90 minutes. Occasionally she excuses herself from the meetings before they end, so she can get to the toilet fast enough. In the past 3 months, she has avoided six outdoor events planned by her family and friends. She used to love spending time with her grandkids and close friends. She denies any urinary leaks when she coughs, laughs, or exercises. She is diagnosed with overactive bladder without urinary incontinence. She is willing to try drug therapy in addition to nonpharmacologic interventions. She wants to avoid side effects as much as possible. She has a good employer-sponsored insurance plan for prescription drugs.

What information is suggestive of overactive bladder?

What additional information is necessary to differentiate overactive bladder from stress, overflow, and functional urinary incontinence? Are there any exacerbating factors?

What additional information do you need to know before creating a treatment plan for this patient?

- Menopause
- Cognitive impairment
- Obesity
- Increasing age

SUI is exceedingly rare in males unless the sphincter mechanism is compromised by surgery or trauma. The most common surgeries predisposing to SUI in men are radical prostatectomy for prostate cancer and transurethral resection of the prostate for benign prostatic hyperplasia (BPH).

Urgency Urinary Incontinence[5]

UUI is related to the overactivity of detrusor muscle in the bladder, which contracts inappropriately during the filling (urinary storage) phase and generates urgency. The bladder contractions are due to the stimulation of muscarinic cholinergic receptors, especially M2 and M3 subtypes. UUI is associated with large volume leakage (sometimes complete bladder emptying), nocturia and enuresis (may disrupt sleep). Overactive bladder (OAB) is a symptom syndrome with or without associated UUI.[6]

Most women with UUI or OAB have no identifiable causes (idiopathic), while in men similar symptoms are associated with BPH (see Chapter 52). Overactivity may be myogenic and/or neurogenic. Clearly established risk factors for UUI include:

- Older age
- Neurologic disorders (e.g., stroke, Parkinson disease, multiple sclerosis, and spinal cord injury)
- Bladder outlet obstruction (e.g., benign or malignant prostatic enlargement or hyperplasia)
- Hysterectomy
- Recurrent UTIs

Overflow Urinary Incontinence[5]

Overflow urinary incontinence (OUI) is a less common form of UI in men or women. It is related to urethral overactivity and/or bladder underactivity. In short, the bladder is filled to capacity at all times but cannot empty, causing urine to leak out episodically. If caused by bladder underactivity, the progressively weakened detrusor muscle eventually loses the ability to voluntarily contract, which leads to incomplete voiding and large residual urinary volume after micturition. Both myogenic and neurogenic factors have been associated with impaired bladder contractility that leads to OUI. Common neurogenic factors are diabetes, lower spinal cord injury, multiple sclerosis, or radical pelvic surgery.

If OUI is due to urethral overactivity, incomplete bladder emptying occurs because the resistance of the urethra and/or sphincters cannot be overcome by detrusor contractility. In men, this most frequently occurs in cases of long-term chronic bladder outlet obstruction due to BPH, prostate cancer, or abdominal-pelvic surgeries. In women, urethral overactivity is rare but may result from cystocele formation or surgical overcorrection for SUI. In both genders, systemic neurologic diseases such as multiple sclerosis or spinal cord injury may be the etiology.

Functional UI[5]

Functional UI is generally caused by extrinsic factors to the urinary tract, such as:

- Immobility (due to pain, physical limitations)
- Inadequate or delayed access to toileting facilities
- Neurologic impairment (Parkinson disease, multiple sclerosis, spinal cord injury, stroke, apathy due to depression)
- UTIs
- Postmenopausal atrophic urethritis and/or vaginitis

Clinical Presentation of Stress Urinary Incontinence (SUI) Related to Urethral Underactivity[5]

General

Usually occurs during activities like exercise, running, lifting, coughing, or sneezing; much more common in women.

Symptoms

Urine leakage volume is proportional to activity level; not associated with nocturia. No SUI with physical inactivity, especially when supine. May develop urgency and frequency as a compensatory mechanism (or independently as a separate component of bladder overactivity).

Diagnostic Tests

Observation of urethral meatus (opening) while patient coughs or strains.

Clinical Presentation of Urgency Urinary Incontinence (UUI) Related to Bladder Overactivity[5]

General

If sensory input from the lower urinary tract is absent, may have bladder overactivity and urine leakage without urgency. Patient with OAB may not have UUI.

Symptoms

Patients with OAB typically present with symptoms of urgency, frequency, nocturia with or without associated UUI.

Diagnostic Tests

Urodynamic studies are the gold standard for diagnosis. UTI must be ruled out by urinalysis and urine culture.

- Diabetes mellitus (glucosuria leading to polyuria)
- Diabetes insipidus (polyuria due to decreased antidiuretic hormone [ADH])
- Pelvic malignancy (extrinsic pressure on urinary tract structures causing obstruction)
- Constipation or fecal impaction
- Congenital malformations of the urinary tract system

Mixed and Drug-Induced UI[5]

Mixed urinary incontinence (MUI) occurs when two or more types of UI coexist in a given patient, which may lead to diagnostic and therapeutic difficulties. Patients may experience worsening of symptom due to the opposing effects of treatments indicated for specific and different types of UI.

KEY CONCEPT Many medications can influence the lower urinary tract system and precipitate or aggravate existing voiding dysfunction that leads to UI (Table 53–1).

Clinical Presentation of Overflow Urinary Incontinence (OUI) Related to Urethral Overactivity and/or Bladder Underactivity[5]

General

Rare type of UI in both genders. Urethral overactivity is usually due to prostatic enlargement in men or cystocele formation or surgical overcorrection for SUI in women. Bladder underactivity is usually due to a weakened detrusor muscle.

Symptoms

Lower abdominal fullness, **hesitancy**, straining to void, decreased force of stream, interrupted stream, sense of incomplete bladder emptying. May have urinary frequency and urgency, as well as abdominal pain if acute urinary retention occurs.

Signs

Increased postvoid residual urine volume.

CLINICAL PRESENTATION AND DIAGNOSIS

Guidelines are available for the assessment, diagnosis, and management of UI or OAB.[6-10] In general, obtaining a complete medical history and performing a targeted physical examination are essential to correctly classify the type(s) of UI. The degree of annoyance perceived by the patient due to urinary symptoms must also be assessed. However, it may not correlate well with quantitative tests such as symptom frequency/severity, use of absorbent products, and postvoid residual (PVR) urine volume (Table 53–2). Major components of the physical examination include:[5,11]

- Abdominal examination for distended bladder, organomegaly, and masses
- Neurologic evaluation of perineum and lower extremities to evaluate lumbosacral nerve function (includes digital rectal

Table 53–1

Medications Influencing Lower Urinary Tract Function

Medication	Effect
Diuretics	Polyuria, frequency, urgency
α-Adrenoceptor antagonists	Urethral relaxation: may relieve obstruction in males, induces/worsens SUI in females
α-Adrenoceptor agonists	Urethral constriction: aggravates obstruction in males (may cause urinary retention), potential SUI treatment in females
Calcium channel blockers (dihydropyridines)	Reduced bladder contractility (may cause urinary retention)
Opioid analgesics	Impaired bladder contractility (may cause urinary retention)
Sedative-hypnotics	Functional UI due to immobility, delirium, sedation
Psychotherapeutics with anticholinergic properties; anticholinergics	Urinary retention due to impaired bladder contractility or potential UUI treatment
TCAs	Combination of anticholinergic and α-adrenoceptor blocking activities can lead to unpredictable effects on UI
Ethanol	Polyuria and frequency (via effects on ADH), functional UI (delirium, sedation), urgency
ACEIs	Cough leading to SUI (ARBs do not induce cough)
Cyclophosphamide	Hemorrhagic cystitis due to acrolein metabolite (preventable with MESNA)

ACEIs, angiotensin-converting enzyme inhibitors; ADH, antidiuretic hormone (or vasopressin); ARB, angiotensin II receptor blocker; MESNA, sodium 2-mercaptoethanesulfonate; SUI, stress urinary incontinence; TCA, tricyclic antidepressant; UI, urinary incontinence; UUI, urge urinary incontinence.

Table 53–2

Items to Address during Diagnostic Evaluation of UI

Item	Comments
Urine Leakage	
Use of absorbent products	Type(s), quantity, times of day worn
Urine leakage per episode	Dribbling, small or large volumes, intermittently; consistent or varied quantities
Precipitants	Physical activity, excessive fluid intake, drug(s)
Times of day	Daytime/nighttime/both
Symptoms	
Urgency	Frequency, severity, duration from urge onset to micturition
Frequency	Daytime/nighttime/both, how often
Nocturia	How often, proportion associated with UI
Obstructive symptoms	Type(s) (hesitancy, strain to void, decreased force of stream, start and stop stream, sense of incomplete emptying), severity
Lower abdominal fullness	Frequency, severity
Comorbidities	
Current medication use	See Table 53–1. Remember CAMs, OTCs
Evidence of preexisting or new-onset:	
Diabetes mellitus	
Metastatic or genitourinary malignancy	
Multiple sclerosis or other neurologic disease	
CNS disease above the pons	Usually UUI
Spinal cord injury	UUI or OUI, depending on level and degree of completeness of injury
Recent nongenitourinary surgery	Functional UI
Previous local surgery/radiation	Prostate surgery, lower abdominal cavity surgery (direct injury versus denervation), radiation (direct injury)
Gynecologic history	Childbirth (vaginal versus cesarean section), prior gynecologic surgery, hormonal status (pre- versus peri- versus postmenopausal)
Pelvic floor disease	Constipation, diarrhea, fecal incontinence, dyspareunia, sexual dysfunction, pelvic pain
UTI	Dysuria, CVA tenderness, frequency
Gross Hematuria	Possible bladder or other genitourinary cancer

CAM, complementary and alternative medications; CVA, costovertebral angle; OTC, over-the-counter; OUI, overflow urinary incontinence; UTI, urinary tract infection; UUI, urge urinary incontinence.

examination to check rectal tone, reflexes, ability to perform a voluntary pelvic muscle contraction in women; size and surface quality of prostate in men)

- Pelvic examination in women for evidence of prolapse of bladder, small bowel, rectum, or uterus, or signs of estrogen deficiency
- Genital/prostate examination in men
- Urinalysis, PVR urine volume
- Direct observation of urethral meatus (opening) when patient coughs/strains (urine spurt consistent with SUI)
- Perineal examination for skin maceration, redness, breakdown, ulceration, and evidence of fungal skin infection

Clinicians could inquire about UI and OAB with open- and closed-ended questions.[12]

- Do you leak urine when you cough, sneeze, laugh, etc?
- Do you have to get up more than once at night to urinate?
- Do you feel the urge to urinate frequently?
- How many times do you typically urinate from waking in the morning until going to bed in the evening?
- How many times do you typically wake up to urinate from going to sleep at night until waking in the morning?
- How often do you have a sudden compelling desire to urinate, which is difficult to postpone?
- How often do you leak urine because you cannot postpone the sudden desire to urinate?

A validated three-item questionnaire helps clinicians discern the common incontinence subtypes by asking participants whether they experienced UI during the past 3 months, whether they experienced involuntary urinary leaking, and when they experienced it most often.[11]

TREATMENT

Desired and realistic treatment outcomes should be individualized and discussed with each patient. KEY CONCEPT The treatment goals for UI may change with time, and often require reaching a compromise between efficacy and tolerability of drug therapy.

Desired Outcomes

- Restoration of continence
- Reduction of the number of UI episodes (daytime and nighttime) and nocturia
- Prevention or delaying of complications associated with UI (e.g., pressure ulcers, skin conditions)
- Minimization of adverse effects and costs related to treatment
- Improvement in quality of life

Nonpharmacologic Treatment

At the primary care level, nonsurgical, nonpharmacologic intervention constitutes the chief approach to the management of UI.

It has no adverse reactions, is minimally invasive, and can be utilized adjunctively with other treatment modalities. KEY CONCEPT Nonpharmacologic treatment gives at least an additive effect in efficacy when combined with drug therapy. It can allow the use of lower doses of drug therapy. It is ideal for patients who fit the following scenarios:

- Being medically unfit for surgery
- Planning for pregnancies/childbirths, which can compromise the long-term results of certain types of continence surgery
- Having OUI whose condition is not amenable to surgical or drug treatment
- Avoiding drug therapy or surgery due to safety concern or patient preference

These approaches include lifestyle or behavioral modifications, fluid management, scheduled voiding regimens, pelvic floor muscle rehabilitation (PFMR; common term "Kegel exercises"), external neuromodulation, anti-incontinence devices, acupuncture, and supportive interventions.[5,11,13,14] Many of these are best utilized through attendance at multidisciplinary UI clinics staffed by specialized healthcare providers. Weight loss and exercise are recommended for all types of UI in women who are overweight or obese. Weight loss of 5% to 10% gives similar efficacy as other nonpharmacologic treatments for SUI.[8,10] Smoking cessation should be considered in patients with all types of UI. Other lifestyle modification strategies include management of constipation, avoidance of excessive fluids, reduced intake of caffeine, carbonated beverages, diet beverages, and alcohol. Frequent intake of small amounts of fluid (e.g., 4 to 5 oz per hour) up to 2 L/day in lieu of large, episodic fluid intake (e.g., 36 oz in one drink) can be helpful.[11]

Time voided measures or voiding at intervals that are tailored to each patient (e.g., every 2 to 3 hours) during the day can reduce UI episodes.[11] Bladder training and prompted voiding improve symptoms of UUI and MUI. PFMR is an effective treatment for adult women with SUI and MUI.[8] Combination therapy with PFMR plus behavioral training achieved better outcomes than drug therapy in women with UUI. However, these methods require motivation from patients. Medical conditions, such as cognitive dysfunction, may interfere with active participation and thus compromise efficacy. Regular follow-ups are important for monitoring outcomes and for providing reassurance and support. Lifestyle or behavioral interventions should be continued during drug therapy in patients with UI, even if the results have not fully achieved the desired outcomes. PFMT is strongly recommended for SUI; bladder training may be recommended for UUI; and the combination of both is strongly recommended for MUI.[8,10]

External neuromodulation may include nonimplantable electrical stimulation, percutaneous tibial nerve stimulation, or extracorporeal magnetic stimulation. This treatment option is typically prescribed when traditional PFMR has failed. Anti-incontinence devices, such as bed alarms, catheters, pessaries, penile clamps, and external collection devices, are reserved for special situations depending on patient's symptoms, cognition, mobility status, and overall health status. Supportive interventions such as physical therapy may be beneficial for patients with muscle weakness and slow gait that hinder their ability to reach to the toilet in a timely manner. Last, absorbent products provide greater patient confidence in dealing with unpredictable urine loss.[5]

Surgery is rarely an initial treatment for UI; only considered in patients with significantly bothersome symptoms, and when nonsurgical options are undesired or ineffective. Surgery is not as helpful for bladder underactivity but can be used to manage urethral overactivity due to BPH and bladder outlet obstruction (via endoscopic incision using a cystoscope). It is most effective for SUI by stabilizing the urethra and bladder neck and/or augmenting urethral resistance. Common approaches are injection of periurethral bulking agents and midurethral sling procedure. SUI in men is best treated by implanting an artificial urinary sphincter.[5]

There are three approved procedural treatments in the United States for women with persistent urgency incontinence symptoms or medication intolerance: percutaneous tibial nerve stimulation, sacral neuromodulation, and onabotulinumtoxin A injections into the bladder. Percutaneous tibial nerve stimulation is an office-based percutaneous treatment for UUI or OAB. Therapy consists of weekly 30-minute treatments with a needle placed

Patient Encounter 1, Part 2

PMH: Hypertension for 5 years, hyperlipidemia for 3 years, diabetes mellitus type 2 for 3 years, seasonal allergies for 10 years

SH: Married for 31 years, recently widowed and lives alone. Works as a financial advisor in a big corporate firm. One son (age 30), one daughter (age 28), and five grandkids. Drinks one glass of wine with dinner; drinks one cocktail at bedtime (started when her husband passed away due to stroke last year). Consumes two cups (total 16 oz) of cappuccino coffee in the morning and one cup (8 oz) of regular coffee after lunch. Former smoker, quit for 5 years ago

All: NKDA

Meds: Losartan 50 mg once daily, atorvastatin 10 mg once daily, metformin 500 mg twice daily, fexofenadine 60 mg twice daily

ROS: Alert and pleasant. Denies dysuria, lower abdominal fullness, decreased force of stream, or other urological symptoms besides her chief complaints

PE:

VS: BP 155/87 mm Hg, HR 78 beats/min, RR 18 breaths/min, T 36.8°C (98.3°F), Wt 199 lbs (90 kg), Ht 5′7″ (170 cm)

HEENT: PERRLA; EOMI, TMs WNL

Neck/LN: Supple w/o LAD or masses

Lungs/Thorax: CTA

CV: RRR w/o murmurs, rubs, gallops

Abd: soft, NT/ND w/o masses; normal bowl sounds

GU: WNL; no atrophic vaginitis or uterine prolapse

MS/Ext: WNL, no edema

Neuro: DTRs 2+, CN II–XII intact

Labs: All within normal limits. SCr 1.0 mg/dL (88 μmol/L), fasting glucose 130 mg/dL (7.2 mmol/L), lipid profile and hepatic function tests within normal limits, HbA1c 8.0%

Given this additional information, what is your assessment of the patient's condition?

What are the goals of pharmacotherapy for this patient?

What nonpharmacologic and pharmacologic options are available to the patient?

posterior to the medial malleolus of the ankle over the course of 3 months, followed by monthly maintenance therapy. The efficacy is similar to oral drug therapy with 60% subjective improvement and low rates of transient local adverse events. However, long-term efficacy and safety data are lacking.[5,11]

Surgical treatment for UUI generally consists of implantation of a sacral nerve stimulator (neuromodulation) or endoscopic office-based injection of botulinum toxin A directly into the smooth or striated muscle.[5,11] Sacral neuromodulation is an outpatient procedure in which an implanted electrode is placed along the third sacral nerve root to deliver nerve stimulation. After a successful test, a permanent external stimulator can be implanted (lasts 5 years). It is 60% to 90% effective with a cure rate of 30% to 50%.[5,11] Intrabladder (intravesical) onabotulinumtoxin A (100 U) injections are performed in the office generally with local anesthesia. The duration of effect of the toxin is about 4 to 8 months after which repeated injections are necessary to maintain effect. The drug blocks the presynaptic release of acetylcholine to decrease muscarinic receptor activation involved in detrusor contraction and increase bladder capacity/compliance. The efficacy is similar to or better than that of oral anticholinergics (about 65% at 6 to 12 months).[5,11] It reduced more UI episodes than sacral neuromodulation but with increased rates of UTI and urinary retention (need for catheterization).[15]

Patients with UUI and an elevated PVR volume may require intermittent self-catheterization along with frequent voiding between catheterizations. Surgical placement of a suprapubic catheter may be necessary in cases when intermittent catheterization is not possible. Catheterization can be combined with pharmacologic treatment for symptom relief.[5]

Pharmacologic Treatment

The ideal treatment agent must have clinical efficacy, minimal side effects, minimal drug–drug or drug–disease interactions, convenient administration, and affordability. **KEY CONCEPT** Patient characteristics (e.g., age, comorbidities, concurrent drug therapies, ability to adhere to the prescribed regimen including drug affordability) can influence drug therapy selection.[5]

▶ *Urgency Urinary Incontinence*

Anticholinergic/Antimuscarinic Antimuscarinic agents are the second-line treatment for UUI or OAB after nonpharmacologic interventions (Table 53–3).[6] They are effective in suppressing premature detrusor contractions, enhancing bladder storage, and relieving symptoms. When used with or without bladder training, these agents improved symptoms and quality of life in patients with UUI or OAB. However, they restore continence in less than 15% of patients and reduce UI episodes by only 0.5 to 1 episodes per day.[16] They are considered equally effective based on statistical superiority over placebo or active controls. Their efficacy ranges from 53% to 80% reduction in UI episodes and 12% to 32% reduction in urinary frequency (placebo 30% to 47%, and 8% to 15%, respectively). About 50% of patients experience symptom control with common side effects of dry mouth and constipation. Less than half of individuals continue therapy beyond 6 months and less than 36% beyond 1 year.[11]

All antimuscarinic agents have similar contraindications and precautions, including urinary retention, gastric retention, and uncontrolled narrow-angle glaucoma.[5,11] Older immediate release (IR) agents, such as oxybutynin and tolterodine, have been associated with high rates of dry mouth, constipation, headache, dyspepsia, dry eyes, cognitive impairment, tachycardia, and urinary retention (Table 53–4). Older patients are especially susceptible to these adverse events. Significant dry mouth may cause dental caries, ill-fitting dentures, and swallowing difficulty. Chewing sugarless gum or use of saliva substitutes can help to alleviate dry mouth.

Orthostatic hypotension and sedation can be particularly troublesome to frail patients with cognitive impairment or at risk for falls. Issues with tolerability and multiple daily dose administration associated with IR products may jeopardize medication adherence and can prevent dose titration. Thus, IR products are generally not preferred in patients with functional limitations and/or those who are already taking complicated drug regimens. Nevertheless, adverse events are not universal and the severity varies with individuals. Older agents, when initiated at the lowest possible dose and gradually titrated, are reasonable to consider in cases when long-acting products are undesirable (e.g., need to crush medications due to inability to swallow).

Extended-release (ER) agents (oxybutynin XL, tolterodine LA, trospium ER, darifenacin ER, fesoterodine ER) cause less dry mouth compared with IR products.[5,7] These products cannot be chewed, crushed, or divided, and must be swallowed whole. Oxybutynin transdermal patch and topical gel are alternatives for patients who cannot take or tolerate oral drugs. They cause less dry mouth but more application site reactions. Rotation of application sites may help to minimize local side effects.

Patients receiving any antimuscarinic agent should be informed about sedation as a possible side effect and warned against operating heavy machinery, such as driving, especially during the initial phase of therapy. Patients with existing cognitive dysfunction or difficulty with balance should be monitored closely for mental status change and fall risk. Older individuals are more prone to experience constipation because they may take medications which affect bowel function. Patients should contact their physicians in case of severe abdominal pain or constipation that lasts for 3 or more days. Clinicians should monitor potential drug interactions between antimuscarnic agents and acetylcholinesterase inhibitors for dementia (antagonism), as well as concomitant use with anticholinergic agents (additive side effects).

KEY CONCEPT Antimuscarinic agents should be initiated at the lowest possible dose and gradually dose-titrated based on clinical response; not to exceed the maximum recommended dose. A trial of at least 4 weeks is required to evaluate its efficacy. Consider switching to another agent if the patient reports intolerable side effects or inadequate symptom relief despite optimized dose and therapy duration.

Mirabegron Mirabegron, a β_3-adrenergic agonist, is also considered the second-line therapy for OAB. It reduces

Patient Encounter 1, Part 3

Based on the information presented, create a care plan for this patient. Your plan should include:

(a) A statement of the drug-related needs and/or problems

(b) A patient-specific detailed therapeutic plan, including patient counseling to enhance medication adherence, ensure successful therapy, and minimize adverse effects

(c) A plan for follow-up to evaluate therapeutic outcome and drug tolerability

Table 53–3

Approved Drugs for the Management of UUI in Adults

Parameter	Oxybutynin	Tolterodine	Trospium Chloride	Solifenacin	Darifenacin	Fesoterodine	Mirabegron
Dosage forms	IR tablets, solution SR-ER tablets, SR-TD patch, topical gel	IR tablets SR-LA capsules	IR tablets ER tablets	IR tablets	ER tablets	ER tablets	ER tablets
Dosing	IR: 2.5–5 mg 2–4 times daily (pediatrics 0.3–0.5 mg/kg/day in three doses) SR (oral): 5–30 mg once daily (pediatrics: 0.3–0.5 mg/kg/day) SR (TD): 3.9 mg/day patch applied twice weekly; available over-the-counter SR (gel): 1 sachet (100 mg) applied once daily	IR: 1 or 2 mg twice daily (pediatrics: 1 mg twice daily) ER: 2 or 4 mg once daily (pediatrics: 2 mg once daily)	IR: 20 mg twice daily ER: 60 mg once daily	5–10 mg once daily	7.5–15 mg once daily	4–8 mg once daily	25 mg once daily, then 50 mg once daily after 8 weeks
Kinetics	Active metabolite (*N*-desethyl) Not altered in renal or hepatic disease or advanced age	Active metabolite (5-hydroxymethyl) Polymorphic metabolism (CYP 2D6) Not altered in advanced age. Significantly altered in hepatic disease (decreased CL in cirrhosis) and renal disease (decreased CL)	Food: decreased F by 70%–80% Significantly altered in renal disease (decreased CL) but not in hepatic disease or advanced age	Metabolized via CYP 3A4 but only one active metabolite (4-hydroxy) Significantly altered in severe renal impairment, moderate hepatic impairment (Child-Pugh B), and advanced age (decreased CL in all)	Complex metabolism (polymorphic CYP 2D6, CYP 3A4) Not altered in advanced age, renal impairment, mild hepatic impairment (Child-Pugh A) Significantly altered in moderate hepatic impairment (Child-Pugh B) (decreased CL)	Prodrug (for 5-hydroxmethyl tolterodine) Inactive metabolites Not altered in advanced age Significantly altered in renal disease (decreased CL) and moderate hepatic impairment (Child-Pugh B) (decreased CL)	Terminal elimination half-life 50 hours Moderate inhibitor of CYP 2D6
Contraindications and precautions	Use with caution if CYP 3A4 inhibitors are also being taken (decreased oxybutynin CL)	Reduce dose 50% in those taking CYP 3A4 inhibitor(s) or with hepatic cirrhosis or with CrCl < 30 mL/min (0.50 mL/s) Antacid-SR (oral) prep, interaction (dose-dumping) (not seen with PPIs)	Give on empty stomach Do not use ER when CrCl < 30 mL/min (0.50 mL/s); use IR 20 mg once daily at bedtime	Do not exceed 5 mg/day if CrCl < 30 mL/min (0.50 mL/s), patient has moderate hepatic impairment, or patient is taking CYP 3A4 inhibitor(s) If severe hepatic impairment, do not use	Do not exceed 7.5 mg/day if patient is taking potent CYP 3A4 inhibitor(s) Use caution if patient is taking moderate CYP 3A4 inhibitor(s) or CYP 3A4 or 2D6 substrate(s) Do not chew, divide, or crush the ER tablets	Do not exceed 4 mg/day if CrCl < 30 mL/min (0.50 mL/s) or patient is taking potent CYP 3A4 inhibitor(s) If severe hepatic impairment, do not use	Limit dose to 25 mg once daily if severe renal impairment or moderate hepatic disease Avoid in end-stage renal disease or severe hepatic impairment, or more BP 180/110 mm Hg Monitor for increased BP and urinary retention Do not chew, divide, or crush

BP, blood pressure; CL, total body clearance; CrCl, creatinine clearance; ER, extended release; F, bioavailability; IR, immediate release; LA, long acting; PPIs, proton pump inhibitors; SR, sustained release; TD, transdermal.

Table 53–4

Adverse Event Incidence Rates with Approved Drugs for Bladder Overactivity[a]

Drug	Dry Mouth (%)	Constipation (%)	Dizziness (%)	Vision Disturbance (%)
Oxybutynin IR	71	15	17	10
Oxybutynin XL	61	13	6	14
Oxybutynin TDS	7	3	NR	3
Oxybutynin gel	10	1	3	3
Tolterodine	35	7	5	3
Tolterodine LA	23	6	2	4
Trospium chloride IR	20	10	NR	1
Trospium chloride XR	11	9	NR	2
Solifenacin	20	9	2	5
Darifenacin	24	18	2	2
Fesoterodine	27	5	NR	3
Mirabegron ER	3	3	3	NR

[a] All values constitute mean data, predominantly using product information from the manufacturers.

IR, immediate-release; LA, long-acting; NR, not reported; TDS, transdermal system; XL, extended-release; XR, extended-release.

urinary frequency and UI episodes by less than one per day (see Table 53–3).[6,17] It increases bladder capacity by relaxing the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle. It requires 4 to 8 weeks of therapy for optimal efficacy.[17] It is as effective as antimuscarinics (symptom control rates range from 43% to 46% at 1 year of therapy.[11]

Mirabegron is available as ER tablets and should be swallowed whole without chewing, dividing, or crushing. Most commonly reported adverse reactions are hypertension (7%–11%), nasopharyngitis (4%), UTI (3%–6%), and headache (3%–4%). Patient should be monitored for increased blood pressure and urinary retention, particularly in patients with bladder outlet obstruction or those who are taking anticholinergic drugs.[5] Mirabegron and solifenacin combination therapy provided improvement in OAB symptoms over monotherapies with good tolerability in a 1-year study.[18] Other β_3-adrenergic agonists in the drug development pipeline are solabegron, ritobegron, vibegron, and others.[19-21]

Older Agents[5] Tricyclic antidepressants (TCA), such as desipramine, nortriptyline, imipramine, and doxepin, are generally no more effective than oxybutynin IR. They may cause potentially serious adverse effects (e.g., orthostatic hypotension, cardiac conduction abnormalities, dizziness, and confusion). Thus, TCA use is limited to individuals who have one or more indicated comorbidities (e.g., depression or neuropathic pain), MUI (because of their effect of decreasing bladder contractility and increasing outlet resistance), and possibly nocturnal incontinence associated with altered sleep patterns. Other older agents, including propantheline, flavoxate, dicyclomine, and hyoscyamine are not recommended for UI.[5]

▶ *Stress Urinary Incontinence*

The goal of pharmacologic therapy of urethral underactivity is to improve the urethral closure mechanism by:

- Stimulating α-adrenoceptors in the smooth muscle of the proximal urethra and bladder neck
- Enhancing the supportive structures underlying the urethral mucosa
- Enhancing the positive effects of serotonin and norepinephrine in the afferent and efferent pathways of the micturition reflex

In general, systemic pharmacologic therapy is not recommended for SUI.[8,10] PFMT is the first-line therapy in women with SUI.[10] Nevertheless, SUI in women is frequently curable by surgery, thus obviating years of drug therapy that may not provide adequate symptom relief. Surgery (tension-free vaginal tape sling) is a more cost-effective therapy of SUI than duloxetine in women failing PFMR.[22] Automatic pelvic exercise devices, incontinence pessaries, and disposable intravaginal bladder support devices can also be considered for SUI.[10]

Estrogens[5] KEY CONCEPT Local vaginal estrogen preparations can effectively relieve the genitourinary syndrome of menopause, including urinary complaints of frequency, urgency, and SUI.[23] Estrogen products are believed to work by a trophic effect on uroepithelial cells and underlying collagenous subcutaneous tissue, enhancement of local microcirculation by increasing the number of periurethral blood vessels, and enhancement of the number and/or sensitivity of α-adrenoceptors.

Local estrogens (conjugated equine estrogen cream, estradiol rings) have demonstrated subjective improvement in SUI and UI in general.[24] Local products, such as the estrogen ring, may have dual effects: functioning like an incontinence pessary by supporting the bladder neck while simultaneously providing estrogen locally (Table 53–5). In contrast, oral hormone replacement therapy increases the risk of new-onset SUI, UUI, MUI while carrying numerous risks, including mastodynia, uterine bleeding, nausea, thromboembolism, cardiac or cerebrovascular ischemic events, and breast or endometrial cancer.[24]

α-Adrenoceptor Agonists[5] Phenylpropanolamine, ephedrine, and pseudoephedrine have been used alone or with estrogen for mild and moderate SUI. However, recent data showed that they are not better than placebo or PFMR.[23] The major impediment to using α-adrenoceptor agonists is the extensive list of contraindications (see Table 53–5). Side effects of pseudoephedrine, an over-the-counter medication, include hypertension, headache, dry mouth, nausea, insomnia, and restlessness.

Duloxetine This selective serotonin-norepinephrine reuptake inhibitor is approved to treat SUI in Europe but is off-label in the United States. It enhances central serotonergic and adrenergic tone, which is involved in ascending and descending control of urethral smooth muscle and the internal urinary sphincter, and thereby enhances urethral and urinary sphincter smooth muscle

Table 53–5

Drugs Used for SUI[a]

Parameter	Estrogens	Pseudoephedrine	Duloxetine
Dosage forms	Avoid systemic (parenteral, oral, TD); use vaginal: tablet, cream, intravaginal ring	Tablets, solution	DR capsules
Dosing	Estradiol 25-mcg vaginal tablets (insert one PV daily for 14 days, then one PV twice weekly) Estradiol vaginal cream (0.1 mg/g) (2–4 g daily PV for 1–2 weeks; then 1 g PV daily or less frequently) CEE vaginal cream (0.625 mg/g) (0.5–2 g daily PV; consider 3 weeks on, 1 week off; may be able to decrease frequency of use over time) Estradiol 2-, 12.4-, 24.8-mg vaginal rings (1 ring PV every 3 months)	15–60 mg three times daily	40–80 mg/day in one or two doses for 12 weeks (titrate and taper dosage)
Kinetics	Use local route to minimize systemic F and side effects Estradiol less likely to be absorbed; CEE 1 mg or more daily sufficiently absorbed to cause systemic side effects	Less than 1% of dose is metabolized (inactive metabolites) Primarily renal elimination of unchanged drug Would not expect hepatic impairment to have an effect (no data) Expect significant effect if renal impairment and no effect if advanced age (beyond decreased CrCl with age) (no data)	Extensive metabolism via CYP 2D6 and 1A2 (inactive metabolites) Not altered in advanced age, mild-to-moderate renal impairment (CrCl 31–80 mL/min [0.51–1.34 mL/s]), mild hepatic impairment (Child-Pugh A) Significantly altered in severe renal disease (CrCl < 30 mL/min [< 0.50 mL/s]) and moderate hepatic impairment (Child-Pugh B)
Contraindications/ precautions	Known or suspected breast or endometrial cancer Abnormal genitourinary bleeding of unknown etiology Active thromboembolism (or history of TE associated with previous estrogen use)	Hypertension, tachyarrhythmias, coronary artery disease, MI, cor pulmonale, hyperthyroidism, renal failure, narrow-angle glaucoma	Multiple drug–drug interactions possible with CYP 2D6 and 1A2 substrates/inhibitors Avoid if CrCl < 30 mL/min (0.50 mL/s) and in all patients with hepatic disease Can raise BP Do not discontinue abruptly (withdrawal syndrome) Suicide risk even in patients without psychiatric disease Avoid in uncontrolled narrow-angle glaucoma (causes mydriasis) Hepatotoxic; avoid in alcoholics even if signs/symptoms of hepatic disease are absent

[a] None of these agents are FDA approved for treatment of SUI. Duloxetine is approved in Europe only.

BP, blood pressure; CEE, conjugated equine estrogens; CrCl, creatinine clearance; CYP, cytochrome P-450; DR, delayed-release; F, bioavailability; MI, myocardial infarction; PV, per vagina; TD, transdermal; TE, thromboembolism.

tone during the filling phase.[25] It may benefit incontinence and quality of life in men with SUI after radical prostatectomy.[26]

The use of duloxetine in SUI is complicated by intolerability (e.g., high rate of nausea), numerous precautions or contraindications, CYP P450 drug–drug interactions, and the possibility of withdrawal symptoms if abruptly discontinued.[25] It may be considered if there are comorbidities such as depression, anxiety, fibromyalgia, diabetic neuropathy, and chronic musculoskeletal pain. The usual dosage is 40 to 80 mg/day (in one or two doses) for 12 weeks. Gradual dose titration (starting from 20 mg once daily for at least 1 week, then titrate no shorter than weekly interval) may help to reduce the risks of nausea, dizziness, and premature therapy cessation. Similarly, dose reduction of 50% for 2 weeks before discontinuation or slow tapering over 4 to 6 months is reasonable to minimize withdrawal symptoms.

▶ *Overflow Incontinence*[5]

There is no established effective pharmacologic therapy for OUI due to bladder underactivity (atonic bladder). A trial of bethanechol (25–50 mg three or four times daily) may be reasonable if contraindications do not exist. Bethanechol is a cholinomimetic with uncertain efficacy and bothersome and potentially life-threatening side effects (muscle and abdominal cramping, hypersalivation, diarrhea, and bronchospasm), particularly in patient with preexisting conditions. α-Adrenoceptor antagonists, such as silodosin, prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin, may be beneficial for OUI by relaxing the bladder outflow tract and hence reducing outflow resistance. If pharmacologic therapy fails, intermittent urethral catheterization three or four times per day is recommended. Less satisfactory alternatives include indwelling urethral or suprapubic catheters, or urinary diversion. In OUI due to obstruction, such as BPH, the goal of treatment is to relieve the obstruction.

▶ *Mixed Urinary Incontinence*[5]

MUI is usually a combination of UUI plus SUI with one dominant component. It accounts for one-third of UI cases in women. A reasonable management approach is a combination of lifestyle or behavioral modifications and PFMR with pharmacotherapy appropriate to the dominant type of UI. For instance, antimuscarinics can be offered in UUI-predominant cases, whereas duloxetine, local estrogen, and α-adrenoceptor agonists in SUI-predominant cases. In some cases, the less dominant form of UI may respond, but usually not to a degree that is considered adequate by the patient. Most experts feel that SUI-predominant MUI is best treated initially using nonpharmacologic approach plus surgery for SUI. Unfortunately, these patients with MUI are expected to have a lower success rate with surgery compared to those with pure SUI. The urge component may improve, stay the same, or worsen after surgery.

▶ *Nocturia*

Desmopressin Nocturia may be caused by a wide array of factors, such as uncontrolled diabetes mellitus, congestive heart failure, bladder or prostate diseases, and use of medications (e.g., diuretics). Intranasal desmopressin, a synthetic vasopressin analog, was approved in 2017 in the United States for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void. Its use is limited due to multiple contraindications. The manufacturer announced the discontinuation of this product in 2019.[27] A sublingual formulation is approved in Canada for nocturia. Desmopressin oral and sublingual formulations are indicated for primary nocturnal enuresis.

OUTCOME EVALUATION

- Monitor the patient for symptom relief. Has the treatment achieved the desired outcomes jointly developed by the healthcare team, patient, and caregiver? If so, to what degree? Inspect the daily diary completed by the patient or caregiver and quantitate the clinical response (e.g., micturitions, UI

Patient Care Process: Urinary Incontinence

Collect Information:

- Identify urinary symptoms and ask the patient how the symptoms affect his or her daily living.
- Identify exacerbating factors and UI complications.
- Review concurrent medical conditions and obtain a thorough medication history, including use of prescription, nonprescription, and complementary/alternative products.
- Identify allergies or serious adverse events related to the use of medications and other substances.
- Ask the patient and caregiver about their goals of therapy and socioeconomic factors that affect medication access and other aspect of care. In cognitively intact elderly patients, focus communications to elicit the preferences of the patient, not those of potential proxies.

Assess the Information:

- Assess the severity of urinary symptoms. Assess changes in quality of life (physical, psychological, social functioning, and well-being).
- Based on reported signs, symptoms, and exacerbating factors, determine whether a referral to specialized professional is required.
- Evaluate whether or not urinary symptoms could be exacerbated by disease states or drugs (see Table 53–1). Determine if any current or previous treatments are/were helpful for UI.

Develop a Care Plan:

- Help the patient and caregiver to set realistic goals of therapy.
- Consider whether lifestyle or behavioral modifications, fluid management, and other nonpharmacologic treatment are feasible or desirable.
- Determine whether pharmacotherapy is indicated or desired by patient. Choose appropriate treatment regimen (drug choice, dosage, administration) for his or her type(s) of UI.
- Evaluate the patient for medication adherence, drug-related adverse events, allergies, and drug interactions with concomitant medications or disease states.

Implement the Care Plan:

- Educate the patient on lifestyle modifications that may improve symptoms: smoking cessation, weight reduction (for those patients with SUI and UUI), constipation prevention in patients at risk, caffeine reduction, and diet or fluid modification. Note the timing and quantity of fluid intake, as well as possibility of avoiding foods or beverages that worsen UI.
- Provide patient education regarding the disease state, lifestyle modifications, and drug therapy (see Tables 53–3 and 53–5).
- Address any patient or caregiver concerns about disease state and its management, including timing of medication intake, potential adverse events, potential drug–drug or drug–disease interactions, and importance of treatment adherence.

Follow-up: Monitor and Evaluate:

- Monitor for patient response in 1 or 2 weeks after therapy initiation.
- Develop a plan to assess efficacy after a minimum of 4 weeks.
- Determine whether the patient is experiencing any adverse effects or drug interactions.

episodes, and pad use) since the last visit. If a diary has not been used, ask the patient how many incontinence pads have been used and how they have been doing in terms of "accidents" since the last visit. If appropriate, administer a short-form instrument to measure the impact of symptoms, including quality of life. Compare the findings with previous results.

- Ask patients about adverse effects of drug therapy using a nonleading approach. Ask the patient or caregiver to judge their severity and what measures, if any, they have used to alleviate. Assess medication adherence (ask patient or caregiver about missed doses or do a pill count if the prescription containers are available at the visit).
- Clinical response and tolerability should guide the dose titration or tapering of drug therapy. Consider stopping/tapering off the regimen and initiate another drug option if bothersome adverse effects compromise patient safety and/or medication adherence.

PEDIATRIC ENURESIS

INTRODUCTION

UI, or pediatric enuresis, is a common problem. In children less than 5 years old, treatment is unnecessary because spontaneous cure is likely. After 5 years of age, a child with intermittent or continued incontinence is considered to have pediatric enuresis. Pediatric enuresis is subdivided into categories to clarify expectations of the condition and response to therapy:[28,29]

- Monosymptomatic enuresis: Enuresis in children without other lower urinary tract symptoms or bladder dysfunction
- Primary enuresis: Enuresis in children who have never been consistently dry throughout the night
- Secondary enuresis: Enuresis in patients who have resumed wetting after a period of dryness of at least 6 months in duration
- Nonmonosymptomatic enuresis: Enuresis in children with other lower urinary tract symptoms (e.g., urgency, frequency, daytime incontinence, genital or lower urinary tract pain)

Emotional and developmental impacts from enuresis are significant and include social stigma and low self-esteem. Missing camp getaways and sleepovers can have a negative effect on peer relationships.[30]

EPIDEMIOLOGY AND ETIOLOGY

A total of 5 to 7 million children and adolescents in the United States suffer from nocturnal enuresis; however, with each year of maturity, the percentage of bed-wetters may decline by 15% without treatment.[29,31,32] In the enuretic population, 75% are monosymptomatic, 5% to 10% are nonmonosymptomatic, and less than 5% have an organic cause.[32] Primary enuresis is twice as common as secondary enuresis.[33] The prevalence of enuresis is as follows:

- 5 years of age: 15% to 25%
- 7 years of age: 5% to 10%
- 12 years of age: 8% (boys) and 4% (girls)
- During adolescence: 1% to 3%

The etiology of enuresis is poorly understood. A genetic link has been identified but with a discordance between enuretic genotype and phenotype.[29] Loci for enuresis are located on chromosomes 5, 12, 13, and 22. Risk factors may be familial; when both parents have a history of enuresis as children, the child's incidence is 77% as compared to 44% with one parental history.[30,33] Sleep apnea, attention deficit disorder, autism, and obesity are also associated with pediatric enuresis.[30,31] Drug-induced causes of pediatric enuresis include lithium, clozapine, risperidone, valproic acid, selective serotonin reuptake inhibitors, and theophylline. In a minority of cases, psychological factors (e.g., divorce of parents, school trauma, sexual abuse, or hospitalization) may contribute to secondary enuresis. Potentially treatable organic causes of enuresis are listed in Table 53–6.

Table 53–6

Major Potentially Treatable Organic Causes of Enuresis

Potentially Treatable by Surgery
- Ectopic ureter
- Lower UTI congenital anomalies
- Neurogenic bladder
- Bladder calculus (stone) or foreign body
- Obstructive sleep apnea

Potentially Treatable by Medications
- UTI
- Diabetes mellitus
- Diabetes insipidus
- Fecal impaction
- Constipation

UTI, urinary tract infection.

PATHOPHYSIOLOGY

Microstructural abnormalities and maturational delays of neuronal circuits have been identified in the frontal cortex of children with enuresis.[30] Physiological factors associated with pediatric enuresis include reduced bladder function and/or capacity, altered arousal to a full bladder, detrusor overactivity at night, and/or nocturnal polyuria from lack of circadian rhythm of nocturnal ADH secretion.[30]

Patient Encounter 2, Part 1

An 8-year-old girl is brought into your clinic. Her father seeks advice regarding his child's inability to stay dry for more than a few nights in a row. In the last 2 weeks, the child has also been having hard stools on defecation. Her father had a history of bedwetting as a child until 11 years of age, when it resolved. He is asking for an over-the-counter medication to help his child. The child is frustrated because she wants to have a sleepover and concerned about bedwetting. She is having a hard time keeping her grades up this year. Parents have tried giving the child more fluids at night and waking the child every hour to go to the bathroom to get her acclimated to waking up for a full bladder, which is not working. They are very eager to help their daughter.

What additional information do you need to know before creating a treatment plan for this child?

What risk factors does the child have for pediatric enuresis?

Definitions applicable to pediatric patients are helpful in discerning the etiology:[29]

- Bladder capacity: (30 mL + [30 × age in years]). Adult values of 400 mL/day may be reached in adolescence.
- Normal functional bladder capacity: Maximum voided volume greater than 70% of expected bladder capacity for age
- Nocturnal polyuria: Urine production greater than 130% of expected bladder capacity for age

TREATMENT

Desired Outcomes

- Reduction in the number of enuresis episodes and restoration of continence[28]
- Partial response: 50% to 89% reduction
- Response: 90% or more reduction
- Full response: 100% reduction or less than one symptom occurrence monthly
- Prevention of relapse (less than one symptom recurrence monthly) and maintenance of treatment success
- Continued success: No relapse in 6 months after the cessation of treatment
- Complete success: No relapse in 2 years after the cessation of treatment
- Prevention or minimization of disease complications (delay in childhood developmental milestones, adverse psychological effects on the child/caregivers)
- Minimization of adverse effects and treatment costs
- Improved quality of life of the child and caregivers

Clinical Presentation and Diagnosis: Pediatric Enuresis

General

Proper assessment of the child or adolescent with enuresis should be thorough, including the genitourinary and nervous systems. The minimum assessment should also include:[24,29,30]

- Interview of the child and parent(s), being sensitive to the emotional consequences of the enuresis.
- Direct physical examination, looking for enlarged adenoids/tonsils, bladder distention, fecal impaction, abnormal genitalia, spinal cord anomalies, and abnormal neurologic signs (look for an organic cause amenable to surgery or medications; see Table 53–6).
- Obtain urinalysis for glucose, protein, WBC, or leukocyte esterase; obtain urinalysis and urine culture if symptoms of UTI are present.
- A 7- or more day diary of wet and dry nights prior to intervention helps in monitoring the response to treatment.
- Nonmonosymptomatic enuresis may require a more extensive workup, including voiding cystourethrogram, renal and/or bladder ultrasound, urodynamics, and sleep studies.

General Approach to Treatment

Treatment is guided by patient assessment. Referral to a urologist is needed in cases of daytime wetting, abnormal voiding (e.g., unusual posturing, discomfort, straining, poor stream), history of recurrent UTIs, or abnormalities of the genitalia. Psychotherapy is recommended in cases with a psychological cause. Guidelines have been developed for the evaluation and management of nocturnal enuresis.[29,34,35] Management of primary monosymptomatic nocturnal enuresis in children may involve one or a combination of interventions. The management of secondary nocturnal enuresis focuses on addressing the underlying contributing factor. However, most children with secondary enuresis are treated in the same manner as those with primary enuresis. The National Institute for Health Care and Excellence algorithm (Figure 53–1) outlines treatment approaches based on the child's age, maturity, and abilities, and the frequency of enuresis.[35]

Initial management with education and motivational or behavioral therapy, called urotherapy (Table 53–7), is effective in 15% to 20% of patients and should be tried for 3 to 6 months.[32,36] If this fails, an enuresis alarm or pharmacologic treatment may be chosen. **KEY CONCEPT** Enuresis alarms are the most effective and lasting first-line therapy. For a faster response or in unmotivated families, desmopressin is an effective agent for the short-term control of pediatric enuresis, especially for sleepovers or camp attendance. **KEY CONCEPT** Pharmacotherapy is indicated in patients who have difficulty adhering to nonpharmacologic therapy or

Patient Encounter 2, Part 2

PMH: Unremarkable pregnancy/delivery. Developmental milestones WNL

Immunization: Up to date

FH, SH: Lives with both parents and two siblings, ages 4 and 10 years. School performance is compromised

Meds: None

ROS: (+) Nocturnal incontinence five to six nights per week; no daytime incontinence; no UTIs, urgency, frequency, dysuria, or other lower urinary track symptoms; abdomen feels full, with possible fecal impaction

PE:

VS: BP 110/70 mm Hg, P 72 beats/min, RR 16 breaths/min, T 37.0°C (98.6°F), Weight 25 kg

Resp: Clear breath sounds bilaterally

CV: Clear to auscultation, no murmurs

Abd: Slightly firm, nontender, nondistended; (+) bowel sounds; bladder not palpable

Neuro: WNL (gross sensory, motor, reflexes)

GU, Rectal: Deferred

Labs: Urinalysis WNL. Urine production: 200 mL/day while awake

Given this additional information, what is your assessment of this child's enuresis?

Identify your treatment goals for this patient.

What nonpharmacologic and pharmacologic interventions are appropriate for this child?

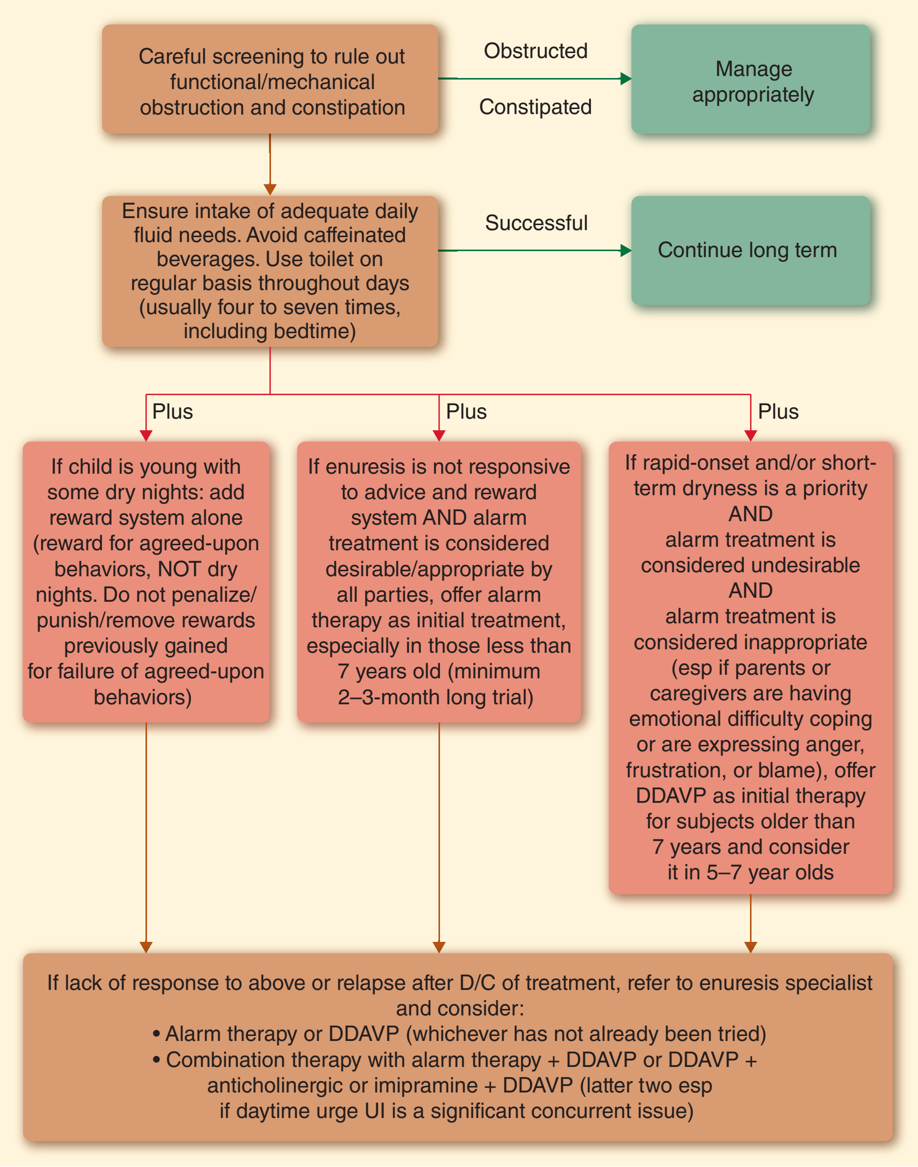
Careful screening to rule out functional/mechanical obstruction and constipation
Obstructed
Constipated
Manage appropriately
Ensure intake of adequate daily fluid needs. Avoid caffeinated beverages. Use toilet on regular basis throughout days (usually four to seven times, including bedtime)
Successful
Continue long term
Plus
Plus
Plus
If child is young with some dry nights: add reward system alone (reward for agreed-upon behaviors, NOT dry nights. Do not penalize/punish/remove rewards previously gained for failure of agreed-upon behaviors)
If enuresis is not responsive to advice and reward system AND alarm treatment is considered desirable/appropriate by all parties, offer alarm therapy as initial treatment, especially in those less than 7 years old (minimum 2–3-month long trial)
If rapid-onset and/or short-term dryness is a priority AND alarm treatment is considered undesirable AND alarm treatment is considered inappropriate (esp if parents or caregivers are having emotional difficulty coping or are expressing anger, frustration, or blame), offer DDAVP as initial therapy for subjects older than 7 years and consider it in 5–7 year olds
If lack of response to above or relapse after D/C of treatment, refer to enuresis specialist and consider:
• Alarm therapy or DDAVP (whichever has not already been tried)
• Combination therapy with alarm therapy + DDAVP or DDAVP + anticholinergic or imipramine + DDAVP (latter two esp if daytime urge UI is a significant concurrent issue)

FIGURE 53–1. Enuresis treatment protocol. (D/C, discontinuation; DDAVP, desmopressin; UI, urinary incontinence.) (Modified from Nunes VD, O'Flynn N, Evans J, Sawyer L; Guideline Development Group. Management of bedwetting in children and young people: summary of NICE guidance. BMJ. 2010;341:c5399.)

Table 53–7

Initial Management of Pediatric Enuresis

Education and Advice to Children and Caregivers

- Enuresis is common; it occurs at least once per week in up to 25% of 5-year-old children; enuresis resolves on its own in the majority of children.
- Enuresis is the fault of neither the child nor the caregivers; children should not be punished for bedwetting.
- Reduce the impact of bedwetting by using bed protection and washable/disposable products.
- Keep a calendar of wet and dry nights to determine the effect of interventions.
- Encourage daily fluid intake in the morning and early afternoon. Restriction of fluids in the early evening can be attempted and continued if successful.
- The child should attempt to void every 2–3 hours during the day and just before going to bed.
- Teach the child to delay urination in the daytime to increase bladder capacity.
- Avoid high-sugar and caffeine-based drinks, particularly in the evening hours.
- Encourage the child to decide whether they wish to use diapers and pull-ups.

Motivational Therapy

- Motivational therapy is a good first-line therapy for nocturnal enuresis in younger children between the ages of 5 and 7 years who do not wet the bed every night.
- Motivate the child by keeping a record of progress and giving rewards for accomplished agreed-upon behavior, such as going to the toilet before bedtime. For example, a sticker on a calendar for each night using toilet at bedtime, a book for seven consecutive, etc. Do not use penalties (ie, removal of previously gained rewards).

if desired outcomes are not achieved with nonpharmacologic therapy. A general approach to therapy selection is:[34,37,38]

1. Child with nighttime normal urine output, normal bladder capacity: either alarm or desmopressin therapy
2. Child with reduced bladder capacity or nocturnal detrusor overactivity: alarm therapy
3. Child with nocturnal polyuria, normal functional bladder capacity: desmopressin
4. Child with excessive urine output and reduced nocturnal bladder capacity: combination of alarm and desmopressin therapy or anticholinergic agents

▶ *Nonpharmacologic Treatment*

Urotherapy The goal of urotherapy is to regulate bladder emptying and storage. Education about the condition, fluid/diet modification, management of constipation, journaling, and behavioral or motivational therapy are the first steps in managing pediatric enuresis (Table 53–7).[30,33,34] Motivational therapy allows about 25% of children to achieve 14 consecutive dry nights and 70% of them achieve at least a partial response. About 5% of children experience more than two wet nights in 2 weeks. If motivational therapy fails to lead to improvement after 3 to 6 months, active interventions, such as enuresis alarms (Table 53–8) or desmopressin, may be added.[39,40]

Alarm Therapy Enuresis alarms are an established first-line therapy and indicated for motivated families and children.[29] They are the most effective way of controlling nocturnal enuresis and preventing relapses and may be used in children younger than 7 years.[41] They condition the child or caregiver to wake to the alarm sound or vibration and stop urinating until they go to the toilet. There are two kinds of alarm, one that is attached to the child and another that is placed by the bedside. Both are equally effective.[34,36] The alarm signals the child to wake enough to inhibit bladder contraction in response to the physiologic conditions present before wetting the bed completely. Enuresis alarms are curative in 60% to 80% of patients, with long-lasting effects in 55% of children.[30,31] Alarm therapy is as effective as desmopressin and more effective than TCAs and anticholinergic agents.[33,34,38,42] Enuresis alarms can be combined with pharmacotherapy in patients who are partial- or nonresponders to drug therapy alone.[42]

The advantage of this therapy is providing a real cure without adverse effects. Because alarms modify conditioning, they are slow in onset and require patience and motivation. Other disadvantages include alarm failure, inability to wake the child, disruption of caregivers and family members, and cost, since most are not covered by insurance.[34] Follow-up should be assessed 1 to 2 weeks after initiating alarm therapy to ensure caregiver understanding of the alarm. A full response, classified as a minimum of 14 consecutive dry nights, is not expected until 3 to 6 months of use.[32,38] Relapse may occur in up to one-third of cases, in which case the alarm can be reinitiated.[32,34,38] If there is no improvement with alarm therapy, alternative interventions should be considered. If enuresis persists after other interventions, alarm therapy may be tried again every 2 years regardless of initial response.[29]

Measures that have limited effectiveness include:[30,43]

- Bladder stretching exercises
- Hypnotherapy
- Dietary changes
- Allergen desensitization
- Acupuncture
- Chiropractic

▶ *Pharmacologic Therapy*

Desmopressin (DDAVP)[37,44] A synthetic analogue of arginine vasopressin, desmopressin decreases urine production by enhancing water reabsorption in the collecting tubules. It is indicated for nocturnal enuresis in children 6 years or older who do not respond to initial management (Figure 53–1), or when a fast response is needed. Desmopressin is most effective in a child with nocturnal polyuria and normal functional bladder capacity. It decreases the number of wet nights per week by about one night. About 30% of children become full responders and another 30% of children are partial responders.[29] However, 62% to 82% of them experience relapses.[30,38] Therapies for pediatric enuresis are listed in Table 53–9.

KEY CONCEPT Desmopressin is a pharmacologic first-line therapy in the management of pediatric enuresis.[29] Desmopressin is an alternative therapy to enuresis alarms. It works faster, which allows the child to attend camp or sleepovers on short notice. Oral tablets may be started at 0.2 mg (one tablet) 1 hour before

Table 53–8

Behavioral Treatments for Enuresis

Lifting	Procedure wherein the caregiver takes the child to the toilet at regular intervals during the night to urinate without fully awakening him or her may work as a short-term measure
Night awakening	Procedure wherein the caregiver fully awakens the child to void at regular intervals or randomly, used on a short-term basis
Alarm	An alarm device and a moisture-sensitive sensor are used in combination, with the sensor being placed under the sheets, or more commonly, attached to the child's pajamas or underwear near the urethra. The arousal device is usually an auditory alarm and/or a vibrating belt or pager
Overlearning	This is started at a minimum of 2 weeks after the alarm has rendered the child dry; the child drinks 500 mL (about 16 oz) during the hour before going to bed; alarm use is continued until he or she is dry for 14 consecutive nights with the extra fluid intake; is used to reduce relapse rates seen with alarm use alone
Dry-bed training	This begins with an intensive first night of training that involves increased fluid consumption, hourly awakenings, praise when the bed is dry at hourly awakenings, and, when the alarm goes off, cleanliness training (child changes wet clothes and bed linens, remakes the bed, resets the alarm); before going to bed and after each wetting, the child engages in 20 practice trials of appropriate toileting (ie, positive practice): for each practice trial, the child lies in bed, counts to 50, arises and attempts to urinate in the toilet, then returns to bed; on subsequent nights, child is woken only once, usually about 3 hours after the child has gone to bed; after a dry night, the night awakening moves up 30 minutes earlier; it is discontinued when it is scheduled to occur 1 hour after bedtime; after 7 consecutive dry nights, the alarm is discontinued, but is reinstated if two episodes of wetting occur in a 1-week period

Table 53–9

Therapies for Pediatric Enuresis

Therapy (FDA approval)	Dosage form	Dose (generic)	Advantages	Disadvantages	Adverse effects
Enuresis alarms	Sound and/or vibration		• Best response • Low relapse rates	• Requires motivation • Slow-acting	• Sleep disruption
Desmopressin (≥ 6 years of age)	Oral, tablet 0.1 mg, 0.2 mg (generic)	0.2 mg, increased to 0.4 mg (maximum 0.6 mg)	• Reduces urine volume at night • Faster acting than enuresis alarms	• Low response rate • High rate of relapse	• Water intoxication, hyponatremia, seizures
Imipramine (≥ 6 years of age)	Oral, tablet 10 mg, 25 mg, 50 mg (generic)	10 to 25 mg (maximum: 50 mg if < 12 years of age; 75 mg if > 12 years of age)	• Reduces bladder contractions • Equally effective to desmopressin	• High rate of relapse	• Cardiac conduction disturbances; myocardial depression
Anticholinergics: oxybutynin (≥ 5 years of age)	Oral, tablet 5 mg; Syrup 5 mg/mL (generic)	2.5 to 5 mg once or twice a day	• Reduces bladder contractions • Effective in patients with low functional bladder capacity	Ineffective as monotherapy, use in combination therapy	• Constipation, dry mouth
Anticholinergics: solifenacin (≥2 years of age)	Oral, suspension 5 mg/5mL (expected availability 2020)	5–10 mg once a day	• Reduces bladder contractions • Effective in patients with low functional bladder capacity	Ineffective as monotherapy, use in combination therapy, limited data in children	• Constipation, dry mouth

bedtime to reach peak effects. Effects persist for 8 to 10 hours after administration.[33] If response is not achieved in 10 to 14 days, the oral dose may be increased by 0.2 mg to a maximum dose of 0.6 mg.[34,36] If the child cannot swallow the tablet, it may be crushed and consumed with soft foods. Sublingual tablets are not approved by the FDA in pediatric patients. The intranasal formulation is no longer FDA-approved for the management of primary nocturnal enuresis due to postmarketing reports of seizures caused by hyponatremia. Desmopressin lyophilizate oral quick-melting tablets are not FDA approved but are available outside the United States. The starting lyophilizate dose is 120 to 240 mcg at night. Potential advantages of this formulation are improved bioavailability and antidiuretic effect.

Treatment response should be assessed within 1 to 2 weeks after dosage adjustments. If ineffective, desmopressin should be discontinued.[29] If effective, it can be continued for 3 to 6 months, administered nightly or as needed. When it is administered daily, desmopressin should be withheld for 1 week every 3 months to determine whether continued use is necessary.[29,37] Lack of response to desmopressin may be due to reduced nocturnal bladder capacity, daytime wetting, or suboptimal dosing. To minimize relapses, daily desmopressin should be tapered over a 2- or 4-week period, by reducing the daily dose by one-half or giving the dose every other day.[29,45]

The most serious complication of desmopressin therapy is water intoxication from dilutional hyponatremia, and seizures. This occurs most frequently with the nasal formulation. Electrolyte monitoring in patients taking the oral formulation is recommended if comorbidities may exacerbate renal or electrolyte complications. To reduce risk of hyponatremia, children should drink no more than 8 oz (240 mL) of fluid from 1 hour before to 8 hours after administration of desmopressin. During episodes of fluid and/or electrolyte imbalance (e.g., diarrhea, vomiting, vigorous exercise, fever, or dehydration), more water intake may be allowed or treatment can be interrupted.[29,31]

Diuretics play a minor role in the treatment of enuresis and are not recommended. However, in cases of poor response to desmopressin or symptom deterioration after established positive response, oral furosemide 0.5 mg/kg in the early morning may be helpful. Furosemide works by reversing the abnormal circadian rhythm of renal tubular sodium handling, which is common in individuals with enuresis.[46]

Anticholinergics Anticholinergic agents increase bladder capacity during sleep and reduce detrusor muscle overactivity. They are the primary therapy for a child with low bladder functional capacity and a second-line option in the treatment of pediatric enuresis.[29] Monotherapy is typically ineffective in monosymptomatic enuresis, so it is common to use them in combination with other therapies. Residual urine and constipation should be successfully treated before starting therapy and if enuresis resurges after an initial successful response. Several anticholinergic agents have been used for the treatment of nocturnal enuresis, including oxybutynin, solifenacin, tolterodine, and fesoterodine. Tolterodine and fesoterodine are not approved by the FDA in children.

Oxybutynin is approved in children 5 years of age and older and available in tablets and syrup (5 mg/5 mL). Initial doses of IR oxybutynin are 2.5 to 5 mg orally.[29] Doses are administered 1 hour before bedtime. In a child who has concomitant daytime incontinence, oxybutynin may be administered two or three times a day. Maximal therapeutic effects occur within 2 months. If the response is not optimal and the patient is not experiencing adverse effects, either oxybutynin dose may be increased or desmopressin may be added.[29,34,36] If response is achieved, medications are discontinued gradually every 3 months.[29] Children should be monitored for potential adverse events, such as urinary retention (may lead to UTIs), constipation (worsens urinary tract dysfunction), tachycardia, blurred vision, behavioral changes, and dry mouth (can lead to dental caries).

Solifenacin was recently approved by the FDA in children aged 2 years and older for neurogenic detrusor overactivity. It is available as an oral suspension administered once daily. Doses range from 2.5 to 10 mg orally 1 hour before bedtime. Adverse effects are similar to those reported with oxybutynin. In addition, QT prolongations and anaphylaxis have been reported with solifenacin.

Tricyclic Antidepressants Imipramine was first used to treat enuresis in the 1960s. It is FDA-approved for pediatric enuresis for children aged 6 years and older but is considered a third-line pharmacotherapy option for monosymptomatic enuresis.[29] TCAs are as effective as desmopressin but are associated with more adverse reactions.[34,38] Their place in therapy is in a child who has failed an alarm, desmopressin, and anticholinergic therapies. Mechanisms of action include anticholinergic and antispasmodic effects, relaxing detrusor muscle, elevating plasma ADH concentrations, and lowering arousal threshold.[31,33] Although trials involving other TCAs have been performed, there is insufficient evidence to assess their efficacy compared with imipramine.

Response to imipramine, defined as one less wet night per week, is expected in 50% of children.[29] However, relapse rates are up to 67%.[30] The usual initial dose is 10 to 25 mg at bedtime which may be increased if there is no response after 1 week. The usual dose is 25 to 50 mg orally once daily, 1 hour before bedtime.[29,34] The dose should not exceed 50 mg in children 6 to 12 years old and 75 mg in children 12 or older. After 1 month of successful response, the dose should be reduced to the lowest effective amount. As the patient continues the therapy, the medication may be discontinued for 2 weeks every 3 months to reduce drug tolerance and reevaluate necessity of drug therapy.[34] When discontinuing imipramine, the dose should be reduced gradually by 50% over 1 to 2 weeks.[29]

About 25% of children treated with TCAs experience gastrointestinal symptoms. Neurologic adverse effects including nervousness, personality change, or sleep disturbances occur in approximately 5% of patients. Clinicians should monitor for increased suicidality, particularly in children and young adults with preexisting depressive symptoms.[31]

Other serious adverse effects of TCAs include cardiac conduction disturbances, QT prolongation, and myocardial depression, particularly in cases of overdose. A history of syncope or palpitations in the child or family history of sudden cardiac death may preclude the use of TCAs unless cleared by a pediatric cardiologist. Safer options should be considered before starting any TCA for pediatric enuresis.

Combination Therapies In children who fail to respond to one therapy or who have frequent relapses, combinations of urotherapy, imipramine, oxybutynin, desmopressin, and/or alarm therapy can improve response.[30,31] In a child with small bladder volume and refractory enuresis, combination therapy with desmopressin and anticholinergic agents is more effective than desmopressin alone. The combination of alarm and desmopressin is not useful in the long-term.[34,44] Imipramine in combination with oxybutynin was shown to be more effective than imipramine monotherapy.[47] Imipramine and desmopressin therapy was as effective as imipramine alone but more effective than desmopressin alone.[47,48]

Other Drugs Other medications, including indomethacin, phenmetrazine, sertraline, amphetamine sulfate, ephedrine, atropine, furosemide, diclofenac, aripirazole, clonidine, and chlorprothixene, have been used. Data suggest that indomethacin, diclofenac, and diazepam are superior to placebo, but not better than desmopressin.[49] Current guidelines do not recommend any of these agents for pediatric enuresis.

▶ *Comparison of Therapies*

Multiple meta-analyses have compared treatments for enuresis, although most trials enrolled a small number of subjects and were of poor methodological quality.[47,49] Overall, enuresis alarms are the most effective treatment method from the standpoint of effectiveness and reduced relapse rate. The initial rate for success (less than one wet night per month) is 66%, with 55% long-term success rate after discontinuation. Alarm therapy is as effective as desmopressin but has significantly lower relapse rates (46% vs 60%–70% for desmopressin).[33,34,38] Combining enuresis alarms and other complex behavioral therapy further reduces relapse rates. However, the data are inadequate to compare various commercial brands of alarms available.

▶ *Treatment of Relapse*

A relapse is defined as more than one wet night per month after a period of dryness.[33] When it occurs, clinicians should consider reinitiation of the intervention which was previously effective (Figure 53–1). For children with multiple recurrences after discontinuation of desmopressin, gradual dose tapering of desmopressin may be helpful. For relapse following successful treatment with alarm therapy, adding desmopressin may be effective.[35] Management of therapy-resistant monosymptomatic nocturnal enuresis may include periodic new trials of the enuresis alarm with or without desmopressin, desmopressin alone, or a trial of imipramine, or a combination therapy that includes oxybutynin.[30]

Nonresponders experience less than 50% improvement in symptoms despite active interventions.[28] When motivated children and families do not respond to at least a 3-month trial of enuresis alarm and/or desmopressin, referral to a specialist (e.g., developmental-behavioral pediatrician, pediatric urologist) may be warranted.[30]

OUTCOME EVALUATION

- Monitor the patient for symptom relief in 2 weeks, 1 month, and every 3 months until symptom resolution. Has the treatment plan achieved the desired outcomes developed by the healthcare team, the patient, and parents/guardians? If so, to what degree?
- Evaluate the diary completed by the patient or parents/guardians since the last clinic visit and quantify the clinical response (number of dry nights per week, number of nights with two or more enuresis episodes, etc). If a diary has not been kept, elicit from the patient and caregiver the clinical response since last visit. Consider dosage modification or alternative therapy depending on patient response and adverse effects of therapy.
- Elicit adverse events of therapy, including severity, using a nonleading manner. Ask the patient or parents/guardians

Patient Encounter 2, Part 3

Based on the information available, develop a care plan for this patient's enuresis. Your plan should include:

(a) A statement about the drug-related needs and/or problems

(b) A patient-specific detailed therapeutic plan

(c) Monitoring parameters to assess efficacy and safety

Patient Care Process: Pediatric Enuresis

Collect Information:

- Identify urinary symptoms, exacerbating factors, and family issues.
- Review medical history.
- Obtain a thorough medication history, including use of prescription, nonprescription, and complementary/alternative drug products.

Assess the Information:

- Determine whether the enuresis is due to secondary causes. Assess whether there are any exacerbating factors or enuresis-related complications.
- Are there any potentially treatable organic or drug-induced causes of enuresis (Table 53–6)? Assess parental motivation when attempting nonpharmacologic approaches.
- Could patient's medical/medication history contribute to enuresis (Table 53–6)? Determine which, if any, treatments in the past have helped.

Develop a Care Plan:

- Establish realistic treatment goals with the involvement of the child and caregiver.
- If patient is already receiving nonpharmacological interventions and/or drug therapy, assess treatment choice, drug dosing, efficacy, adverse effects, adherence, etc.
- Have the child and caregiver given the current treatment plan an adequate duration of trial? How is the child responding to the current treatment plan?
- Patient-specific detailed therapeutic plan for therapies for pediatric enuresis (Table 53–9).

Implement the Care Plan:

- Educate the patient and/or caregiver on pediatric enuresis, urotherapy, and motivational therapy (Table 53–7). The patient and/or caregiver should be offered behavioral therapy and/or enuresis alarm with proper education using the "teach back" method (Table 53–8).
- Provide the patient and/or caregiver with education regarding drug therapy (timing of drug administration, adverse effects, potential drug–drug interactions, etc).

Follow-up: Monitor and Evaluate:

- Evaluate the patient for adverse events, allergies, and interactions (drug–drug and drug–disease) and adherence.
- Evaluate treatment response in 1 to 2 weeks after therapy initiation. Adjust medication dosing if needed.
- Allow at least 3 months to assess efficacy of treatment.
- Identify expected adverse effects and educate regarding avoidance and management of these adverse effects.

what measures, if any, were used to alleviate adverse effects. Assess therapy adherence.

- The balance of clinical response, tolerability, and burden on the caregiver will determine the management approach. As most nonpharmacologic approaches are "all or none" and drug titration is limited by the maximum recommended dose, clinicians may consider changing therapy if clinical results are inadequate.
- Refer patients with refractory enuresis to a healthcare professional who specializes in the management of bedwetting.

Abbreviations Introduced in This Chapter

ADH	Antidiuretic hormone
BPH	Benign prostatic hyperplasia
CYP	Cytochrome P450
DDAVP	Desmopressin
ER	Extended release
IR	Immediate release
MUI	Mixed urinary incontinence
OAB	Overactive bladder
OUI	Overflow urinary incontinence
PFMR	Pelvic floor muscle rehabilitation
PVR	Postvoid residual
SUI	Stress urinary incontinence
TCA	Tricyclic antidepressant
UI	Urinary incontinence
UTI	Urinary tract infection
UUI	Urge urinary incontinence

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Drug Hypersensitivity Reactions

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the potential incidence of immunoglobulin-E (IgE)- and non-IgE-mediated (immune and nonimmune) drug hypersensitivity reactions and why it is difficult to obtain accurate estimates.
2. Understand the Gell and Coombs categories of immunologic reactions and more recently described immunologic mechanisms.
3. Identify the classes of drugs most commonly associated with IgE- and non–IgE-mediated drug hypersensitivity reactions.
4. Recommend specific treatment for anaphylaxis.
5. Recommend an approach to drug selection in patients with multiple drug sensitivities.
6. Understand the utility of drug challenge and desensitization procedures.

INTRODUCTION

Drug hypersensitivity reactions collectively encompass immunoglobulin E (IgE)- and non–IgE-mediated (immune and nonimmune, previously "pseudoallergic") drug hypersensitivity reactions. These reactions are rarely confirmed by testing and are subject to both overreporting and underreporting, making statistical analysis imprecise. KEY CONCEPT Approximately 5% to 10% of adverse drug reactions occur on an allergic or immunologic basis. However, these represent a disproportionate 24% of reported adverse drug reactions in hospitalized patients and are costly, with accompanying morbidity and mortality.[1,2] Between 10% and 20% of hospital inpatients experience drug adverse events versus 7% in the general population, with about one-third possibly due to hypersensitivity; however, many such reactions may not be reported, especially in pediatrics.[1,3,4] Costs of inpatient drug hypersensitivity reactions (in US dollars) are estimated at up to $600 million annually in 2002, which equates to at least $850 million in 2020.[5] Financial burden calculations include indirect costs: time and lost labor, use of more expensive alternative medications, and treatment failures, in addition to direct reaction treatment costs. Accurate data regarding outpatient reaction rates are even more elusive. The term "drug allergy" in a patient record/electronic medical record (EMR) often conveys little medical meaning, as such information is self-reported, and may not delineate symptoms or incorporate provider assessment of probable causality (eg, adverse effect vs IgE-mediated). Potential clinical outcomes might therefore range from inappropriately excessive treatment to lack of recognition of anaphylaxis risk. Clearly, an understanding of mechanisms of drug hypersensitivity reactions and how these might be accurately identified, documented, managed, and ideally prevented is of vital importance.

PATHOPHYSIOLOGY

Drug hypersensitivity reactions are a result of diverse mechanisms of immune recognition and activation, resulting in a broad array of clinical findings. The fundamental Gell and Coombs classification, used for decades, remains a framework for considering mechanisms of immunologic drug reactions (Table 54–1).[6,7]

With advances in immunologic understanding, the underlying mechanisms for many drug hypersensitivity reactions have been found to be more complex and interrelated than suggested by the Gell and Coombs classification.[8] Yet, this classification remains the most commonly used initial method to describe drug hypersensitivity reactions. KEY CONCEPT Immediate or type I reactions describe classic allergic reactions mediated by drug-specific IgE antibodies; type II reactions are cytotoxic reactions mediated by drug-specific IgG or IgM antibodies; type III reactions result from deposition of immune complexes circulating in the serum; and type IV reactions are mediated by diverse cellular mechanisms and may be further subcharacterized by specific effector cell.[9]

Immune Mechanisms

The cellular immune mechanisms involved in drug hypersensitivity are notably complex.[10] The immune system must first recognize nonself material (antigens). This recognition is predominantly controlled by T lymphocytes. Two distinct signals are typically required for T-cell activation, namely, the presentation of a foreign substance by an antigen presenting cell (APC) to the T-cell with a concomitant second activation signal. If the second signal is not provided, the T-cell becomes nonresponsive or anergic. Thus, the second signal controls whether a T-cell immune response will occur.

Dependent on antigen exposures and the specific cytokines (immune chemical messengers) involved in activation, naïve

Table 54–1

Reaction Classification, Clinical Symptoms, and Potential Causative Drugs[6,7]

Gell and Coombs Classification	Immune Response	Clinical Symptoms	Potential Causative Drugs[a]
Type I	IgE	Anaphylaxis, urticaria	β-Lactam antibiotics: penicillins (primarily), cephalosporins, carbapenems Non–β-lactam antibiotics: sulfonamides, vancomycin Others: insulins, heparin
Type II	IgG	Hemolytic anemia, thrombocytopenia	Quinidine, methyldopa, penicillins, heparin
Type III	IgG, IgM	Vasculitis, serum sickness, lupus	Penicillins, sulfonamides, radiocontrast agents, phenytoin, minocycline
Type IV			β-Lactam antibiotics, sulfonamides, phenytoin
Iva	Th1 cytokines	Tuberculin reaction eczema	See text for examples
IVb[b]	Th2 cytokines	Maculopapular and bullous exanthema	
IVc[b]	Cytotoxic T cells (CD4 and CD8)	Same as IVb, also eczema, pustular exanthema	
IVd	T-cells (IL-8)	Pustular exanthema	

[a] These drugs represent a list of causative agents. Many drugs can cause these reactions.

[b] IVb and IVc reactions may combine to produce erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Ig, immunoglobulin; IL, interleukin; Th, T-helper cell.

T-helper cells (CD4+ T-cells) can differentiate into disparate specialized effector T-helper cell groups. Each of these groups possesses a unique regulatory element, pattern of cytokine production, and function. Type 1 effector T-helper cells (Th1) are associated with T-cell recruitment of phagocytic cells, via cytokines such as interferon-gamma (IFNγ), and activation of B-cells to produce IgG antibody. Th1 responses can cause delayed hypersensitivity reactions (type IV Gell-Coombs); notably, this is the same mechanism for a positive purified protein derivative (PPD) test indicating tuberculosis. Th2-immune responses induce IgE production from B-cells yielding an immediate allergic reaction (type I Gell-Coombs) or can increase tissue eosinophils, causing a type of delayed hypersensitivity. In type I reactions, specific IgE antibody is produced in response to an antigen (in allergic reactions, "allergen") causing membrane-binding of that IgE to mast cells. Upon antigen (allergen) reexposure, crosslinking of IgE occurs on mast cells resulting in rapid and massive release of preformed mediators including histamine (H). More recently described T-helper-effector cell subtypes including Th22 may be responsible for certain inflammatory patterns seen in drug hypersensitivity.[11]

Drugs as Antigens

Many drugs are small molecules not normally recognized as antigens. As a result, there are several models explaining how drugs might elicit an immune response.[10] The first one widely accepted was the hapten mechanism, in which the drug becomes covalently bound to a normal "self" protein. This drug–protein conjugate becomes large enough to be recognized as foreign, yielding an immune response in susceptible people.[10] The related pro-hapten mechanism involves a nonreactive drug becoming chemically reactive during metabolism and then covalently binding to self-proteins. An example of this is sulfamethoxazole metabolism to sulfamethoxazole-nitroso, the latter being highly reactive. Thirdly, a drug (or metabolite) can directly bind to the T-cell receptor, initiating a pharmacologic interaction immune response, or *p-i* mechanism. In this case, T-cells are activated directly without an APC, bypassing usual signaling requirements.

The location of drug metabolism often plays a critical role in the reaction seen in an organ or organ system. The fact that many drugs are primarily hepatically metabolized helps explain why the liver is frequently involved in drug hypersensitivity reactions. Skin, via keratinocytes, is increasingly recognized as a site of drug metabolism. This may also help explain the skin involvement common to many forms of reactions elicited by different drugs.[12] Some of the most common life-threatening drug reactions are predominantly cutaneous, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS).[13]

Nonimmune (Non-IgE) Drug Reactions

KEY CONCEPT Reactions occur that clinically resemble IgE-mediated or immune drug reactions but lack an immune basis, previously called "pseudoallergic" "anaphylactoid." These reactions include the entire spectrum of clinical severity, but occur via other, less well understood mechanisms.

Nonimmune drug hypersensitivity reactions are important in counseling and management considerations. They represent common nonspecific occurrences such as direct histamine release by vancomycin or opiates, whereas immunologic (or IgE-mediated) reactions are based on drug structure and the immune system. Even a history of mild IgE-triggered symptoms to a drug may portend risk of anaphylaxis on readministration. In contrast, nonimmune drug reactions tend to remain constant, whether mild or severe, and are dose-related. Ionic radiocontrast media administration, as a classic example, can consistently cause urticaria in some and life-threatening hypotension in others.

Nonimmune drug hypersensitivity reactions, then, are reactions where the components of the immune system react similarly, but without the "learning" response by T-cells and generally without the much greater danger that true immunologic sensitization implies. Indicators of immune activation are not observed with such reactions but direct release of preformed mediators from mast cells occurs, via a recently identified G coupled protein regulator.[14] A prototypical example is seen with vancomycin infusion. Pruritus and an erythematous rash involving the face, neck, and upper torso (referred to as vancomycin flushing) are commonly associated with vancomycin infusions administered over less than 1 hour, previously known as a "red man" reaction.[15]

Clinical Presentation and Diagnosis of IgE-mediated and Other Immune Drug Reactions

Reaction	Mediators Involved	Signs and Symptoms
Anaphylaxis	IgE-driven reaction resulting in mast cell degranulation and histamine release.	Skin (eg, pruritus, urticaria), respiratory tract (eg, dyspnea, wheezing), gastrointestinal tract (eg, nausea, cramping), and cardiovascular system (eg, hypotension, tachycardia)
Note: Onset is usually within 30 minutes, but can be 2 hours or more. Treatment must begin immediately. Anaphylaxis may recur 6 to 8 hours after initial exposure, warranting observation for up to 12 hours.		
Cytotoxic Reactions	Drug-specific IgG or IgM antibodies	Hemolytic anemia, thrombocytopenia, granulocytopenia, or agranulocytosis
Immune Complex Reactions	IgG, IgM deposition	Serum sickness-like syndrome (eg, arthralgias, fever, malaise, and urticaria) that typically develops 7 to 14 days after exposure to the causative antigen
Dermatologic Reactions	IgE or cellular mechanisms (see Table 54–1)	See below for dermatologic reaction types

- *Urticaria*: These are itchy, raised, swollen areas on the skin; also known as hives.
- *Maculopapular rash*: A rash that contains both macules and papules. A macule is a flat, discolored area of the skin, and a papule is a small raised bump. A maculopapular rash is usually a large area that is red and has small bumps.
- *Erythema multiforme*: A rash characterized by papular (small raised bump) or vesicular (blister) lesions and reddening or discoloration of the skin, often in concentric zones about the lesion.
- *Stevens-Johnson syndrome*: A severe expression of erythema multiforme (known as erythema multiforme major). It typically involves the skin and mucous membranes, with the potential for severe morbidity and even death.
- *Toxic epidermal necrolysis*: A life-threatening skin disorder characterized by blistering and peeling of the top layer of skin.

PROBLEMATIC DRUG CLASSES AND TREATMENT OPTIONS

The first priority is to avoid doing serious harm by administering a drug the patient cannot tolerate. One can frequently establish the likelihood of a relationship between the suspected drug and observed reaction, and also whether it is likely to be an immune or idiopathic event, by objectively reviewing the time course and specific signs and symptoms. Associated physical findings and available laboratory values in the context of preexisting diseases may further clarify the need to change treatments and treat the reaction.

Table 54–2

Problematic Drug Classes

β-Lactam antibiotics
Sulfonamide antibiotics
Aspirin and nonsteroidal anti-inflammatory drugs
Radiocontrast media
Opiates
Cancer chemotherapy
Anticonvulsants

Reviewing the original indications for the treatment that caused the reaction is important. If definitive indications for treatment are established, options must be evaluated including adjusting the dose or administration rate, finding an effective and unrelated alternative, or desensitizing the patient to the original drug.

When adverse drug reactions occur, all aspects of the reaction and the potential for it to recur should be carefully evaluated. The term "drug allergy" is often associated with anaphylaxis, potentially increasing patient anxiety. Thus, a label of drug allergy may hamper future medical care, with treatment refusals, nonadherence to therapy, or resultant use of more toxic or less effective alternative treatments. When the original reaction is clearly documented, healthcare providers can appropriately counsel patients about risk.

Anaphylaxis is a true medical emergency and must be treated immediately. Otherwise, managing drug reactions begins with holding the offending agent and considering alternative options. Understanding risk of an allergic reaction and potential for cross-allergenicity between similar drugs is critical to decision making. Desensitization (discussed later in the chapter) is a management option for certain IgE-mediated drug reactions if there is a definitive indication and alternative therapies are not available. Although any agent may cause an allergic (IgE-mediated), immune or nonimmune (pseudoallergic) reaction, several drugs and drug classes are strongly associated with such reactions (Table 54–2). These classes will be discussed individually.

β-Lactam Antibiotics

Hypersensitivity reactions with β-lactam antibiotics, especially penicillin, may encompass any of the types I through IV Gell-Coombs classifications. The most common reactions are maculopapular and urticarial eruptions.[16] Although rare (< 0.05%), anaphylactic reactions to penicillins cause the greatest concern, because they are responsible for the majority of all drug-induced anaphylaxis deaths in patients, accounting for 75% of all anaphylaxis cases in the United States.[6,17] The treatment of anaphylaxis is given in Table 54–3.[18,19]

The healthcare professional is faced with a difficult task when approaching a patient who notes a history of penicillin allergy. Although as many as 12% of hospitalized patients report an allergy to penicillin, about 90% will have negative penicillin skin tests.[20] Penicillin skin testing has been successful as an antimicrobial stewardship initiative resulting in a reduction of carbapenems, aztreonam, vancomycin, and other broad spectrum agents used.[21]

KEY CONCEPT Penicillins and cephalosporins both have a β-lactam ring joined to an S-containing ring structure (penicillins: a thiazolidine ring; cephalosporins: a dihydrothiazine ring). The extent

Table 54–3

Pharmacologic Management of Anaphylactic Reactions[18,19]

Immediate Intervention

Epinephrine 1:1000 (1 mg/mL)
- Adults: 0.3–0.5 mg IM, repeat every 5 to 15 minutes as needed
- Pediatrics: 0.01 mg/kg (maximum 0.3 mg) IM, repeat every 5–15 minutes as needed

Subsequent Interventions

Normal saline infusion
- Adults: 1–2 L at a rate of 5–10 mL/kg in the first 5 minutes, followed by slow infusion
- Pediatrics: up to 30 mL/kg in the first hour

Epinephrine infusion

If patient is NOT responding to epinephrine injections and volume resuscitation:
- Adults: epinephrine infusion (1 mg in 250 mL D_5W): 1–4 mcg/min, titrating based on clinical response or side effects
- Pediatrics: epinephrine infusion (0.6 × body weight [in kg] = number of mg diluted to a total of 100 mL normal saline: 1 mL/hour delivers 0.1 mcg/kg/min)

Other Considerations after Epinephrine and Fluids

Diphenhydramine
- Adults: 25–50 mg IV or IM
- Pediatrics: 1–1.25 mg/kg (maximum of 300 mg/24 hours)

Famotidine
- Adults: 20 mg IV over 2 minutes
- Pediatrics: 0.25 mg/kg, (maximum 20 mg/dose) IV over 2 minutes

Inhaled β-agonist (bronchospasm resistant to epinephrine)
- 2.5–5 mg in 3 mL of normal saline, nebulized, repeat as needed

Dopamine (hypotension refractory to fluids and epinephrine)
- 2–20 mcg/kg/min titrated to maintain systolic blood pressure > 90 mm Hg

Hydrocortisone (severe or prolonged anaphylaxis)
- Adults: 250 mg IV (prednisone 20 mg can be given orally in mild cases)
- Pediatrics: 2.5–10 mg/kg/24 hours

D_5W, dextrose 5% in water; IM, intramuscularly; IV, intravenous.

Adapted from Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol. 2010;126:477–480 and LoVerde D, Iweala O, Enginli A, et al. Anaphylaxis. Chest. 2018;153:528–543.

Patient Encounter 1

A 65-year-old man is admitted to the hospital with a skin infection. When asking about allergies, the patient states he believes he is allergic to penicillin. When questioned further, the patient cannot remember the type of reaction but was told by his mother 50 years ago that he was allergic to penicillin. Because of this history, the physician wants to use meropenem to treat the infection instead of nafcillin. The staphylococcus causing the infection is susceptible to both. The patient doesn't remember if he has received penicillin since his youth.

How might this patient be managed at present?

Once steps have been taken to confirm the allergy status, what should be noted in the patient's medication reaction history?

of cross-allergenicity appears to be relatively low, with an estimate of approximately 2%.[22] Cross-allergenicity is less likely with newer generation cephalosporins compared with the first-generation agents. Anaphylactic reactions to cephalosporins are rare, with a predicted range of 0.0001% to 0.1%. Minor skin reactions including urticaria, exanthems, and pruritus are the most common allergic reactions with cephalosporins, showing severe reactions less often than with penicillins.[23]

For other β-lactam agents, the recommendations are fairly straightforward. Carbapenems should be considered potentially cross-reactive with penicillins and used with caution.[24] Monobactams (eg, aztreonam) do not cross-react with any β-lactam drugs except ceftazidime because they share an identical R-group side chain. Other cephalosporins sharing identical R-group specific side chains share cross-reactivity as well.

Sulfonamide Antibiotics

Sulfonamides are compounds that contain a sulfonamide moiety (ie, SO_2NH_2). This group includes sulfonamide antibiotics (sulfonylarylamines), and nonarylamine sulfonamides such as furosemide, thiazide diuretics, sulfonylureas, and celecoxib. The sulfonamide antibiotics contain an aromatic amine at the N4 position and a substituted ring at the N1 position. Newer evidence suggests that most patients allergic to antimicrobial sulfonamides will tolerate nonarylamine sulfonamides.[25] Predisposition to allergic reactions is a more likely reason for dual sensitivity than cross-reactivity between these differing molecules.[26] The term "sulfa allergy" should not be used as it can be confusing to patients and healthcare providers. The sulfonamide antibiotics are significant because they account for the largest percentage of antibiotic-induced TEN and SJS cases.[27]

KEY CONCEPT Reactions to sulfonamide antibiotics, ranging from mild (most common) to life-threatening (rare), occur in 2% to 4% of healthy patients, with rates as high as 65% in patients with acquired immunodeficiency syndrome (AIDS).[28] Anaphylaxis or nonimmune anaphylactoid reactions almost always occur within 30 minutes but may happen up to 90 minutes after exposure, most commonly after parenteral administration. Isolated angioedema or urticaria can occur within minutes to days. Serum sickness occurs within 1 to 2 weeks. Fixed drug eruptions (lesions) occur within 30 minutes to 8 hours. These lesions resolve within 2 to 3 weeks after drug removal. The more severe conditions of SJS and TEN tend to occur 1 to 2 weeks after initiation of therapy. Because trimethoprim-sulfamethoxazole is the drug of choice for patients with *Pneumocystis jiroveci* pneumonia, desensitization may be necessary. A history of SJS or TEN is an absolute contraindication for the desensitization procedure.

Patients With Multiple Antibiotic Allergies

Addressing a history of multiple antibiotic reactions can be challenging. Combining knowledge of cross-allergenicity with a careful assessment of specific history may be helpful in designing an antimicrobial regimen. Table 54–4 outlines a series of questions that can be useful in treatment planning.[29] If available and indicated, drug challenge (discussed later in the chapter) or allergy skin testing may help complete the puzzle and often may allow use of an antibiotic of choice when the patient's initial history might have precluded it. Based on data gathered, the patient's record should reflect antibiotics safe to use, those to be avoided, and antibiotics requiring desensitization. Although Table 54–4 was designed with antibiotics in mind, it can be modified for other multiple drug allergy situations.

Table 54–4

Multiple Antibiotic Allergies: Obtaining Background Information[29]

For **each** antibiotic to which the patient claims to be allergic, gather the following information:

- What type of infection was being treated?
- Have you ever received the drug without experiencing a reaction?
- How many times have you received the drug and experienced a reaction?
- What was the drug dose and route of administration with the last reaction?
- How many doses did you take before the onset of the last reaction?
- How many doses did you take after the last reaction?
- Can you describe the adverse reaction?
- What was the duration of the reaction?
- What treatment was given for the reaction?
- Was there any permanent damage?

For **each** antibiotic the patient has received and does not claim allergy, gather the following information:

- What was the last type of infection being treated?
- What was the drug dose and route of administration?
- Have you received this drug more than once without reactions?

Other information to be gathered:

- Have you had adverse reactions to any other drugs? If so, give dates and describe the reaction.
- Document any risk factors for allergic reactions such as chronic urticaria, liver or kidney disease, HIV (human immunodeficiency virus), or any other immune deficiencies.

Adapted from Macy E. Multiple antibiotic allergy syndrome. Immunol Allergy Clin North Am. 2004;24:533–543.

Aspirin and Nonsteroidal Anti-Inflammatory Drugs

Aspirin and the nonsteroidal anti-inflammatory drugs (NSAIDs) can induce allergic and nonallergic reactions. Because these drugs are so widely used and over-the-counter, the healthcare professional must have a basic understanding of the types of reactions that can occur and how to prevent them. Three general types of reactions occur: bronchospasm with rhinoconjunctivitis, urticaria/angioedema, and anaphylaxis. Those with gastric discomfort or bruising from these agents may also inappropriately describe themselves as being "allergic."

Two specific nonallergic/non-IgE–mediated conditions—aspirin-exacerbated respiratory disease (AERD) and chronic idiopathic urticaria (CIU)—are important because they are commonly seen. AERD may include asthma, rhinitis with nasal polyps, and aspirin sensitivity.[30] Upon exposure to aspirin or NSAID, patients with AERD experience rhinorrhea, nasal congestion, conjunctivitis, laryngospasm, and bronchospasm/asthma. CIU exacerbations with aspirin/cyclooxygenase (COX)-1 inhibiting NSAID are characterized by worsening urticaria or angioedema following administration.[31] Cross-reactivity between aspirin and older COX-1 inhibiting NSAIDs exists in those with either AERD or CIU. Despite COX-2 inhibitor NSAID product warnings contraindicating use in these conditions, there are no reports of cross-reactivity in AERD and only rare reports in CIU.[32]

KEY CONCEPT IgE-mediated urticarial/angioedema reactions and anaphylaxis are associated with aspirin and NSAIDs. Urticaria is the most common form of an IgE-mediated reaction. However, most reactions are the result of metabolic idiosyncrasies, such as AERD, which may produce severe and even fatal bronchospasm. This class is second only to β-lactams in causing anaphylaxis. Most reactions in this class are nonallergic/non-IgE–mediated and instead are due to a complex metabolic pattern, which causes increasingly recurrent and severe nasal polyps and often refractory asthma. The metabolic problem is constant once it emerges, accounting for the persistence and difficulty of these clinical problems. The same metabolic process is also capable of causing severe, sometimes fatal, acute reactions to aspirin, and many, if not all, other NSAIDs. Rare reports of non–cross-reactive severe reactions suggest possible specific IgE-mediated reactions to individual NSAIDs, and there are some occurrences of urticaria related to specific NSAIDs as well. Because aspirin therapy is highly beneficial in coronary artery disease (CAD), aspirin desensitization should be considered in select patients. Aspirin single dose or graded drug challenges can be considered for patients with vague histories or those with adverse effects mischaracterized as drug allergy. Desensitization is contraindicated in patients who have experienced aspirin-induced (nonallergic) anaphylaxis, hypotension, tachypnea, or altered consciousness. Alternate agents must be used. A comprehensive approach to aspirin-sensitive patients with CAD has been described.[33]

Radiocontrast Media

KEY CONCEPT Radiocontrast media may cause serious, immediate nonimmune hypersensitivity reactions, such as urticaria/angioedema, bronchospasm, shock, and death. These reactions have been reduced with the introduction of nonionic, lower osmolality products. Because a small percentage of patients who have reacted previously to radiocontrast media will react if reexposed, several preventive steps (listed below) should be taken. These steps should also be followed in those with known risk factors: asthma, β-blocker use, and cardiovascular disease.[5] The steps are as follows:

- Determine whether the study is essential.
- Be sure the patient understands the risks.
- Ensure adequate hydration.
- Use nonionic, lower osmolar agents.
- Typical protocols include pretreatment with prednisone 50 mg orally 13, 7, and 1 hour(s) before the procedure and diphenhydramine 50 mg orally 1 hour before the procedure.

Reactions with nonionic radiocontrast media occur in 0.7% to 3% of patients.[34] Although reactions are occasionally severe, most are mild and manifest as maculopapular rashes, fixed eruptions, erythema multiforme, and urticarial eruptions.

Patient Encounter 2

A 17-year-old male is hospitalized for cellulitis that failed outpatient treatment with clindamycin. He is started on vancomycin. Five minutes into the infusion he complains of itching. When evaluated by his nurse, he has significant flushing in his face and torso without additional symptoms.

What kind of reaction did the patient experience with vancomycin?

Could vancomycin be used for treatment of this current infection? Discuss rationale.

Opiates

KEY CONCEPT Opiates (morphine, meperidine, codeine, hydrocodone, and others) stimulate mast cell mediator release directly, resulting in pruritus and urticaria with occasional mild wheezing. Though these reactions are not IgE-mediated, many patients state they are "allergic" to one or more of the opiates. Pretreatment with an antihistamine may reduce these reactions which are rarely, if ever, life-threatening.[6] Avoiding other mast cell degranulating medications while patients require opiates also reduces the chances of frightening and uncomfortable reactions. Patients may also commonly state they are "allergic" if they have experienced gastrointestinal upset or constipation with opiates. Obtaining a thorough history from the patient will prove useful. If a more serious reaction has occurred, a nonnarcotic analgesic should be selected.

Cancer Chemotherapy

Hypersensitivity reactions have occurred with all chemotherapy agents. Reactions are most common with the taxanes, platinum compounds, asparaginases, and epipodophyllotoxins.[16] Reactions range from mild (flushing and rashes) to severe (dyspnea, bronchospasm, urticaria, and hypotension). IgE-mediated type I reactions are the most common. To reduce the risk, patients are routinely premedicated with corticosteroids and H_1- and H_2-receptor antagonists. The platinum compounds have produced anemia, probably via a cytotoxic immunologic mechanism.

Anticonvulsants

A wide range of hypersensitivity reactions, ranging from mild maculopapular skin eruptions to severe life-threatening reactions, can occur with anticonvulsants.[35] Aromatic anticonvulsants, primarily phenytoin, carbamazepine, phenobarbital, and primidone as well as some of the newer agents (lamotrigine, oxcarbazepine, felbamate, and zonisamide) can cause a life-threatening syndrome with symptoms including fever, a maculopapular rash, and evidence of systemic organ involvement. The rash may be mild at first but can progress to exfoliative dermatitis, erythema multiforme, SJS, or TEN. This syndrome is known as anticonvulsant hypersensitivity syndrome (AHS), or DRESS. The causative agent should be withdrawn immediately. Cross-sensitivity among aromatic anticonvulsant drugs ranges between 40% and 80%.[36] If a patient is hypersensitive to an aromatic anticonvulsant, a nonaromatic agent (ethosuximide, gabapentin, levetiracetam, topiramate, lacosamide, valproic acid) or the benzodiazepines may be useful.[36]

Biologic Therapies and Immune Checkpoint Inhibitors

Biologically derived antibodies and cytokines used as therapeutic agents have the potential to cause nonimmune cytokine release and infusion-related adverse drug reactions. Rarely, an IgE-mediated anaphylaxis can occur to these products. Desensitization is possible for both allergic and nonallergic reactions to these agents.[37] Immune checkpoint inhibitors promote or inhibit T-cell activation, and have a range of associated adverse effects including autoimmunity.[38]

Drug Desensitization

Drug desensitization, also referred to as temporary induction of drug tolerance, may be undertaken for some drugs in the absence of useful alternative medications. The risk of severe systemic reactions and anaphylaxis associated with desensitization must be compared with the risk of not treating the patient with a drug of concern. A thorough evaluation should establish that the drug probably caused the reaction. Because of the dangers involved with drug desensitization, an expert review of the patient's indication for the drug should be conducted. Consider an alternative therapeutic choice or the possibility that the patient does not really need the drug.

KEY CONCEPT Desensitization is a potentially life-threatening procedure and requires continuous monitoring in a hospital setting, with suitable access to emergency treatment and intubation if required. It should only be undertaken under the direction of healthcare providers with suitable training and experience. In such hands, desensitization may present less risk than treatment failure with a less effective alternative medication.

The possibility of readministering a suspected drug may be safely tested by gradual dose escalation in some cases, and there are certainly many more patients who are harmed by inappropriately withholding medications than there are those who suffer significant harm from testing and desensitization.[39]

Induction of drug tolerance is not limited to IgE-mediated mechanisms but can be utilized for non-IgE–immune mechanisms, pharmacologic and unknown mechanisms. Desensitization may occur within hours to several weeks, unlike specific immunotherapy injections for inhalant allergy (ie, "allergy shots," which have effects over months to years). Like immunotherapy injections, temporary drug tolerance is accomplished by administration of incremental drug doses. The mechanism of drug desensitization is poorly understood but produces temporary drug-specific tolerance of the offending drug. Any interruption of therapy of 24 hours or more requires full repeat desensitization, and abrupt significant increases of dosage have been reported to break through the tolerance with some drugs.

The desensitization process probably involves either: (a) cross-linking small subthreshold numbers of bound IgE molecules gradually depleting mast cells of their mediators, or (b) binding of the IgE by monomers or hapten-protein entities that cannot cross-link the antibody. The low doses used at the beginning of all protocols would provide small amounts of antigen, favoring these mechanisms. Both drug-specific IgE and IgG serum concentrations increase after successful desensitization, but skin test positivity generally decreases.[40]

Oral and intravenous (IV) protocols are available for most drugs in this category, with the oral route producing somewhat milder reactions, but the IV route providing more precision in dosing. IV administration can also be used in unresponsive patients for whom the oral route is not feasible. Protocols generally begin at about 1% of the therapeutic dose and increase in intervals defined by the patient's reaction and the distribution and metabolism of the drug itself. Half-$\log_{10}$ dose increases (about threefold) are often tolerated.

Penicillin desensitization is the most common drug desensitization protocol. It is required for penicillin-allergic patients when penicillin is clearly the only treatment option. Protocols have been adopted for most antibiotics. Specific procedures for oral and IV penicillin desensitization have been developed.[41]

Aspirin desensitization is useful in diseases for which low-level antiplatelet action is needed and in the care of patients with aspirin sensitivity and intractable nasal polyps.[42, 43] As with all desensitizations, constant daily administration is required once the desired dose is reached.

All desensitization procedures are expected to produce mild symptoms in the patient at some point, and the patient must be made to understand this before doses are started. Mild sensitivity

Patient Encounter 3

A 26-year-old woman develops fever on day 14 of sulfasalazine. She is managed by her rheumatologist for autoimmune dysfunction. She later develops full body rash and itching. She presents to the emergency department for evaluation. Her complete blood count (CBC) demonstrates elevated absolute eosinophil count and liver function enzymes.

What type of reaction to the sulfa drug does this patient have?

What would be the management of this drug hypersensitivity in the future?

Would she be a candidate for drug desensitization?

to the drug still remains, and large dose increases as well as missing doses should be avoided. Late complications, such as urticaria, may occur with type I desensitization, and serum sickness or hemolytic anemia may also occur with high-dose therapy in allergic, desensitized patients.

Some regimens are designed for outpatient administration over much longer time periods and have been used with allopurinol dermal reactions. Such late-onset morbilliform reactions, sometimes overlapping with erythema multiforme minor, are difficult to evaluate because it is often unclear to what extent the patients were at risk for a recurrent reaction.

Severe life-threatening reactions not mediated by IgE, such as SJS and TEN, are absolute contraindications to testing, desensitization attempts, and readministration.

Drug challenge, where the suspected drug is administered as described below, should be considered for patients in whom likelihood of drug allergy is negligible. It is not used to determine if allergy is present to a drug but rather to confirm that drug allergy does not exist. Again, meticulous history regarding the reaction and temporal relationship with the drug must be ascertained. In certain instances, as with penicillin, skin testing for detection of IgE specificity can be performed prior to graded drug challenge, decreasing the risk for reaction.

To perform a drug challenge, usually two doses of the drug are given, although up to five steps have been described. A graded drug challenge does not affect the drug-immune response. Care must be taken to avoid temporary induction of drug tolerance which can occur when small incremental doses are given. Traditionally, the two-step drug challenge begins with 1/10 of the full drug dose followed by the full dose 1 hour later. The type of reaction determines the interval time between steps. Graded drug challenges are contraindicated in non-IgE–mediated severe life-threatening reactions like SJS, TEN, and DRESS. However, exceptions are made if benefits of the drug outweigh the risk, such as when the treatment could be life-saving without safer alternative therapies.[6]

KEY CONCEPT Drug challenge is performed to rule out drug allergy. It should be performed by an experienced physician familiar with risks and treatment of immediate and delayed drug reactions. It is not intended to change an individual's immune response to a drug or to induce drug tolerance.

OUTCOME EVALUATION

To successfully treat a patient with IgE-mediated or non-IgE (immune or nonimmune) drug hypersensitivity, several goals must be accomplished:

- If a reaction occurs, it must be identified and managed quickly.
- The patient should be educated about the reaction.

Patient Care Process

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements.
- Review the medical history and physical assessment findings.
- Speak with patient or caregiver to gain their perspective on the reaction.

Assess the Information:

- Based on the medication history, physical examination, and review of systems, determine the likelihood of the reaction being a drug-related problem. See Clinical Presentation and Diagnosis of IgE-mediated and Other Immune Drug Reactions. Tables 54–1 and 54–2 may also be helpful.
- Use questions given in Table 54–4 to establish the nature of the reaction and the likelihood it was caused by the suspected drug. For nonantibiotics, the first question regarding infection type is not needed.

Develop a Care Plan:

- Document the reaction, in detail, in the patient's medical record.
- Recommend an alternative choice if the prescribed drug is contraindicated, and develop a plan to assess safety and effectiveness.
- Consult with healthcare professionals trained in desensitization if the patient has a true allergy and no acceptable alternative medication is available.

Implement the Care Plan:

- If reaction is anaphylactic in nature, see Table 54–3.
- The offending drug should be discontinued.
- The treatment goal is relief of symptoms. For mild symptoms such as rash or itching, an antihistamine such as diphenhydramine may be used. For wheezing, bronchodilators such as albuterol may be helpful.
- Recommend an alternative option for the contraindicated drug, or if no alternative is available, consult with appropriate healthcare professional regarding desensitization.
- Educate patients about drug hypersensitivities so they are able to work with healthcare providers to avoid these reactions in the future.

Follow-up: Monitor and Evaluate:

- Follow up daily or more often, if necessary, to ensure resolution of the reaction and optimal response to alternate therapy.

- True drug contraindications should be avoided if possible.
- Patients should receive the medications they need or a suitable alternative. If this is not possible due to an IgE-mediated mechanism, desensitization should be considered.
- Patients should always be monitored for adverse drug reactions.

Abbreviations Introduced in This Chapter

AERD	Aspirin-exacerbated respiratory disease
AHS	Anticonvulsant hypersensitivity syndrome
AIDS	Acquired immunodeficiency syndrome
APC	Antigen presenting cell
CAD	Coronary artery disease
CIU	Chronic idiopathic urticaria
CBC	Complete blood count
COX	Cyclooxygenase
D_5W	Dextrose 5% in water
DIHS	Drug-induced hypersensitivity syndrome
DRESS	Drug reaction with eosinophilia and systemic symptoms
EMR	Electronic medical record
H (H_1, H_2)	Histamine
HIV	Human immunodeficiency virus
IFNγ	Interferon-gamma
Ig	Immunoglobulin (followed by the specific type of immunoglobulin: E, G, or M)
IL	Interleukin
IM	Intramuscular
IV	Intravenous
NSAIDs	Nonsteroidal anti-inflammatory drugs
p-i	Pharmacologic interaction
PPD	Purified protein derivative
SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis
Th	T-helper cell

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55 Solid Organ Transplantation

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the reasons for solid organ transplantation.
2. Differentiate between the functions of cell-mediated and humoral immunity and how they relate to organ transplant.
3. Describe the roles of antigen-presenting cells (APCs) in initiating the immune response.
4. Compare and contrast the types of rejection including hyperacute, acute, chronic, and antibody-mediated rejection.
5. Define the terms "host–graft adaptation" and "tolerance," paying close attention to their differences.
6. Discuss the desired therapeutic outcomes and appropriate pharmacotherapy utilized to avoid allograft rejection.
7. Compare and contrast currently available immunosuppressive agents in terms of mechanisms of action, adverse events, and drug–drug interactions (DDI).
8. Develop a therapeutic drug-monitoring plan to assess the efficacy and safety of immunosuppressive drugs.
9. Design an appropriate therapeutic regimen for the management of immunosuppressive drug complications based on patient-specific information.
10. Write appropriate patient education instructions and identify methods to improve medication adherence following transplantation.

INTRODUCTION

In the early 1900s, French surgeon Alexis Carrel pioneered the art of surgical techniques for transplantation.[1] Together with Charles Guthrie, Carrel experimented in artery and vein transplantation. Using revolutionary methods in **anastomosis** operations and suturing techniques, Carrel laid the groundwork for modern transplant surgery. He was one of the first to identify the dilemma of rejection, an issue that remained insurmountable for nearly 50 years.[1]

Prior to the work of Carrel, malnourishment was the prevailing theory regarding the mechanism of **allograft** rejection.[1] However, in 1910, Carrel noted tissue damage in the transplanted organ was likely caused by multiple, circulating biological factors. It was not until the late 1940s, with the work of Peter Medawar, that transplant immunology became better understood. Medawar defined the immunologic nature of rejection using skin allografts. In addition, George Snell observed that grafts shared between inbred animals were accepted but were rejected when transplanted between animals of different strains.[1]

The seminal work by early transplant researchers eventually led to the concept of histocompatibility.[1] Histocompatibility describes the process by which polymorphic genes encode cell membrane antigens that serve as targets for immune response, even within a species. Further research in transplant immunobiology led to more accurate understanding of the alloimmune response.[1]

Joseph Murray performed the first successful organ transplant in 1954, a kidney transplant between identical twins.[1] This was a success largely because no immunosuppression was necessary as donor and recipient were genetically identical. Murray's achievement laid the groundwork for modern-day transplantation. Organ transplants performed in the United States reached a record high of 39,036 in 2020, an almost 15% increase from 2017.[2]

EPIDEMIOLOGY AND ETIOLOGY

Heart

More than 6 million Americans are afflicted with heart failure. Cardiac transplantation is the treatment of choice for patients with severe end-stage heart failure. Candidates for cardiac transplantation generally present with New York Heart Association (NYHA) class III or IV symptoms and have an ejection fraction of less than 20% (0.20). General indications for cardiac transplantation include rapidly declining cardiac function, requirement of intravenous (IV) inotropes, and a projected 1-year mortality rate of greater than 75%. Mechanical support with an implantable left ventricular assist device may be appropriate bridge-therapy while patients await a viable organ.[1] Most heart transplants are **orthotopic**; however, in certain situations, **heterotopic** transplants have been performed. There were 3658 heart transplant procedures in the United States in 2020.[2] Indications for heart transplant include:

- Cardiomyopathy (ie, dilated myopathy, hypertrophic cardiomyopathy, restrictive myopathy)
- Congenital heart disease
- Coronary artery disease
- Valvular heart disease

Intestine

Intestinal transplant may involve the use of an entire small bowel or shortened segment. Most intestine transplants completed in the United States involve the transplant of the full small intestines and are often performed in conjunction with liver transplantation. Although most intestine transplants involve organs harvested from a deceased donor, recent advances have made it possible for living donor intestinal segment transplants. There were only 91 intestine transplants in the United States in 2020.[2] Indications for intestine transplant include:

- Functional bowel problems (ie, Hirschsprung disease, neuronal intestinal dysplasia, pseudoobstruction, protein-losing enteropathy, microvillous inclusion disease)
- Short gut syndrome (ie, intestinal atresia, necrotizing enterocolitis, intestinal volvulus, massive resection secondary to inflammatory bowel disease, tumors, mesenteric thrombosis)

Kidneys

Nearly 37 million Americans have chronic kidney disease (CKD), with an additional 20 million at increased risk for kidney disease. End-stage renal disease (ESRD) constitutes a small portion of CKD patients, with more than 700,000 patients living with ESRD in the United States today. All patients with ESRD should be considered for renal transplantation if they are healthy enough to undergo surgery.

Most kidney transplants are heterotopic, where the kidney is implanted above the pelvic bone and attached to the patient's iliac artery and vein. The ureter of the transplant kidney is attached directly to the recipient's bladder or native ureter. The native kidneys are usually not removed, and data have shown that removal of the native kidneys does not influence patient survival (ie, survival of the transplant patient, without regard to function or survival of the allograft) and allograft survival.[1] There were 22,817 (17,583 deceased donor and 5234 living donor) kidney transplants performed in the United States in 2020.[2] Indications for kidney transplant include:

- Congenital, familial, and metabolic disorders (ie, congenital obstructive uropathy, Fabry disease, medullary cystic disease, nephrolithiasis)
- Diabetes mellitus (DM)
- Glomerular diseases (ie, antiglomerular basement membrane disease, focal segmental glomerular sclerosis, Immunoglobulin [Ig] A nephropathy, hemolytic uremic syndrome, systemic lupus erythematosus, Alport syndrome, amyloidosis, membranous nephropathy, Goodpasture syndrome)
- Hypertension
- Neoplasm (ie, renal cell carcinoma, Wilms tumor)
- Polycystic kidney disease
- Renovascular disease
- Tubular and interstitial diseases (ie, analgesic nephropathy, drug-induced nephritis, oxalate nephropathy, radiation nephritis, acute tubular necrosis, sarcoidosis)

Liver

Liver transplantation may involve the use of the entire organ or a segment. The majority of cases involve utilizing the full organ. In recent years, segmental transplants have been conducted using living donors. This procedure requires donation of the left hepatic lobe, which accounts for nearly 60% of the overall liver mass. This is possible because the liver can regenerate; therefore, both donor and recipient, in theory, will have normal liver function shortly after the transplant procedure. There were 8906 (8415 deceased donor and 491 partial lobe-living donor) liver transplants done in the United States in 2020.[2] Indications for liver transplant include:

- Acute hepatic necrosis (ie, chronic or acute hepatitis B or C)
- Biliary atresia
- Cholestatic liver disease/cirrhosis (ie, primary biliary cirrhosis)
- Metabolic disease (ie, Wilson disease, primary oxalosis)
- Neoplasms (ie, hepatoma, cholangiocarcinoma, hepatoblastoma, bile duct cancer)
- Nonalcoholic fatty liver disease (ie, nonalcoholic steatohepatitis, isolated steatosis)
- Noncholestatic cirrhosis (ie, alcoholic cirrhosis, postnecrotic cirrhosis, drug-induced cirrhosis)

Lungs

Lung transplants may involve deceased donation of two lungs or a single lung. More recently, lobar transplants from blood group-compatible living donors have been performed for a small segment of the population. Most have been performed on cystic fibrosis patients. On rare occasions, a simultaneous heart-lung transplant occurs, but is reserved for patients with severe pulmonary and cardiac disease. There were 2539 (all deceased donor) lung transplants and 58 simultaneous heart–lung transplants in the United States in 2020.[2] Indications for lung transplant include:

- α-1-Antitrypsin deficiency
- Congenital disease (ie, Eisenmenger syndrome)
- Cystic fibrosis
- Emphysema/chronic obstructive pulmonary disease
- Idiopathic pulmonary fibrosis
- Primary pulmonary hypertension

Pancreas

Exact nationwide prevalence of all diseases of the pancreas has not been fully quantified; however, DM, both types 1 and 2, affects nearly 34 million people in the United States. Some people suffering from DM may also be afflicted with ESRD. A small percentage of these patients undergo a simultaneous pancreas-kidney (SPK) transplant. Transplant of a pancreas may involve either the entire organ or a pancreas segment. Currently, whole-organ transplant is the most common procedure, with a portion of the duodenum often transplanted along with the pancreas. Living donors are often the source of segmental transplants. In recent years, isolation and transplantation of β-islet cells alone have been completed. Islet transplantation is intended to treat organ dysfunction by replacing nonfunctioning islet cells. Islet transplants are still experimental, and long-term benefit and/or risk of this procedure needs to be studied extensively. Future success of islet cell transplantation is dependent on identifying a nontoxic immunosuppressive combination. There were 135 pancreas transplants and 827 SPK procedures in the United States in 2020.[2] Indications for pancreas transplant include:

- DM (ie, type 1 and 2, DM secondary to chronic pancreatitis or cystic fibrosis)
- Pancreatic cancer

PATHOPHYSIOLOGY

Major Histocompatibility Complex

The primary target of the immune response posttransplant is the major histocompatibility complex (MHC).[1,3] The MHC is a region of highly polymorphic genes located on the short arm of chromosome 6. The human MHC is known as human leukocyte antigen (HLA). HLA is a set of glycoproteins expressed on the surface of most cells. These proteins are involved in immune recognition, which is the discrimination of self from nonself, but are also the principal antigenic determinants of allograft rejection.[1,3]

HLA have been classified into two major groups, class I and II:

- Class I: expressed on surfaces of all nucleated cells and recognized by CD8$^+$ cells (ie, cytotoxic T-cells); subclasses are HLA-A, HLA-B, and HLA-C.
- Class II: expressed solely on antigen-presenting cells (APCs). The APCs serve to stimulate CD4$^+$ cells (ie, helper T-cells); subclasses are HLA-DP, HLA-DQ, and HLA-DR.

T and B Lymphocytes

Lymphocytes are one of five types of white blood cells. Mature lymphocytes are astonishingly diverse in their functions. The most abundant are T lymphocytes (ie, T-cells) and B lymphocytes (ie, B-cells).

▶ *T Lymphocytes*

KEY CONCEPT T-cells play a major role in the cell-mediated immune response. These cells are produced in the bone marrow, but mature in the thymus, hence the abbreviation "T." There are three recognized subclasses of T-cells:

- Cytotoxic T-cells (CD8$^+$) promote target cell destruction by activating cellular apoptosis or killing via the release of cytotoxic proteins.
- Helper T-cells (CD4$^+$), once activated, proliferate and secrete cytokines that regulate the function of effector cells. Some helper T-cells secrete cytokines that recruit cytotoxic T-cells, B-cells, or APCs, whereas others secrete cytokines that turn off the immune response.
- Regulatory T-cells, or suppressor T-cells, suppress activation of immune responses.

▶ *B Lymphocytes*

B-cells play a key role in the humoral immune response. In humans, B-cells are produced and mature in the bone marrow. The human body produces several types of B-cells. Each is unique, with a distinctive cell surface receptor protein that binds to only one particular antigen. Once B-cells encounter their antigen and receive a cytokine signal from helper T-cells, they can further differentiate into plasma or memory B-cells. Plasma cells secrete antibodies that destroy target antigens through complement recruitment and/or opsonization. Memory B-cells play a role in long-term immunity, as they are capable of rapidly responding to subsequent exposures to their target antigen.

Antigen-Presenting Cells

KEY CONCEPT An APC is a cell that displays a foreign antigen complexed with MHC on its cell surface. Its major responsibility is to present foreign antigens to T-cells, which identify this complex using their T-cell receptors (TCRs). There are three main types of APCs: dendritic cells (DCs), macrophages, and activated B-cells. DCs are present in tissues in contact with the environment, such as skin and the lining of the nose, lungs, stomach, and intestines. They are responsible for phagocytosis, after which they express the foreign antigen on their cell surface and then migrate to lymphoid tissues to interact with T- and B-cells to initiate the immune response. Macrophages' main role is removal of pathogens and necrotic debris. However, like DCs, macrophages also phagocytize antigens. The first time an antigen is encountered, the DCs and macrophages act as the primary APCs. However, if the same antigen is encountered again, memory B-cells become the most important APC because they initiate the immune response quickly after antigen presentation. It appears that both DCs and macrophages have the most activity in terms of allorecognition.

Allorecognition

KEY CONCEPT Recognition of the antigens of the transplanted organ (alloantigens) is the main event that initiates the antiallograft immune response. There are currently two accepted pathways for allorecognition:

- Direct pathway: Donor APCs migrate from the allograft into the recipient's lymph nodes and present donor MHC molecules to the recipient's T-cells.
- Indirect pathway: Recipient APCs migrate into the graft and phagocytize alloantigens. The recipient's APCs present donor MHC molecules to the recipient T-cells in lymph nodes.

T-Cell Activation

Whether it is by direct or indirect pathways, T-cells become activated against the allograft via two interactions or signals that take place between the APCs and recipient's T-cells[1,3]:

- Signal 1 is the interaction of the TCR with foreign antigens presented by APCs.
- Signal 2 is an interaction between one of several costimulatory receptors and paired ligands on the cell surfaces of APCs and T-cells, respectively. Both interactions must occur simultaneously as Signal 1, in the absence of Signal 2, induces T-cell anergy.
- Signal 3 follows T-cell activation and is the process by which T-cells undergo clonal expansion under the influence of cytokines, specifically interleukin-2 (IL-2). These steps elicit an antidonor T-cell response resulting in graft damage.

Mechanisms of Acute Rejection

After activation, cytotoxic T-cells infiltrate the graft and trigger the immune response. These cells induce graft destruction via two mechanisms: (a) secretion of cytotoxic proteins (ie, perforin, granzyme) and (b) induction of cellular apoptosis through interaction. Besides the cytotoxic T-cells, several other cell lines may play a role in allograft destruction, including B-cells, granulocytes, and natural killer (NK) cells.

Types of Rejection

▶ *Hyperacute Rejection*

Hyperacute rejection is an immediate recipient immune response against the allograft due to the presence of preformed recipient antibodies directed against the donor's HLA. This type of reaction generally occurs within minutes of transplantation. The organ must be removed immediately to prevent severe systemic responses. In the case of cardiac or lung transplantation, in which the organ cannot be promptly removed, short-term mechanical circulatory support is required until an alternative organ becomes available. Those at the highest risk for hyperacute rejection include any patients who have preformed HLA or ABO blood group antibodies, including those with a history of organ transplant or multiple blood transfusions, as well as women who have had children. Hyperacute rejection has been largely eliminated due to routine pretransplant surveillance testing.

▶ *Acute Rejection*

Acute rejection is a cell-mediated process that generally occurs early posttransplant; however, it can occur at any time after transplant. This reaction is mediated through alloreactive T-cells. Table 55–1 presents organ-specific signs and symptoms of acute rejection.[1]

▶ *Antibody-Mediated Rejection*

Antibody-mediated rejection (AMR) is the process of creating graft-specific antibodies.[4] This occurs less frequently than cell-mediated acute rejection. Histologic findings are similar to those of hyperacute rejection, but the severity of rejection is usually less with AMR. AMR is generally characterized by deposition of immunoglobulins and complement in allograft tissues. However, AMR may be diagnosed without the presence of complement. Although rare, donor-specific antibodies (DSA) may be present or develop later following transplant. Presence of DSA is a strong predictor of AMR which might lead to allograft injury and failure posttransplantation. Treatment for this type of rejection is not well defined; however, several reports have shown that plasmapheresis, immunoglobulin therapy, or bortezomib may be effective.[4]

▶ *Chronic Rejection*

Chronic rejection has traditionally been thought of as a slow, insidious form of acute rejection, resulting in worsening organ function over time. Exact immunologic processes of chronic rejection are poorly understood; however, many believe both the cell-mediated and humoral immune systems, along with drug-induced toxicities, play a vital role in its development. Currently, retransplantation is the only effective treatment option.[1,3]

Host–Graft Adaptation

"Host–graft adaptation" describes the decreased immune response against the allograft over time.[1,3] This phenomenon is evident by the reduced incidence of acute rejection seen months after transplantation. In theory, host–graft adaptation is thought to be secondary to a weakened T-cell response to donor antigens while patients receive maintenance immunosuppression.[1,3]

Tolerance

Tolerance is the process that allows organ-specific antigens to be accepted as self.[1] This means the immune system would cease to respond to the allograft, and immunosuppressive medications would not be required. Immune tolerance has been achieved in the lab, but rarely in humans.[1]

Immunologic Barriers to Transplantation

One of the more common barriers to transplantation is the presence of preformed HLA antibodies or ABO blood group incompatibility.[4] In cases in which these antibodies exist, if they are not adequately removed prior to transplant, they are likely to result in AMR and poor graft survival. To improve outcomes, assessment of pretransplant immune risk factors plays an important role in prevention of immune-mediated allograft injuries. The introduction of pretransplant cross-matching and the use of ABO-compatible donors has largely eliminated hyperacute rejection. However, these immunologic barriers are present in several potential recipients with willing organ donors, and patients are left to wait for a deceased donor, undergo pretransplant

Table 55–1

Organ-Specific Signs and Symptoms of an Acute Rejection Episode[1]

Organ	Clinical Symptoms	Laboratory Signs
Heart	Lethargy, weakness, SOB, DOE, hypotension, tachycardia, atrial flutter, ventricular arrhythmias	Leukocytosis, biopsy positive for mononuclear infiltrates
Kidney	Weight gain, decreased urine output, malaise, hypertension, edema	Increased SCr, donor-derived cell-free DNA, BUN, leukocytosis, biopsy positive for lymphocytic infiltration
Intestine	GI symptoms (ie, bloating, cramping, diarrhea, increased stomal output)	There are no reliable biochemical markers for intestine transplant rejection, but biopsies may be helpful
Liver	Graft tenderness and swelling, back pain, anorexia, ileus, tachycardia, jaundice, ascites, encephalopathy	Abnormal LFTs, increased bilirubin, alkaline phosphate, transaminases, biopsy positive for mononuclear cell infiltrate with evidence of tissue damage
Lung	Fever, impaired gas exchange, SOB, malaise, anxiety	Decreased FEV, infiltrate on CXR, biopsy positive for lymphocytic infiltration
Pancreas	Graft tenderness and swelling, polyuria, abdominal pain	Increased FBS, leukocytosis, decreased C-peptide and urinary amylase levels

BUN, blood urea nitrogen; CXR, chest x-ray; DOE, dyspnea on exertion; FBS, fasting blood sugar; FEV, forced expiratory volume; GI, gastrointestinal; LFTs, liver function tests; SCr, serum creatinine; SOB, shortness of breath.

immunomodulation in an attempt to prevent these antibodies from affecting the allograft, or enter a donor exchange program.[4]

▶ *ABO Incompatibility*

The expanding deceased donor waiting list encouraged some centers to evaluate the use of ABO desensitization protocols in transplant patients who had willing, but ABO-incompatible, donors.[4] The desensitization protocol most commonly used involves reducing ABO antibody titers through plasmapheresis with IV immunoglobulin (IVIG). Use of plasma exchange to achieve an ABO antibody titer of less than 1:8 to 1:32 resulted in long-term renal transplant results that are comparable to those of ABO-compatible transplants, despite an incidence of acute AMR that approaches 10% to 30%.[4] High rates of AMR in this population have resulted in most ABO incompatible donors-recipient pairs being entered into kidney exchange programs.

TREATMENT

Desired Outcomes

KEY CONCEPT The major focus of pharmacotherapy in transplantation is to achieve long-term patient and allograft survival while avoiding major adverse events.[1,3,5,6] Short-term outcomes (eg, acute rejection rates, 1-year graft survival) have improved significantly since the first successful transplant due to an improved understanding of the immune system, enhancements in surgical techniques and organ procurement, immunosuppression, and posttransplant care. However, the frequency of graft loss remains higher than desired.[1,3,5,6]

It is imperative that transplant practitioners be aware of specific advantages and disadvantages of available immunosuppressants, as well as adverse reactions and drug–drug interaction (DDI) profiles. There are generally three stages of medical immunosuppression: (a) induction therapy, (b) maintenance therapy, and (c) treatment of rejection. KEY CONCEPT Immunosuppressive regimens utilize multiple medications working on different targets. Refer to Table 55–2 for a list of all available immunosuppressive agents.[1,5,6]

Induction Therapy

KEY CONCEPT The goal of induction therapy is to provide a high level of immunosuppression in the early posttransplant period, when the risk of acute rejection is highest.[5] This stage of immunosuppression is initiated intraoperatively and concluded within the first 1 to 10 days after transplantation. Antibody induction

Table 55–2

Currently Available Immunosuppressive Agents[1,5,6]

Generic Name (Brand Name)	Common Dosage	Common Adverse Effects
Induction Therapy Agents		
Alemtuzumab (Campath)	30 mg × single dose	Flu-like symptoms, chills, rigors, fever, rash, myelosuppression
Antithymocyte globulin equine (ATGAM)	15 mg/kg IV × 5–14 days	Flu-like symptoms, chills, rigors, fever, rash, myelosuppression
Antithymocyte globulin rabbit (Thymoglobulin)	0.75–1.5 mg/kg IV × 3–7 days	Flu-like symptoms, chills, rigors, fever, rash, myelosuppression
Basiliximab (Simulect)	20 mg IV × 2 doses	None reported compared to placebo
Maintenance Immunosuppressants		
Cyclosporine (Sandimmune, Neoral, Gengraf)	1–4 mg/kg/day by mouth twice a day	Neurotoxicity, gingival hyperplasia, hirsutism, hypertension, hyperlipidemia, glucose intolerance, nephrotoxicity, electrolyte abnormalities
Tacrolimus (Prograf, Astagraf XL, Envarsus XR)	0.05–0.1 mg/kg by mouth twice a day or once daily if using Astagraf XL; 0.14 mg/kg once daily if using Envarsus XR	Neurotoxicity, alopecia, hypertension, hyperlipidemia, glucose intolerance, nephrotoxicity, electrolyte abnormalities
Azathioprine (Imuran)	1–3 mg/kg by mouth once a day	Myelosuppression, GI disturbances, pancreatitis
Mycophenolate mofetil (CellCept)	0.5–1.5 g by mouth twice a day	Myelosuppression, GI disturbances
Enteric-coated MPA (Myfortic)	720 mg by mouth twice a day	Myelosuppression, GI disturbances
Sirolimus (Rapamune)	1–10 mg by mouth once a day	Hypertriglyceridemia, myelosuppression, mouth sores, hypercholesterolemia, GI disturbances, impaired wound healing, proteinuria, lymphocele, pneumonitis
Everolimus (Zortress)	0.75-1 mg by mouth twice daily	Hypertriglyceridemia, myelosuppression, mouth sores, hypercholesterolemia, GI disturbances, impaired wound healing, proteinuria, lymphocele, pneumonitis
Prednisone (Deltasone)	Maintenance: 2.5–20 mg by mouth once a day	Mood disturbances, psychosis, cataracts, hypertension, fluid retention, peptic ulcers, osteoporosis, muscle weakness, impaired wound healing, glucose intolerance, weight gain, hyperlipidemia
Belatacept (Nulojix)	De Novo therapy: 10 mg/kg on postop days 1 and 4; 10 mg/kg at the end of postop weeks 2, 4, 8, and 12; 5 mg/kg at the end of postop week 16 and every 4 weeks thereafter Conversion therapy: 5 mg/kg every 2 weeks × 5 doses; followed by 5 mg/kg every 4 weeks thereafter	GI disturbances, electrolyte abnormalities, headache

GI, gastrointestinal; IV, intravenous; MPA, mycophenolic acid.

therapy is not a mandatory stage of recipient immunosuppression and is typically predicated on immunologic risk. However, since acute rejection is a major concern in solid organ transplant (SOT) recipients and its impact on chronic rejection is undeniable, induction therapy is considered essential in some organs, such as kidney, pancreas, and intestine transplantation.[5] The use of induction therapy among heart and lung transplant recipients is also becoming more common.

▶ *Goals of Induction Therapy*

KEY CONCEPT Induction agents are highly immunosuppressive, allowing for significant reductions in acute rejection and improved 1-year graft survival.[5] Due to their unique pharmacologic effect, these agents are often considered essential in patients at high risk for poor short-term outcomes, such as patients with preformed antibodies, history of previous transplants, multiple HLA mismatches, or transplantation of organs with prolonged cold ischemic time or from expanded-criteria donors. Induction therapy plays an important role in preventing early-onset calcineurin inhibitor (CNI)–induced nephrotoxicity. With induction therapy, CNI initiation can be delayed until the graft regains some degree of function. Induction therapy is imperative when employing corticosteroid sparing or avoidance protocols.[5]

The improved short-term outcomes gained from induction therapy come with a degree of risk.[5] By using highly immunosuppressive agents, particularly the antilymphocyte antibodies (ALA; the antithymocyte antibodies and alemtuzumab), risk of opportunistic infections and malignancy is increased. Cytokine release syndrome is a common complication of T-cell depleting agents and may require use of diphenhydramine and acetaminophen before infusions.[5]

▶ *Currently Available Induction Therapies*

Induction agents are categorized as depleting and nondepleting. Depleting agents exert their pharmacological effects through depletion of T and B lymphocytes (antithymocyte globulin rabbit [r-ATG], antithymocyte globulin equine [e-ATG], alemtuzumab), while nondepleting agents exert their pharmacological effects through inhibition of T-cell activation (basiliximab).

Basiliximab Basiliximab, a chimeric monoclonal antibody, acts as an IL-2 receptor antagonist and inhibits IL-2–mediated activation of lymphocytes, which is an important step in T-cell clonal expansion.[5,7] Basiliximab is not a T-cell depleting agent and can be given with or without premedications.

The basiliximab dose is 20 mg IV given 2 hours prior to transplant, followed by a second 20 mg dose on postoperative days 2 to 4.[5,7] This dosing schedule can be used for children greater than or equal to 35 kg (77 lb) and adults. Two 10 mg doses with the same schedule should be used for children less than 35 kg (77 lb). There are no dosage adjustments needed in renal or hepatic impairment.[5,7] Incidence of adverse reactions with basiliximab was similar to placebo in trials, and there are no reported DDIs with basiliximab.[5,7]

Antithymocyte Globulin Rabbit r-ATG is a polyclonal antibody that induces T-cell clearance, but more importantly, alters T-cell activation, homing, and cytotoxic activities.[7] It is also believed r-ATG plays a role in inducing T-cell apoptosis. This agent is typically dosed at 0.75-1.5 mg/kg/day and is usually administered for 3 to 7 days after transplantation.[5] Many renal transplant centers aim to initiate the first dose intraoperatively to reduce organ reperfusion injury.[8]

Adverse reactions are common and may include fever (63.4%), chills (57.3%), headache (40.2%), nausea (36.6%), diarrhea (36.6%), malaise (13.4%), dizziness (8.5%), leukopenia (57.3%), thrombocytopenia (36.6%), and generalized pain (46.3%).[9-11] Incidence of infection is 36.6%, with cytomegalovirus (CMV) disease occurring in 13.4% of patients. There are no reported DDIs with the use of r-ATG.[5,7]

Antithymocyte Globulin Equine e-ATG is a polyclonal antibody that contains antibodies against several T-cell surface markers, similar to r-ATG. However, e-ATG is rarely used in transplantation due to poor outcomes in comparison to r-ATG.

Alemtuzumab Alemtuzumab is a monoclonal antibody that binds to CD52, which is present on most B and T lymphocytes, macrophages and NK cells, and a subpopulation of granulocytes.[5,7] After complexing with CD52, alemtuzumab induces antibody-dependent cell lysis. This agent produces a rapid and extensive lymphocyte depletion that takes several months to years to return to pretransplant levels. Although not Food and Drug Administration (FDA) approved for use in organ transplantation, studies have demonstrated that a single dose of 30 mg IV at the time of transplant is effective in preventing acute rejection.[5]

Alemtuzumab is associated with serious adverse reactions including anemia (47%), neutropenia (70%), thrombocytopenia (52%), headache (24%), dysesthesias (15%), dizziness (12%), nausea (54%), vomiting (41%), diarrhea (22%), infusion-related reactions (15%–89%), and infection (37%; CMV viremia occurred in 15% of patients).[7] Premedication with acetaminophen and diphenhydramine 30 minutes before infusion will reduce the incidence of infusion-related reactions, but subcutaneous administration will also prevent these reactions.[5]

Comparative Efficacy There are a few studies that help to delineate the ideal induction therapy agent in renal transplant. Studies comparing r-ATG and e-ATG show that r-ATG is more effective in lowering acute rejection rates and improving 1-, 5-, and 10-year allograft outcomes.[9,10,12] Conversely, a study evaluating the use of basiliximab versus r-ATG demonstrated similar short-term efficacy between both groups.[13] However, other analyses of these two agents demonstrated similar results for allograft and patient survival, but a benefit for r-ATG in lowering incidence of acute allograft rejection.[11,14] An analysis showed that alemtuzumab improved transplant outcomes when compared with basiliximab in patients with a low immunologic risk, and similar outcomes compared to r-ATG in patients with high immunologic risk.[15] Alemtuzumab is associated with significantly higher rates of DSA formation when compared to basiliximab and r-ATG, but the impact on long-term allograft function has not been evaluated.[16] When choosing an agent for induction therapy, one must weigh the risks versus benefits. Overall, the ALAs are considered to be most effective, but are associated with higher incidence of infectious disease and malignancy.[5]

Maintenance Immunosuppressive Therapy

Goals of maintenance immunosuppression are to prevent rejection and optimize patient and graft survival.[6] Antirejection medications require careful selection and dose titration to balance the risks of rejection with toxicities.

KEY CONCEPT Maintenance immunosuppressive agents include:

- Calcineurin inhibitors (CNI; cyclosporine and tacrolimus)
- Antiproliferatives (azathioprine and mycophenolic acid [MPA] derivatives)

Patient Encounter Part 1

A 64-year-old man presents to your transplant center to undergo cardiac transplant after a suitable organ was identified for him.

PMH:

- Ischemic cardiomyopathy—myocardial infarction 10 years ago, status post drug-eluting stent.
- Heart failure (NYHA III)
- Hypothyroidism
- Paroxysmal atrial fibrillation
- Depression
- Gout
- Insulin-dependent DM type 2

FH: Father is alive and living with a history of cardiovascular disease and mother is alive and living with a history of basal cell carcinoma.

SH: Patient is a retired school teacher. He used to drink alcohol socially (three or four drinks per week) but stopped after worsening heart failure and denies any tobacco or IV drug use.

Admission Meds:

- Aspirin 81 mg by mouth once daily
- Sacubitril/valsartan 49 mg/51 mg by mouth twice daily
- Metoprolol succinate 40 mg by mouth once daily
- Spironolactone 25 mg by mouth once daily
- Rosuvastatin 40 mg by mouth once daily
- Torsemide 20 mg by mouth twice daily
- Levothyroxine 50 mcg by mouth once daily
- Sertraline 50 mg by mouth once daily
- Allopurinol 100 mg by mouth once daily
- Insulin glargine inject subcutaneously 13 units every night
- Insulin aspart 6 units inject subcutaneously three times daily with meals

Allergies/intolerance:

- Sulfa drugs—hives
- Prednisone—Labile glucose

Misc:

- CMV Serostatus: Donor is CMV IgG-positive.
- CMV Serostatus: Recipient is CMV IgG-negative.
- Epstein Barr Virus (EBV) Serostatus: Donor is EBV IgG-positive.
- EBV Serostatus: Recipient is EBV IgG-negative.

Identify your treatment goals for this patient.

Create a plan for induction therapy (ie, would you recommend induction therapy, and if so, which agent?).

- Target of rapamycin (ToR) inhibitors (sirolimus and everolimus)
- Corticosteroids
- Costimulatory blockade (belatacept)

Maintenance immunosuppression is generally achieved by combining two or more medications from the different classes, specifically targeting unique components of the immune response.[6] Refer to Figure 55–1 for a schematic representation of different drug mechanisms and Figure 55–2 for an example protocol for administration of immunosuppressive medications posttransplant. This method of medication selection also minimizes toxicities by choosing agents with different adverse event profiles. Immunosuppressive regimens vary between organ types and transplant centers, but most often include a CNI with an adjuvant agent, plus corticosteroids. Selection of an immunosuppressive regimen should be patient-specific, and one must take into account the patient's comorbidities, medication regimens, and preferences.[6]

▶ *Calcineurin Inhibitors*

KEY CONCEPT Cyclosporine and tacrolimus are the cornerstone of modern immunosuppressive protocols. The CNIs work by complexing with cytoplasmic proteins (cyclosporine with cyclophilin and tacrolimus with FK binding protein-12).[6,7] These complexes inhibit calcineurin phosphatase, which results in reduced IL-2 gene transcription and a reduction in IL-2 synthesis. This diminishes T-cell activation.[6,7]

Cyclosporine Cyclosporine USP was first approved in 1983, but was associated with a variable oral absorption. The development of a newer formulation, cyclosporine microemulsion USP (ie, modified), introduced in 1994, allowed for more consistent drug exposure due to a more reliable pharmacokinetic profile.[1] Cyclosporine modified is the formulation of choice for most transplant centers utilizing cyclosporine. The two formulations are not interchangeable.[6]

The usual oral adult dose of cyclosporine ranges from 2 to 8 mg/kg/day in two divided doses.[7] Appropriate selection of the starting dose depends on the organ type, the patient's comorbidities, and other concomitant immunosuppressive agents utilized. Cyclosporine modified is available as 25 mg and 100 mg capsules and an oral solution. An IV formulation of conventional cyclosporine is also available. When converting a patient from oral to IV, the dosage should be reduced to approximately one-third of the total daily oral dose.[7]

Cyclosporine whole-blood trough concentrations (C_0) have traditionally been obtained to help monitor for efficacy and safety. Therapeutic C_0 may range from 50 to 400 ng/mL (mcg/L; 42–333 nmol/L). Target levels should be individualized for each patient, usually depending on the organ transplanted, patient's condition, method of assay (liquid chromatography coupled to tandem mass spectrometry [LC-MS/MS], or various immunoassay techniques), and time since transplantation.[6]

Tacrolimus Tacrolimus was approved in 1997. Oral starting doses range from 0.1 to 0.2 mg/kg/day in two divided doses. Tacrolimus is available in 0.5 mg, 1 mg, and 5 mg capsules and as an injectable.[7] Two once-daily tacrolimus formulations are also available. LCP-Tacrolimus once daily is associated with lower incidence of neurotoxicity and is theorized to be a better option for patients considered to be rapid metabolizers. Due to improved bioavailability, the recommended LCP-Tacrolimus starting dose is 0.14 mg/kg/day, given as a single dose. Tacrolimus C_0 should be monitored and maintained between 4 and 15 ng/mL (mcg/L;

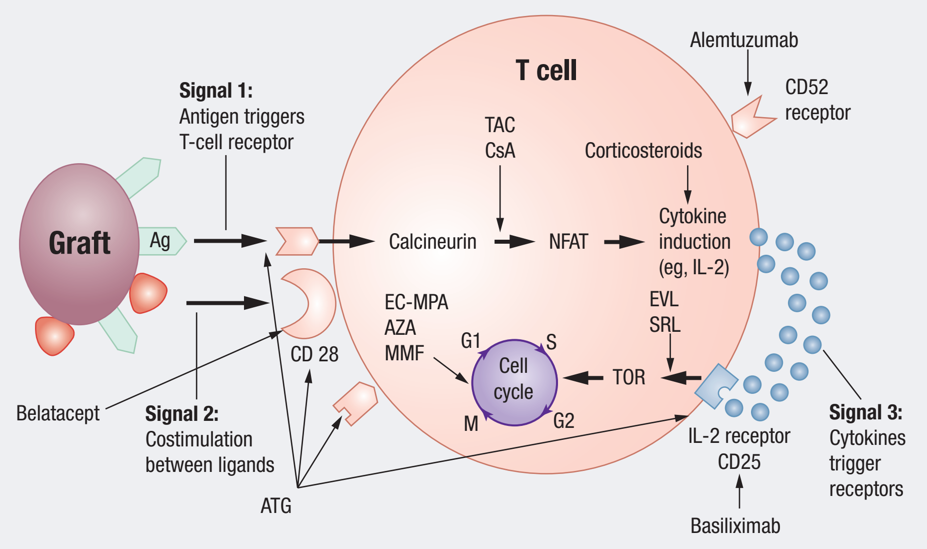

FIGURE 55–1. Identification of the sites of action of the various immunosuppressive medications. Allograft recognition through Signal 1 occurs when the antigen-major histocompatibility complex (MHC) molecule is recognized by the T-cell receptor (TCR). A costimulatory signal, Signal 2, initiates signal transduction with activation of second messengers, one of which is calcineurin. Together, Signal 1 and Signal 2 activate calcineurin phosphatase, which removes phosphates from the nuclear factors, allowing them to enter the nucleus with a subsequent increase in interleukin-2 (IL-2) gene transcription. Signal 3 occurs with the interaction of IL-2, with the IL-2 receptor on the cell membrane surface. This culminates in a signal that passes through the mammalian target of rapamycin (ToR) and induces cell proliferation and production of cytokines specific to the T-cell. (ATG, antithymocyte globulin; AZA, azathioprine; CsA, cyclosporine; EC-MPA, enteric-coated mycophenolic acid; EVL, everolimus; MMF, mycophenolate mofetil; NFAT, nuclear factors; SRL, sirolimus; TAC, tacrolimus.)

5 and 19 nmol/L), again depending on the transplanted organ, patient's condition, and time since transplant.[6]

One of the major issues with tacrolimus-based therapy is there is significant intrapatient variability seen with this medication. High tacrolimus intrapatient variability has been evaluated as an independent risk factor for shortened graft survival.[17] Nonadherence is often considered to be the dominant factor in high tacrolimus intrapatient variability.

The tacrolimus IV formulation is usually avoided due to the risk of anaphylaxis, because of its castor oil component, and nephrotoxicity.[6] Doses for IV administration are recommended to start at 0.01 mg/kg/day. In an effort to avoid IV tacrolimus, many transplant centers utilize sublingual (SL) tacrolimus in their patients unable to receive the medication by mouth.[6]

Adverse Drug Reactions KEY CONCEPT One of the major disadvantages of the CNIs is their ability to cause nephrotoxicity. Acute nephrotoxicity has been correlated with high doses and is usually reversible.[7] Chronic CNI toxicity, however, is typically irreversible and linked to chronic drug exposure. Table 55–3 expands on the more common CNI–associated adverse events.[1,6]

Comparative Efficacy Even though cyclosporine and tacrolimus are both CNIs, there are several differences between the two. A meta-analysis comparing cyclosporine to tacrolimus in kidney transplantation showed tacrolimus was associated with significantly lower risk of allograft loss at 6 months and lower rates of acute rejection at 1 year.[18] Tacrolimus is the primary CNI in most transplant centers for all organs.[6]

▶ *Antiproliferatives*

These agents are considered to be adjuvant to CNIs.[6]

Azathioprine Azathioprine was approved in 1968. Prior to the advent of cyclosporine, the combination of azathioprine and corticosteroids was the mainstay of immunosuppressive therapy. Use of azathioprine has declined markedly due to superiority of the MPA derivatives. KEY CONCEPT Azathioprine is a prodrug for 6-mercaptopurine (6-MP), a purine analog. 6-MP acts as an antimetabolite and inhibits DNA replication with a resultant reduction in T-cell proliferation.[6] It is available in oral and IV dosage forms.[7] The typical oral dose of azathioprine for organ transplantation is 1 to 3 mg/kg once a day.[7] Thiopurine methyltransferase (TPMT) is the main enzyme for inactivation of azathioprine. Approximately 10% of transplant recipients have reduced TPMT activity and are at risk for drug toxicity. Dose reductions due to drug accumulation are needed to avoid toxicities. In addition, the dose should be adjusted for renal function since 6-MP and its metabolites are renally eliminated.[7] Trough concentrations of 6-MP are not monitored; however, most clinicians often monitor for signs of myelosuppression. KEY CONCEPT Myelosuppression (mainly leukopenia and thrombocytopenia) is a frequent, dose-dependent and dose-limiting complication (greater than 50% of patients) that often prompts dose reductions.[7] Other common adverse events include hepatotoxicity (2% to 10%) and adverse gastrointestinal (GI) events (10% to 15%; mostly nausea and vomiting). Importantly, pancreatitis and venoocclusive disease of the liver occur in less than 1% of patients following chronic azathioprine therapy.[7]

Mycophenolic Acid Derivatives Mycophenolate mofetil was approved in 1995 and enteric-coated MPA in 2004. Both agents are considered adjunctive immunosuppressants.[6] KEY CONCEPT Both mycophenolate mofetil and enteric-coated MPA are prodrugs for MPA. MPA acts by inhibiting inosine monophosphate dehydrogenase, a vital enzyme in the de novo pathway of purine synthesis. Inhibition of this enzyme prevents the proliferation of most cells that are dependent on the de novo pathway for purine synthesis, including T- and B-cells.[6]

Mycophenolate mofetil is available in 250 mg and 500 mg capsules, an oral suspension (100 mg/mL; in cherry syrup),

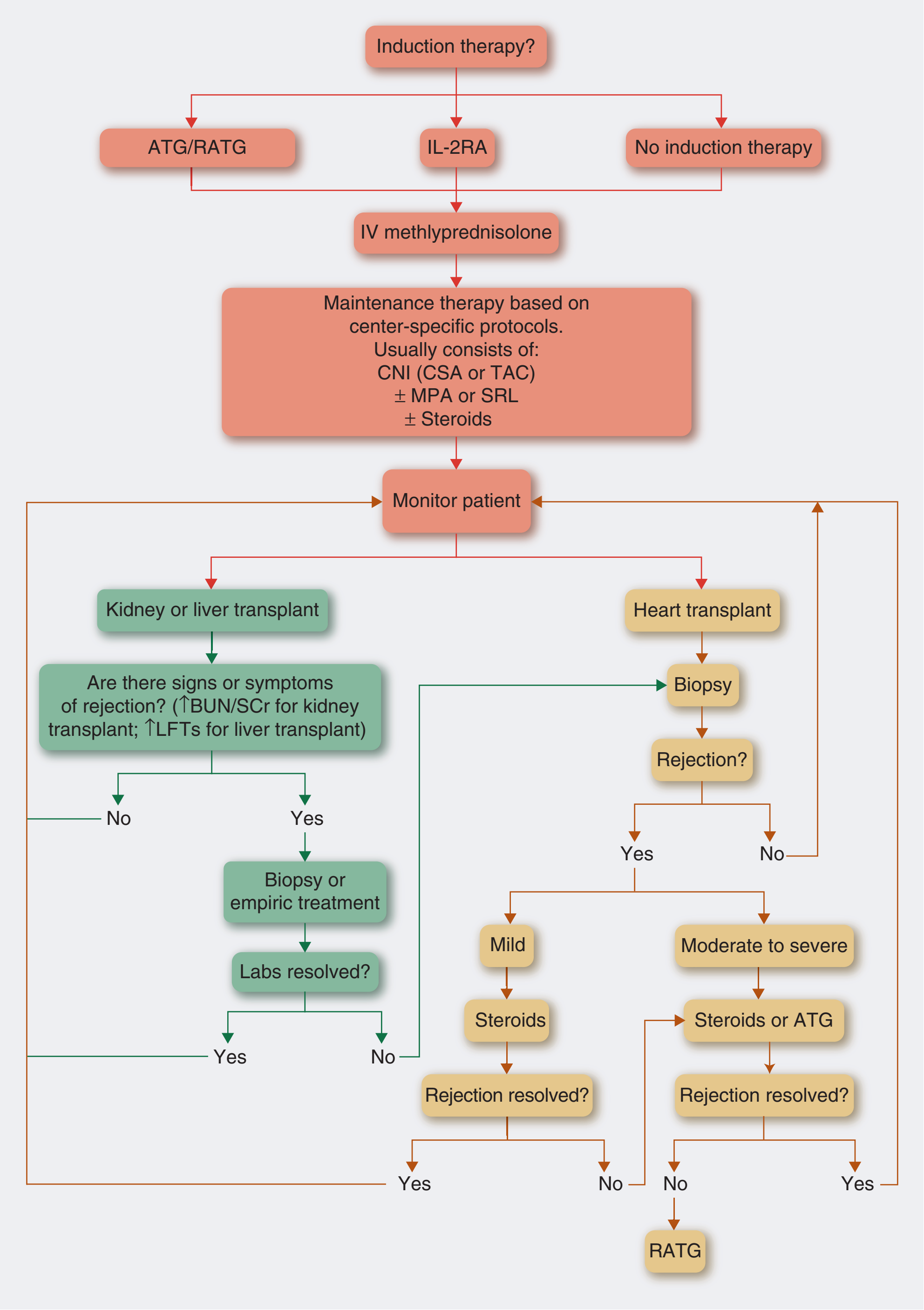
Induction therapy?
ATG/RATG
IL-2RA
No induction therapy
IV methlyprednisolone
Maintenance therapy based on center-specific protocols. Usually consists of: CNI (CSA or TAC) ± MPA or SRL ± Steroids
Monitor patient
Kidney or liver transplant
Heart transplant
Are there signs or symptoms of rejection? (↑BUN/SCr for kidney transplant; ↑LFTs for liver transplant)
No
Yes
Biopsy or empiric treatment
Labs resolved?
Yes
No
Biopsy
Rejection?
Yes
No
Mild
Moderate to severe
Steroids
Steroids or ATG
Rejection resolved?
Rejection resolved?
Yes
No
No
Yes
RATG

FIGURE 55–2. Example protocol of immunosuppressive medication use in organ transplantation. Center-specific protocols may use rabbit antithymocyte immunoglobulin (RATG), an interleukin-2 receptor antagonist (IL-2RA), or no induction therapy. In any situation, patients receive intravenous (IV) methylprednisone prior to, during, or immediately following the transplant operation. The patient then will begin the maintenance immunosuppressive regimen. The center-specific protocol will specify which calcineurin inhibitor (cyclosporine or tacrolimus) is used in combination with mycophenolate mofetil or sirolimus, with or without steroids. Patients are then monitored for signs and symptoms of rejection. If rejection is suspected, a biopsy can be done for definitive diagnosis, or the patient may be treated empirically for rejection. Empirical treatment generally involves administration of corticosteroids. If signs and symptoms of rejection are resolved with empirical therapy, the patient will continue to be monitored according to the center-specific protocol. If rejection is confirmed by biopsy, treatment may be based on the severity of rejection. High-dose corticosteroids are used most frequently for mild to moderate rejection. RATG can be used for moderate to severe rejections or steroid-resistant rejections. Protocols and algorithms may differ across transplant centers. (ATG, antithymocyte globulin; BUN, blood urea nitrogen; CNI, calcineurin inhibitor; CSA, cyclosporine; LFT, liver function test; MPA, mycophenolic acid; SCr, serum creatinine; SRL, sirolimus; TAC, tacrolimus.) (Adapted from Jennings DL, Johnson HJ. Solid organ transplantation. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 11th ed. New York: McGraw-Hill; 2020.)

Table 55–3

Management of Common Adverse Effects of Calcineurin Inhibitors (CNIs)[1,6]

Adverse Event	Most Likely Offending CNI	Monitoring Parameters	Therapeutic Management Options
Nephrotoxicity	Either	• SCr • BUN • Urine output • Biopsy-proven CNI-induced nephrotoxicity	• Reduce CNI dose (if possible) • Use of CCB for hypertension control • Modify regimen (change to non-CNI containing regimen [ToR inhibitor or belatacept])[a]
Hypertension[b]	Cyclosporine	• Blood pressure • Heart rate	• Initiate patient-specific antihypertensive therapy • Reduce cyclosporine dose (if possible) • Modify regimen (change to tacrolimus or non-CNI containing regimen)[a]
Hyperlipidemia[b]	Cyclosporine	• Fasting lipid panel	• Initiate patient-specific cholesterol-lowering therapy • Reduce cyclosporine dose (if possible) • Modify regimen (change to tacrolimus or non-CNI containing regimen)[a]
Hyperglycemia[c]	Tacrolimus	• Blood glucose (fasting and nonfasting) • Hemoglobin A_{1c}	• Lifestyle modifications • Reduce tacrolimus dose (if possible) • Reduce steroids (if patient is taking them and if possible) • Initiate patient-specific glucose-lowering therapy (insulin or oral therapy) • Modify regimen (change to cyclosporine or non-CNI containing regimen)[a]
Neurotoxicities[c]	Tacrolimus	• Fine hand tremor • Headache • Mental status changes	• Reduce tacrolimus dose (if possible) • Modify regimen (change from tacrolimus to cyclosporine or non-CNI containing regimen)[a]
Hirsutism	Cyclosporine	• Patient complains of excessive hair growth or male-pattern hair growth	• Reduce cyclosporine dose (if possible) • Cosmetic hair removal • Modify regimen (change to tacrolimus or non-CNI containing regimen)[a]
Alopecia	Tacrolimus	• Patient complains of excessive hair loss	• Reduce tacrolimus dose (if possible) • Hair growth treatments (ie, minoxidil, finasteride in males only) • Consider use of multivitamin with thiamine and folic acid, and/or biotin 5000 mcg daily • Modify regimen (change to cyclosporine or non-CNI containing regimen)[a]
Gingival Hyperplasia	Cyclosporine	• Patient complains of excessive gum growth • Discuss options for therapy with patient's dentist	• Reduce cyclosporine dose (if possible) • Oral surgery (gum resection) • Modify regimen (change to tacrolimus or non-CNI containing regimen)[a]

[a] Modifying the immunosuppressive regimen increases risk for rejection, even in stable patients. This option should be chosen cautiously and implemented with proper monitoring and follow-up.

[b] Tacrolimus is also associated with hypertension and hyperlipidemia, but to a much lower extent compared to cyclosporine.

[c] Cyclosporine is also associated with hyperglycemia and neurotoxicities, but to a much lower extent compared to tacrolimus.

BUN, blood urea nitrogen; CCB, calcium channel blocker; SCr, serum creatinine; ToR, target of rapamycin.

and as an injectable.[7] The recommended starting dose of mycophenolate mofetil is 1000 to 1500 mg given twice daily. The conversion between oral and IV mycophenolate mofetil is 1:1. Enteric-coated MPA is available in 180 mg and 360 mg tablets. The appropriate equimolar conversion between mycophenolate mofetil and enteric-coated MPA is 1000 mg of mycophenolate mofetil to 720 mg of enteric-coated MPA.[6] Recommended starting dose of enteric-coated MPA is 720 mg given twice daily. Conversion of mycophenolate mofetil to enteric-coated MPA has been proven safe. MPA C_0 can be monitored; however, it is not routinely recommended.[6]

KEY CONCEPT The most common adverse events associated with these agents are GI (18%–54%; diarrhea, nausea, vomiting, and gastritis) and myelosuppression (20%–40%).[7] Despite its enteric coating, enteric-coated MPA has the same degree of GI adverse events as mycophenolate mofetil.[6,19] However, data suggest that there is a benefit in converting patients with documented mycophenolate-induced GI disease from mycophenolate mofetil to enteric-coated MPA or to azathioprine.[20] Both MPA products are governed under a FDA-mandated Risk Evaluation and Mitigation Strategy program due to their teratogenic potential.

Comparative Efficacy The MPA derivatives have replaced azathioprine as the primary antiproliferative agent and are generally considered to provide a more specific immunosuppressive effect compared with azathioprine.[6] Mycophenolate mofetil and enteric-coated MPA have similar safety and efficacy data in transplant recipients.[19] The decision to choose one agent over another is a purely practitioner-dependent preference.

▶ *Target of Rapamycin Inhibitors*

Sirolimus KEY CONCEPT Sirolimus and everolimus inhibit T-cell activation and proliferation by inhibiting activation of the mammalian ToR, which suppresses cellular response to IL-2 and other cytokines (ie, IL-4, IL-15).[6,7,21] Studies have shown that ToR inhibitors may be used safely and effectively concomitantly with either cyclosporine or tacrolimus instead of an antiproliferative.[22] Sirolimus can also be used as an alternative agent for patients who do not tolerate CNIs due to nephrotoxicity or other adverse events.[6]

Sirolimus is available in 0.5 mg, 1 mg, and 2 mg tablets and a 1 mg/mL oral solution. Although some may elect not to do a loading dose, the package insert indicates that the current approved dosing regimen for sirolimus is a 6 mg loading dose followed by a 2 mg/day maintenance dose.[7] Use of a sirolimus loading dose of 5 to 15 mg/day for 1 to 3 days will allow for a more rapid achievement of adequate immunosuppression.[7] Maintenance doses of sirolimus usually range from 1 to 10 mg/day given once daily. Sirolimus blood C_0 should be maintained between 3 and 10 ng/mL (mcg/L; 3 and 11 nmol/L), depending on the institution-specific protocols.[6] Of note, sirolimus has a half-life of approximately 62 hours, meaning it will not reach steady state after dosage changes for several days.[7]

KEY CONCEPT The most common adverse events reported with sirolimus are leukopenia (20%), thrombocytopenia (13% to 30%), and hyperlipidemia (38% to 57%).[7] Other adverse effects include delayed wound healing, anemia, diarrhea, arthralgias, rash, proteinuria, pneumonitis, and mouth ulcers. Sirolimus has a black-box warning in newly transplanted liver and lung recipients due to severe and potentially life-threatening adverse events.[7] The long-term use of sirolimus in these populations may be appropriate, but not in the initial posttransplant period (ie, 3 to 6 months posttransplant).

Everolimus Everolimus is a derivative of sirolimus and has the same mechanism of action.[7,23] Everolimus is only indicated for prevention of rejection in low- to moderate-risk renal and liver transplant recipients. This agent is available in 0.25 mg, 0.5 mg, 0.75 mg, and 1 mg tablets. Recommended starting dose is 0.75 to 1 mg twice daily without the need for a loading dose. Maintenance everolimus doses should be maximized to achieve a C_0 goal of 3 to 8 ng/mL (mcg/L; 3–8 nmol/L).[7,23] With a significantly shorter half-life, everolimus steady state can be reached within 4 to 6 days. The adverse event profile of everolimus is similar to that of sirolimus.[7,23]

For both ToR inhibitors, their primary roles have evolved for use only in patients who have a history of or de novo squamous or basal cell carcinoma, due to antiproliferative activity. However, some centers will continue to utilize these agents in patients intolerant of other oral immunosuppressants.[23]

▶ *Corticosteroids*

Traditional triple-therapy immunosuppressive regimens have consisted of a primary agent (ie, CNI, ToR inhibitor, belatacept), an antiproliferative, and corticosteroids.[6] In recent years, many renal and liver transplant protocols have focused on corticosteroid sparing or avoidance. Corticosteroid withdrawal may be possible in other organs, but is generally reserved for patients intolerant of steroid-induced adverse events. Avoidance or sparing of corticosteroids has been supported in the literature, although more studies are needed to help better characterize which patients should follow these protocols.[6,24] A typical taper includes a bolus of IV methylprednisolone 100 to 1000 mg at the time of transplant, then tapered over days to months, depending on the type of organ, to a maintenance dose of prednisone 5 to 10 mg/day. Although most centers still use low-dose steroids for immunologically high-risk patients, a number of renal and liver transplant programs have developed an immunosuppression protocol that completely withdraws corticosteroids at some point posttransplantation.[6] Therapeutic drug monitoring of corticosteroids is not employed. Corticosteroids are associated with a variety of metabolic toxicities. The most common adverse events are summarized in Table 55–4.[1,6]

KEY CONCEPT Corticosteroids have various effects on immune and inflammatory responses, although their exact mechanism of immunosuppression is not fully understood. It is believed that high doses are directly lymphotoxic, and lower doses inhibit the production of various cytokines.[6,7]

The most commonly used corticosteroids are methylprednisolone (IV and oral) and prednisone (oral), although prednisolone and dexamethasone are also effective for organ transplantation. Corticosteroid doses vary by center-specific protocols, organ type, and patient characteristics.

▶ *Costimulatory Pathway Blocker*

Belatacept KEY CONCEPT Belatacept was approved in 2011 as the first IV biologic maintenance immunosuppressive agent in transplant.[25] Belatacept blocks CD80 and CD86 ligands, found on APCs.[7] The CD80 and CD86 proteins are responsible for stimulating CD28 on inactive T-cells, an essential costimulatory interaction (Signal 2). Signal 1 without a complementary Signal 2 induces T-cell anergy.[25] Studies have shown that in combination with mycophenolate and corticosteroids, belatacept may be used

Table 55–4

Common Adverse Events Associated with Corticosteroids[1,6]

Body System	Adverse Event
Cardiovascular	Hyperlipidemia
	Hypertension
Central nervous system	Anxiety
	Insomnia
	Mood changes
	Psychosis
Dermatologic	Acne
	Diaphoresis
	Ecchymosis
	Hirsutism
	Impaired wound healing
	Petechiae
	Thin skin
Endocrine/metabolic	Cushing syndrome
	Hyperglycemia
	Sodium and water retention
Gastrointestinal	Gastritis
	Increased appetite
	Nausea, vomiting, diarrhea
	Peptic ulcers
Hematologic	Leukocytosis
Neuromuscular/skeletal	Arthralgia
	Impaired growth
	Osteoporosis
	Skeletal muscle weakness
Ocular	Cataracts
	Glaucoma
Respiratory	Epistaxis

in place of CNIs, demonstrating similar patient and allograft survival compared to a cyclosporine-based regimen.[26,27] Belatacept improved renal function; however, the incidence and intensity of acute rejection was significantly higher. Belatacept was also associated with improvements in blood pressure and lipid levels.[25]

Belatacept is available in a 250 mg vial that requires reconstitution prior to administration.[7] The recommended dosing regimen is 10 mg/kg on the day of transplantation, followed by an additional dose 4 days later, and again at the end of weeks 2, 4, 8, and 12 posttransplant. Beginning at the end of week 16 posttransplant, belatacept is dosed at 5 mg/kg every 4 weeks thereafter.[7,25] Belatacept requires access to an infusion center/suite, or a home infusion service to ensure appropriate administration. The monthly administration of belatacept could potentially improve adherence compared to daily oral CNIs. Additionally, the lack of significant drug–drug interactions has the potential to simplify pharmaceutical care in transplant recipients.

In the United States, belatacept is used most commonly months to years after transplant in patients intolerant of tacrolimus.[26] This is called conversion therapy. In patients who are being converted to belatacept from tacrolimus, the most common dosing schedule is 5 mg/kg every 2 weeks for five doses, then the dosing interval is changed to every 4 weeks. Tacrolimus may be discontinued in as little as 3 to 4 weeks, but in some situations may be tapered off over 6 to 12 months following conversion or used (low-dose) in combination with belatacept.[28]

The most common adverse effects associated with belatacept are infectious (urinary tract infection, 37%; upper respiratory infection, 15%), GI (diarrhea, 39%; constipation, 33%; nausea, 24%; vomiting, 22%), metabolic (hyperkalemia, 20%; hypokalemia 21%), and central nervous system (CNS; headache, 21%) complications.[7] Other adverse effects include peripheral edema, anemia, leukopenia, hypotension, arthralgia, and insomnia.[25] **KEY CONCEPT** Belatacept has a black-box warning for increased risk of posttransplant lymphoproliferative disorders (PTLD). Due to this risk, it is recommended that belatacept only be used in patients with a proven preexisting immunity to Epstein-Barr virus (EBV). An additional black-box warning advises against use of belatacept in liver transplant patients due to an increased risk of allograft loss and patient death.[7,25]

Treatment of Acute Rejection Episodes

Acute rejection is generally treated with a course of high-dose methylprednisolone (250–1000 mg/day IV for 3 days), which is usually sufficient to ameliorate the episode. If the acute rejection episode is resistant to the initial course of steroids, a second course may be administered or the patient may begin therapy with r-ATG (1.5 mg/kg/day for 4 to 14 days) or alemtuzumab (30 mg × 1 dose).[1] Cellular rejection refractory to these treatments is rare and likely due to underlying causes such as an antibody-mediated component or other diagnosis. Treatments of refractory acute rejection may include alemtuzumab, high-dose tacrolimus, IVIG, or organ irradiation.

Managing Highly Sensitized Patients and Antibody-Mediated Rejection

The presence of preformed antibodies, high panel-reactive antibodies (PRA), and DSA are major barriers to successful transplantation.[4] This is true because traditional immunosuppressants do not significantly affect the humoral response and are ineffective at management of AMR, which is a leading cause of allograft loss in kidney and heart transplant recipients. Without some form of intervention, antibody formation and rejection can significantly impact morbidity and mortality. Two major strategies are used for reduction of DSA pretransplant: (a) high-dose IVIG and (b) plasmapheresis plus low-dose IVIG. Each approach has advantages and disadvantages.[4]

In plasmapheresis or plasma exchange, patients' plasma is removed and replaced with albumin or fresh-frozen plasma.[4] Plasmapheresis reduces preformed antibodies and allows transplantation to occur. IVIG administration decreases anti-HLA alloantibody synthesis. The other mechanisms of IVIG are inhibition of complement-mediated injury, reduced B-cell proliferation and NK cells, and a decrease in phagocytosis. Most patients require four to five plasmapheresis sessions with IVIG to remove DSA. In patients at risk for bleeding, the use of albumin should be limited, and fresh-frozen plasma or a combination of both agents should be considered.[4]

In patients who develop AMR posttransplant, there are limited therapeutic options, none of which are FDA-approved. Potential options include plasmapheresis and IVIG, rituximab, proteasome inhibition, tocilizumab and/or complement inhibition.[4] All of these agents have an effect on humoral immunity, which may benefit patients with AMR. The mechanisms of plasmapheresis and IVIG were discussed earlier.[4]

Rituximab is a chimeric monoclonal anti-CD20 antibody targeting B-cells.[4,7] This agent directly inhibits B-cell proliferation and induces cellular apoptosis through complement-mediated antibody-dependent-cellular cytotoxicity. In an analysis of AMR treatment, the use of rituximab in conjunction with plasmapheresis/IVIG improved 3-year graft survival (92% versus 50%) and significantly reduced DSA at 3 months compared with high-dose IVIG alone.[29] Unfortunately, plasma cells lack CD20 and are unaffected by rituximab. However, rituximab may play an important role in reducing memory B-cell response. Overall, it appears that rituximab may provide beneficial effects in managing AMR and patients highly sensitized before transplant when used in combination with other therapies.[4]

Bortezomib and carfilzomib are proteasome inhibitors indicated for treatment of multiple myeloma.[4,7] They work by inducing cell-cycle arrest and apoptosis of plasma cells. Desensitization and treatment protocols using bortezomib have utilized doses of 1.3 mg/m^2 from one to four cycles. Acute hepatic dysfunction has rarely been reported; thus, bortezomib should be used cautiously in patients with moderate-to-severe hepatic impairment. Bortezomib has also been associated with significant myelosuppression and peripheral neuropathy. Bortezomib has been used in combination with plasmapheresis and IVIG or rituximab. The reported outcomes of these cases demonstrate graft survival rates of 85% to 100%. Anti-HLA antibodies are decreased by 50% within 2 weeks of therapy and remain suppressed for up to 5 months.[30,31] Bortezomib also seems effective in AMR refractory to plasmapheresis and IVIG.[4]

Tocilizumab is an interleukin-6 receptor antagonist that has been recently used for management of both acute and chronic AMR.[7,32] In a single-center, observational analysis of seven patients, tocilizumab (8 mg/kg/month) resulted in 50% or greater reduction in DSA in four of six treated patients. In all patients, renal function improved or stabilized following treatment with tocilizumab.[32] Further study is warranted to evaluate the efficacy of tocilizumab in the management of AMR.

Eculizumab is a humanized monoclonal antibody directed against complement protein C5.[7] It inhibits the cleavage to C5a and C5b, thus preventing the generation of the membrane attack complex (MAC) and reducing antibody-dependent-cell lysis. C1 esterase inhibitors also inhibit the complement cascade and may provide some benefit in managing AMR. Eculizumab carries an

FDA-boxed warning of meningococcal infection. Meningococcal vaccination is recommended 14 days prior to eculizumab, but infections have been reported even in vaccinated patients. It is highly recommended to continue penicillin or alternative lifetime therapy in these patients. There are only a few case reports demonstrating efficacy of eculizumab or the C1 esterase inhibitors for treating AMR.[4] Eculizumab is an important agent for the prevention and treatment of atypical hemolytic uremic syndrome (aHUS) posttransplant.

Maintenance Immunosuppressive Therapies—Common Drug–Drug Interactions

KEY CONCEPT As the number of medications a patient takes increases, so does the potential for DDIs. Disease severity, patient age, and organ dysfunction are all risk factors for DDIs. In general, DDIs are either pharmacokinetic or pharmacodynamic interactions:

- Pharmacokinetic interactions result when one drug alters the absorption, distribution, metabolism, or elimination of another drug.
- Pharmacodynamic interactions include additive, synergistic, or antagonistic interactions that can affect efficacy or toxicity.

▶ *Pharmacokinetic Interactions*

Pharmacokinetic DDIs pose a major dilemma with the maintenance immunosuppressants. Pharmacokinetic interactions can either result in: (1) increased concentrations of one or more agents, with an increased risk for drug-induced toxicities, or (2) lowered (ie, subtherapeutic) drug concentrations, possibly leading to allograft rejection. These interactions can be seen during drug absorption, distribution, metabolism, and elimination.

Interactions of Absorption Gut metabolism, modifications in active transport, changes in intestinal motility, and chelation interactions alter immunosuppressant absorption. Active transporters (ie, P-glycoprotein [P-gp]) are present in the gut, brain, liver, and kidneys and play an important role in DDIs. P-gp provides a biological barrier, eliminating xenobiotics that accumulate in organ systems, thereby having a significant impact on absorption and distribution of many medications. P-gp affects the absorption of the CNIs and ToR inhibitors. Medications that inhibit or induce the activity of P-gp have a significant impact on bioavailability of some immunosuppressive agents. For example, P-gp inhibitors, such as verapamil or quinidine, increase concentrations of cyclosporine, tacrolimus, sirolimus, and everolimus due to reduced P-gp-dependent drug elimination from systemic circulation.[7]

There is a prominent interaction between the prokinetic agents and the CNIs seen through changes in intestinal motility. Metoclopramide increases the absorption of cyclosporine and tacrolimus by enhancing gastric motility and emptying, resulting in increased CNI concentrations.[7]

Most of the interactions with MPA derivatives result in reductions in intestinal absorption. Proton pump inhibitors decrease the oral absorption of mycophenolate mofetil, but not enteric-coated MPA.[7] Divalent and trivalent cations (ie, aluminum, magnesium, calcium) decrease MPA absorption through chelation. These agents should be administered at least 1 hour before or 2 hours after MPA. Of note, iron does not appear to interact with the MPA preparations. The clinical implications of these DDIs are unknown, but reductions in MPA exposure can theoretically enhance rejection risk.

Interactions of Distribution Interactions of distribution occur most often with highly protein-bound drugs.[7] MPA is the only highly protein-bound (97%) maintenance immunosuppressant with an interaction of distribution. Concomitant administration of MPA with salicylates increases MPA-free concentrations. The adverse sequelae of this interaction are unknown. Drug interaction studies have not been conducted with MPA derivatives and other highly protein-bound drugs.

Interactions of Metabolism Oxidative metabolism by cytochrome P-450 (CYP) isozymes is the primary method of xenobiotic metabolism. The CNIs and ToR inhibitors are substrates of the CYP3A isozyme system. Most CYP-mediated metabolism takes place in the liver; however, CYP is also expressed in the intestine, lungs, kidneys, and brain. As CYP3A substrates, it is anticipated that cyclosporine, tacrolimus, sirolimus, and everolimus would experience similar DDIs with known substrates, inhibitors, and inducers of the CYP3A isozyme system.[6] Table 55–5 details clinically relevant DDIs that occur with the calcineurin and ToR inhibitors due to inhibition or induction of the CYP isozyme system.[7]

Given how extensive some immunosuppressant DDIs are, empiric dose changes are necessitated in some cases when coadministration with an interacting medication cannot be avoided. For example, it is recommended to reduce tacrolimus doses by one-third in patients initiating voriconazole. Some clinicians utilize interactions of metabolism to reduce the dose of an immunosuppressant, such as using diltiazem to treat hypertension, which also helps reduce tacrolimus doses and decrease pill burden.

Not all metabolic DDIs occur through the CYP system. Azathioprine interacts with allopurinol and febuxostat through the inhibition of xanthine oxidase, which is the enzyme responsible for metabolizing 6-MP to 6-thiouricate.[7] Combining these agents can result in 6-MP accumulation and severe myelosuppression. It is recommended that concomitant therapy with azathioprine and allopurinol or febuxostat be avoided, but if necessary, azathioprine doses must be empirically reduced by 75%.[7]

Interactions of Elimination Mycophenolate is metabolized to MPA-glucuronide (MPAG) via hepatic glucuronosyltransferase, then excreted in bile for gut elimination.[7] Deconjugation of MPAG to MPA by intestinal flora results in continued MPA absorption several hours after its administration. Some medications (ie, cyclosporine, bile-acid sequestrants) interfere with the biliary excretion of MPAG, thereby eliminating MPA reabsorption in the intestines and lowering the MPA area under the curve (AUC).[7] In this type of interaction, separation of doses is ineffective; therefore, proper patient monitoring is warranted.

▶ *Pharmacodynamic Interactions*

Pharmacodynamic interactions are the backbone of modern immunosuppressive therapies that employ multiple medications

Patient Encounter Part 2

Identify your treatment goals for the patient in terms of maintenance immunosuppressants.

Create a plan for maintenance therapy for the patient, making sure to compare and contrast the pros and cons of the different maintenance immunosuppressants.

Identify the need to continue the patient's pretransplant medications, and identify any potential DDIs that may exist with the addition of the maintenance immunosuppressants and the medications he is currently taking.

Table 55–5

Potential Drug–Drug Interactions with the Calcineurin Inhibitors and Target of Rapamycin Inhibitors Mediated through the Cytochrome P-450 (CYP) System 3A Isozyme[7]

Substrates[a]	Inducers[b]	Inhibitors[c]
Alfentanil	Apalutamide	Amiodarone
Alprazolam	Bexarotene	Aprepitant
Amiodarone	Bosentan	Atazanavir
Amlodipine	Carbamazepine	Boceprevir
Atorvastatin	Cenobamate	Ceritinib
Boceprevir	Dabrafenib	Cimetidine
Cilostazol	Dexamethasone	Clarithromycin
Cisapride	Efavirenz	Clotrimazole
Chlorpromazine	Enzalutamide	Cobicistat and cobicistat-containing coformulations
Clonazepam	Eslicarbazepine	Conivaptan
Cocaine	Ethosuximide	Crizotinib
Cortisol	Etravirine	Cyclosporine
Cyclophosphamide	Fosphenytoin	Darunavir
Dantrolene	Lorlatinib	Delavirdine
Dapsone	Lumacaftor	Diltiazem
Diazepam	Lumacaftor-ivacaftor	Dronedarone
Disopyramide	Mitotane	Duvelisib
Enalapril	Modafinil	Erythromycin
Estradiol	Nafcillin	Fedratinib
Estrogen	Nevirapine	Fluconazole
Etoposide	Pexidartinib	Fluoxetine
Everolimus	Phenobarbital	Fosamprenavir
Felodipine	Phenytoin	Fosaprepitant
Flutamide	Primidone	Grapefruit juice
Lidocaine	Rifabutin	Idelalisib
Loratadine	Rifampin (rifampicin)	Imatinib
Lovastatin	Rifapentine	Indinavir
Nevirapine	Rilpivirine	Isavuconazole (isavuconazonium sulfate)
Nicardipine	St. John's wort	Isoniazid
Nifedipine		Itraconazole
Omeprazole		Ketoconazole
Paclitaxel		Lefamulin
Propafenone		Letermovir
Progesterone		Lopinavir
Quetiapine		Miconazole
Quinidine		Mifepristone
Rilpivirine		Nefazodone
Rivaroxaban		Nelfinavir
Sertraline		Netupitant
Simvastatin		Nilotinib
Tamoxifen		Ombitasvir-paritaprevir-ritonavir
Testosterone		Ombitasvir-paritaprevir-ritonavir plus dasabuvir
Tolvaptan		Posaconazole
Triazolam		Ribociclib
Vandetanib		Rilpivirine
Venlafaxine		Ritonavir
Vinblastine		Ritonavir and ritonavir-containing coformulations
Warfarin		Saquinavir
Zolpidem		Telapravir
		Tucatinib
		Verapamil
		Voriconazole
		Zafirlukast

[a] Substrates of the CYP3A4 isozyme will compete with cyclosporine, tacrolimus, and sirolimus for metabolism; therefore, concentrations of these medications will be increased (usually by ≤ 20%).

[b] Inducers of the CYP3A4 isozyme will enhance the metabolism of cyclosporine, tacrolimus, and sirolimus; therefore, concentrations of these medications will be decreased.

[c] Inhibitors of the CYP3A4 isozyme will decrease the metabolism of cyclosporine, tacrolimus, and sirolimus; therefore, concentrations of these medications will be increased.

with different mechanisms of action resulting in additive immunosuppression. Unfortunately, pharmacodynamic interactions can also be problematic, such as when medications with similar adverse events are used concomitantly. For example, nephrotoxic agents, such as amphotericin B, and nonsteroidal anti-inflammatory drugs may potentiate the nephrotoxic effects of the CNIs.[7] The use of myelosuppressive agents, such as sulfamethoxazole-trimethoprim (SMZ-TMP) and valganciclovir, could enhance the myelosuppressive effects of induction therapy and maintenance immunosuppression.[7] In addition to reviewing prescription medications, it is essential to question patients about the use of nonprescription agents and dietary supplements, as these products also have the potential for significant interactions through methods discussed previously. For example, St. John's wort induces CNI and ToR inhibitor metabolism, while willow bark can worsen CNI-induced nephrotoxicity.

Management of Immunosuppressive Drug Complications

▶ *Opportunistic Infections*

KEY CONCEPT Organ transplant recipients are at increased risk of infectious diseases, which are a principal cause of early morbidity and mortality.[33] Prevalence of posttransplant infection depends on many factors, including clinical risk factors, environmental exposures, and the degree of immunosuppression. Anti-infectives are universally prescribed in this population, and their use can be split into three different categories:

- Prophylaxis: antimicrobials given to prevent infection
- Empiric: preemptive therapy given based on clinical suspicion of an infection
- Treatment: antimicrobials given to manage a documented infection

Posttransplant infections generally occur in a standard pattern; therefore, prevention is a key management strategy.[33] Information in this section is designed to highlight prophylaxis options routinely used in organ transplant recipients. Refer to Table 55–6 for a list of agents used for the prevention of *Pneumocystis jirovecii* pneumonia and CMV disease.[34,35]

***Pneumocystis jirovecii* Pneumonia** KEY CONCEPT Without prophylaxis, *P. jirovecii* pneumonia occurs in 5% to 15% of transplant recipients.[34] Antipneumocystis prophylaxis is used in all transplant recipients. Duration of prophylaxis is usually 6 to 12 months after transplant, but may be prolonged in highly immunosuppressed patients (ie, active CMV disease, treatment for rejection) or liver or lung recipients. SMZ-TMP is the preferred agent for prophylaxis. One of its major advantages is its broad spectrum of activity. Not only is it effective against *Pneumocystis*, but it

Table 55–6

Prophylactic Options for *Pneumocystis jirovecii* Pneumonia and CMV[34,35]

Medication	Dosing	Common Adverse Events
Antipneumocystis Prophylaxis		
Sulfamethoxazole-trimethoprim (Bactrim, Septra, SMZ-TMP, cotrimoxazole)	One SS tablet by mouth once a day[a] One DS tablet by mouth once a day[a] One DS tablet by mouth every M/W/F[a]	Hyperkalemia Myelosuppression Nephrotoxicity Neutropenia Photosensitivity Rash
Pentamidine (NebuPent)	300 mg inhaled every 4 weeks	Bronchospasm Cough Hypoglycemia or hyperglycemia
Dapsone (Avlosulfon)	100 mg tablet by mouth once a day 50 mg tablet by mouth once a day if combined with pyrimethamine/leucovorin	Hepatotoxicity Myelosuppression Nephritis
Atovaquone (Mepron)	1500 mg suspension by mouth once a day	Elevated liver transaminases Nausea Rash
Antivirals		
Valganciclovir (Valcyte)	450–900 mg by mouth once a day[a]	Stomach upset Myelosuppression Headache
Ganciclovir (Cytovene)	5 mg/kg IV every day[a]	Stomach upset Myelosuppression Rash
Valacyclovir (Valtrex)	1-2 g by mouth four times a day[a]	Stomach upset Myelosuppression Headache
Letermovir (Prevymis)	480 mg once daily	Stomach upset Headache
CMV hyperimmune globulin (CytoGam) and polyvalent IVIG	The maximum recommended total dosage per infusion is 150 mg/kg beginning within 72 hours of transplantation Follow-up doses and time intervals depend on the type of organ transplanted	Stomach upset Fevers and chills Flushing

[a]Dose adjustment required in renal insufficiency.

CMV, cytomegalovirus; DS, double-strength (800 mg SMZ, 160 mg TMP); IVIG, intravenous immunoglobulin; IV, intravenous; M/W/F, Monday, Wednesday, and Friday; SMZ, sulfamethoxazole; SS, single-strength (400 mg SMZ, 80 mg TMP); TMP, trimethoprim.

also has activity against *Toxoplasma* and other common bacterial infections. Patients who have sulfa allergies, glucose-6 phosphate dehydrogenase (G6PD) deficiency, or are intolerant of SMZ-TMP should be given one of the second-line treatments. Unfortunately, the second-line agents are antiparasitics and have no meaningful activity against common bacteria. These agents include dapsone, atovaquone, and pentamidine.[34]

Cytomegalovirus CMV is a concerning opportunistic pathogen in transplantation due to its association with poor outcomes.[35] CMV infection is present in 30% to 97% of the general population, but CMV disease is typically restricted to immunocompromised hosts. Risk of CMV disease is highest among CMV-naive recipients who receive a CMV-positive organ (donor+/recipient–). Other factors augmenting the risk of CMV disease include organ type (lung and pancreas recipients are highest risk) and immunosuppressive agents (ALA use increases risk). CMV disease characteristically occurs within the first 3 to 6 months posttransplantation, but delayed onset disease has been seen in patients receiving antiviral prophylaxis. Patients with CMV disease may present with flu-like symptoms, including fever, chills, aches, malaise, and fatigue. CMV disease may result in more profound symptoms in the immunosuppressed patient, including leukopenia, thrombocytopenia, and organ dysfunction.[35]

KEY CONCEPT Several antivirals have proven effective in preventing and treating CMV.[35] Valacyclovir and valganciclovir, prodrugs of acyclovir and ganciclovir, respectively, have improved bioavailability compared with their parent compounds and offer the advantage of less frequent dosing. Letermovir is a new antiviral agent that is effective against CMV, but is not yet FDA-approved for use in organ transplant recipients. Its use is limited to those intolerant to valganciclovir or with resistant CMV disease. CMV prophylaxis is typically continued for the first 200 days or longer after transplantation. Although valganciclovir and IV ganciclovir are considered the prophylaxis agents of choice in most organ transplant recipients, national guidelines allow for consideration of prophylaxis with CMV hyperimmune globulin in heart and lung transplant populations. Both IV ganciclovir and oral valganciclovir may be used for preemptive therapy or for treatment of established CMV disease. Alternative agents may be used in the event of ganciclovir-resistant CMV disease, such as foscarnet, cidofovir, IVIG, letermovir or even conversion from a CNI to mToR inhibitor-based immunosuppression.[35] Adverse events are similar among these agents and include myelosuppression and GI effects.[7]

Fungal Infections Fungal infections are an important cause of morbidity and mortality in SOT recipients.[36] Immunologic (ie, immunosuppressants, CMV infection), anatomic (ie, tissue ischemia and damage), and surgical (ie, duration of surgery, transfusion requirements) factors contribute to risk for invasive fungal infections. Mucocutaneous candidiasis (ie, oral thrush, esophagitis) is associated with corticosteroids and ALA. KEY CONCEPT Oral nystatin or clotrimazole troches are effective prophylactic options for prevention of thrush. However, clotrimazole inhibits the CYP3A system in the gut and can alter immunosuppressive levels.[7] Use of systemic antifungal prophylaxis, such as oral fluconazole, is controversial due to potential for DDIs and risk of developing resistance. The American Society of Transplantation has recommended antifungal prophylaxis in liver, lung, intestine, and pancreas transplantation.[37,38] Choice of agents depends on fungal risk in that particular population. For example, liver, intestine, and pancreas transplant recipients are at high risk for candidiasis; therefore, use of medications that cover *Candida* spp. is crucial, such as the triazoles (ie, fluconazole, itraconazole) or echinocandins (ie, caspofungin, micafungin, anidulafungin). Lung transplant recipients are at high risk for aspergillosis; therefore, it is imperative to use antifungal prophylaxis that covers *Aspergillus* spp., such as the echinocandins, polyenes (ie, amphotericin B, lipid-based amphotericin B products) or new generation triazoles (ie, voriconazole, posaconazole).[37,38]

Patient Encounter Part 3

Identify your treatment goals for the patient in terms of antimicrobial prophylaxis.

Create a plan for the patient's antimicrobial prophylaxis, making sure to compare and contrast the pros and cons of the different agents in this patient.

Polyomavirus One infection complication seen almost exclusively in renal transplant is polyomavirus. In humans, there are two pathologic polyoma strains, BK and JC. These viruses are rarely associated with disease in immunocompetent individuals. During periods of immunosuppression, the virus is reactivated and can be associated with significant morbidity.[39]

In renal transplant, the major diseases caused by BK virus (BKV) are tubulointerstitial nephritis and ureteral stenosis.[39] Polyomavirus-associated nephropathy (PyVAN) presents with evidence of allograft dysfunction, resulting in either an asymptomatic acute or slowly progressive rise in serum creatinine (SCr) concentrations. Some studies have reported PyVAN may affect up to 10% of renal transplant recipients, frequently resulting in permanent renal dysfunction or allograft loss.[39]

Currently, treatment options for BKV are limited, and management recommendations are generally focused on immunosuppression reductions. There are no directed antiviral interventions; however, some centers have utilized IVIG, cidofovir, or leflunomide to manage BKV infections. All of these agents have been reported to provide some benefit in managing BKV in anecdotal cases.[39]

Hepatitis C With the advent of new antiviral agents, hepatitis C infection can now be cured in most patients. In patients with a history of hepatitis C, antiviral therapy should be initiated prior to transplant, due to complications immunosuppression may play on viral replication.[40] One major avenue opened due to availability of these new agents is use of hepatitis C positive donor organs for transplantation into hepatitis C negative recipients. This allows for use of organs that were often deemed unusable and increases the pool of available organs, possibly reducing wait time for patients and subsequently reducing related morbidity and mortality. In these transplants, antivirals are initiated at time of transplant and given for several weeks following transplant. Viral loads are monitored to ensure hepatitis C infection does not take place.[40]

Vaccination Vaccination is one of the most effective means of preventing infection and related complications.[41] However, there is valid concern that SOT recipients may mount an inadequate response to vaccination due to immunosuppression. Required vaccinations should be administered prior to transplantation so an appropriate antibody response can develop (Table 55–7).[41] If this strategy is pursued, the earlier a vaccine is administered, the more effective it may be, as end-stage organ failure can also contribute to decreased immune response.[41]

In general, the weakest response to vaccine is within the first 6 months posttransplantation due to the intense level of

Table 55–7

Recommended Vaccinations Pre- and Posttransplant[41]

Vaccine	Administration		Additional Information
	Before SOT	After SOT	
Hepatitis A	X		Immunize as soon as possible during course of disease
Hepatitis B	X		Immunize as soon as possible during course of disease (before transplant, administer 40 mcg dose in a series of three to four doses)
Herpes Zoster	X	X	Live[a] virus, can only be administered pretransplant; administer ≥ 14 days before immunosuppressant agents are initiated (experts advise 1 month before) Recombinant herpes zoster vaccine only can be administered after transplantation
Human Papilloma Virus	X		Recommended for men and women ages 9–45, no recommendations for SOT
Influenza	X	X	Annual vaccination with inactivated intramuscular formulation recommended before and after SOT
Measles-Rubella	X		Live[a] virus, administer to patients who are seronegative, *before* transplant, or in women of childbearing age for prevention of congenital rubella syndrome
Meningococcal	X	X	Should be considered in patients at high-risk for antibody-mediated rejection when use of a complement inhibitor may be utilized posttransplant
Pneumococcal	X	X	23-valent polysaccharide vaccine should be given once before transplant and booster at 5 years after initial dose
Tetanus/Diptheria	X		TDaP booster indicated for < 65 years old (may be given ≤ 2 years after last TDaP booster in SOT patients)
Varicella	X		Live[a] virus, administer to patients who are seronegative, *before* transplant

[a] All live vaccines are contraindicated post solid organ transplant (SOT), as they can cause serious infection.

Live vaccines:

- Bacillus Calmette-Guerin
- Herpes zoster
- Live intranasal attenuated influenza
- Live oral typhoid
- Measles-rubella
- Vaccinia (smallpox)
- Varicella

TDaP, tetanus, diphtheria, and pertussis.

immunosuppression during this period.[41] Vaccination within 6 months of transplant may be considered on a case-by-case basis in those patients who are at high risk of developing infection. Use of inactive vaccines is preferred in transplant recipients due to relative risk of infection associated with live vaccines. Healthcare workers and family members who are in close contact with transplant recipients and have received a live vaccine should consider use of respiratory masks for at least 7 days after vaccination and adhere to strict oral and hand hygiene.[41]

▶ *Hypertension*

KEY CONCEPT Cardiovascular disease is the leading cause of death in organ transplant recipients.[42] Posttransplant hypertension is associated with increased cardiac morbidity and patient mortality in transplant patients and is also an independent risk factor for allograft dysfunction. Based on posttransplant morbidity and mortality data, it is imperative that posttransplant hypertension be identified and managed appropriately.[42]

There are several mechanisms responsible for posttransplant hypertension including renal dysfunction, increased sensitivity to endothelin-1 and angiotensin, increased density of glucocorticoid receptors in the vascular smooth muscle, and decreased production of vasodilatory prostaglandins. However, one of the most easily recognized causes of posttransplant hypertension is the use of corticosteroids and CNIs. Corticosteroids cause sodium and water retention, thus increasing blood pressure, whereas CNIs reduce glomerular filtration rate (GFR) and renal blood flow, increase systemic and intrarenal vascular resistance, promote sodium retention, reduce concentrations of systemic vasodilators (ie, prostacyclin, nitric oxide), and increase concentrations of thromboxanes. Compared with cyclosporine, tacrolimus displays significantly less severe hypertension, and patients taking tacrolimus require fewer antihypertensive medications posttransplant.[42]

Treatment **KEY CONCEPT** Controlling hypertension after transplant is essential in preventing cardiac morbidity and mortality and prolonging graft survival. The target blood pressure in transplant recipients should be less than 130/80 mm Hg, consistent with national hypertension guidelines.[42]

Lifestyle Modifications To achieve goal blood pressure, lifestyle modifications including diet, exercise, sodium restriction, and smoking cessation are recommended.[42] Unfortunately, lifestyle modifications alone are often inadequate in high-risk populations, and antihypertensive medications are usually initiated early after transplant.[42]

Immunosuppressive Regimen Modification Because tacrolimus has shown the propensity to cause less severe hypertension compared to cyclosporine, conversion from cyclosporine to tacrolimus may be one way to reduce the severity of hypertension in transplant recipients. **KEY CONCEPT** Conversion to a ToR inhibitor or belatacept, which are not associated with hypertension, may also be an alternative to the CNIs in patients with difficult-to-control hypertension. Corticosteroid taper or withdrawal are effective strategies for lowering blood pressure, but are not warranted in all clinical situations.[42]

Antihypertensive Agents There is no single class of antihypertensive medications recognized as the ideal agent. Numerous factors must be considered when determining appropriate treatment, including the safety and efficacy data of available agents, patient-specific comorbidities, and medication cost.[42] A large majority of patients often require multiple medications to achieve goal blood pressure, and combination therapy is regarded as appropriate first-line therapy.[42]

The limited clinical studies support use of calcium channel blockers (CCB) posttransplantation. Dihydropyridine CCBs have been associated with a higher GFR and lower incidence of allograft loss. Dihydropyridine CCBs have demonstrated an ability to reverse nephrotoxicity associated with cyclosporine and tacrolimus. However, use of diltiazem and verapamil is discouraged for the treatment of hypertension because of potential DDIs and lack of strong evidence in renal and liver transplant recipients. Addition of diltiazem to patients' regimens after cardiac transplant has also been shown to retard progression of cardiac allograft vasculopathy. β-Blockers and thiazide diuretics have proven benefits in reducing cardiovascular disease–associated morbidity and mortality in the general population.[42] Tolerability permitting, these agents are to be considered second and third therapies in most transplant recipients. The angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) have definite benefits in patients with nephropathy and are believed to have renoprotective effects in most patients. However, due to their ability to cause an initial increase in SCr, these agents should be used cautiously when combined with the CNIs. In general, antihypertensive therapy should focus on agents with proven benefits in reducing progression of cardiovascular disease and must be tailored to a patient's needs.[42]

▶ *Hyperlipidemia*

KEY CONCEPT Hyperlipidemia is seen in up to 60% of transplant patients.[43] As a result of elevated cholesterol levels, transplant recipients are not only at increased risk of atherosclerotic events, but also allograft vasculopathy. Hyperlipidemia, along with other types of cardiovascular disease, is now one of the primary causes of morbidity and mortality in long-term transplant survivors.[43]

Elevated cholesterol levels in transplant patients are due to age, genetic disposition, renal dysfunction, DM, proteinuria, body weight, and immunosuppressive therapy. Many immunosuppressive agents can produce elevations in serum lipid levels.[43]

Treatment KEY CONCEPT Lowering cholesterol has been shown to significantly decrease severe rejection and transplant vasculopathy and improve 1-year survival in heart transplant recipients.[44] Although these results cannot be extrapolated to other transplant populations, they do demonstrate the potential benefits of aggressive cholesterol lowering in organ transplant recipients. Due to high prevalence of cardiovascular disease among organ transplant recipients, most practitioners consider these patients to be high risk for lipid lowering. Many guidelines state a target calculated low-density lipoprotein cholesterol (LDL-C) level of less than 100 mg/dL (2.59 mmol/L) in high-risk patients.[44] Note: national guidelines for treating hyperlipidemia in the general population are often followed, despite lack of transplant recommendations. Refer to Chapter 13, "Dyslipidemias," for additional information.

Lifestyle Modifications Generally, lowering cholesterol in patients begins with therapeutic lifestyle changes, including reduction in saturated fat and cholesterol intake and increase in moderate physical activity.[43] However, lifestyle modifications alone rarely allow a patient to achieve goal LDL-C level. Modification of the immunosuppressive regimen and use of cholesterol-lowering medications are often warranted.[43]

Immunosuppressive Regimen Modifications Tacrolimus has shown the propensity to cause less severe hyperlipidemia when compared with cyclosporine. Conversion from cyclosporine to tacrolimus may be one way to counteract dyslipidemia in transplant recipients. Also, the ToR inhibitors have been associated with significant changes in lipids and triglycerides; therefore, conversion from a ToR inhibitor to a CNI or belatacept may be warranted in patients with resistant dyslipidemia.[43]

Cholesterol-Lowering Agents 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, are considered first-line therapy for hyperlipidemia in the general population.[43] However, there is some uncertainty about the pathogenesis of cardiovascular disease in transplant recipients and whether statin therapy will have similar effectiveness in organ transplant recipients. Statins have shown definite advantages when used in heart transplantation, including reduction in LDL-C and major adverse cardiac events (MACE), as well as an apparent cardioprotective effect. In renal transplant recipients, statins lower LDL-C levels and reduce incidence of some cardiac events; however, the ability to lower MACE has not been seen in this population. Despite these mixed results, statins are still considered the primary therapeutic option for hyperlipidemia in organ transplant recipients. When choosing a statin for management of hyperlipidemia in the transplant patient, a focus on potential DDIs is warranted. Use of cyclosporine in conjunction with simvastatin is considered a contraindication due to risk of skeletal muscle effects.[43]

Proprotein convertase subtilisin kexin type 9 inhibitors are a relatively new class of antihyperlipidemics that promote clearance of LDL-C through increased LDL-C receptors.[7] This class has proven effective in cholesterol lowering and prevention of primary and secondary adverse coronary events in the general population; however, their safety and efficacy in organ transplant recipients is unknown. Fibric acid derivatives are an excellent choice for lowering triglycerides, but are not as effective as statins at lowering LDL-C.[43] These agents play a role in conjunction with statins in patients with both elevated cholesterol and triglycerides. Nicotinic acid is very effective at improving the lipid panel, with excellent results in lowering LDL-C, as well as increasing high-density lipoprotein cholesterol (HDL-C). However, patient tolerability is a concern with this agent. The bile acid sequestrants should be avoided in transplant recipients due to their high incidence of GI adverse events, as well as their propensity for pharmacokinetic DDIs with MPA. Ezetimibe has proven safe and effective in lowering LDL-C in renal transplant recipients. Future studies are needed to establish ideal regimens involving antihyperlipidemic and immunosuppressive medications to decrease morbidity and mortality and ultimately prevent cardiovascular events.[43]

▶ *New-Onset DM after Transplantation*

KEY CONCEPT New-onset DM after transplantation (NODAT) is a serious complication that is often underestimated by transplant practitioners.[45] The incidence of NODAT has been reported as 4% to 25% after renal transplant, 2.5% to 25% after liver transplant, 4% to 40% after heart transplant, and 30% to 35% after lung transplant.[46] Even more alarming is that recent studies have revealed an overwhelming prevalence of impaired glucose tolerance, which is also accepted as a risk factor for long-term morbidity and mortality. NODAT is associated with a 22% higher risk of mortality. Patients with NODAT are also more likely to suffer acute rejection episodes and infectious complications.[45]

Prevention KEY CONCEPT NODAT prevention mainly consists of identifying patients at risk before transplant and controlling modifiable risk factors both before and after transplantation.[45] The major modifiable risk factors are choice of immunosuppressive therapy and body mass index (BMI). For example:

- Immunosuppressive medications: Steroid minimization and possibly withdrawal are effective strategies for preventing NODAT. Also, patients with worsening blood glucose who are receiving tacrolimus may benefit from conversion to cyclosporine or belatacept.[45]
- BMI: A reduction in body weight is recommended in obese patients prior to transplant to lower their NODAT risks.[45]

Treatment KEY CONCEPT Lifestyle modifications are recommended in patients who have developed or those who are at increased risk of developing NODAT.[45] Insulin therapy and oral hypoglycemic agents are often utilized in those patients in whom lifestyle modifications alone have not controlled blood glucose. Refer to Chapter 44, "Diabetes Mellitus," for proper instruction on choosing the appropriate treatment regimens in patients with DM.

▶ *Neoplasia*

Cancer Screening in Transplant Patients Transplant recipients are at increased risk for malignancies (Table 55–8).[47,48] The risk of developing Kaposi sarcoma following transplantation is over 200 times that in the general population. In addition, the risk of nonmelanocytic and melanocytic skin cancer is 10 to 20 times higher compared with the nontransplanted population. Transplant recipients are at greatest risk for the types of cancers associated with viral infections, such as PTLD, cervical, and vulvovaginal cancers. Solid organ tumors like colorectal and lung cancers are two to three times higher in transplant recipients when compared with the general population. The American Cancer Society and American Transplant Society recommend cancer screening for most adults who have undergone transplantation (Table 55–9).[47,48] Although clinical research has not yet proven potential benefits of testing outweigh the harms of testing in transplant recipients, most believe transplant recipients should be tested and screened very closely.[47]

Table 55–8

Overall Risk of Different Types of Cancer in Transplant Patients[47,48]

Cancer	Cumulative Incidence (per 100,000)	Male	Female
Kaposi sarcoma	140	17.4	62
Kidney/ureter	1010	14.1	14.6
Lymphoma	80	6.9	29.1
Bladder	126	1.6	3.6
Esophagus	70	2.4	2.8
Cervix	180	–	5.7
Liver	220	4.2	4.5
Melanoma	320	6.9	5.2
Lung/bronchus/trachea	690	2.3	3.6
Colorectal	510	1.6	2.8
Breast	1050	4	1.1
Prostate	1740	1.6	–

Skin Cancer Skin cancer remains the most common malignancy after transplantation. Incidence of these types of cancers increases with time posttransplant, with one study showing a prevalence rate of 35% among patients within 10 years after transplant. Also, skin cancers in transplant recipients tend to grow more rapidly and are more likely to metastasize.[47]

The most common risk factors for skin cancer development after transplant include increased age; excessive ultraviolet (UV) light exposure; high degree of immunosuppression; Fitzpatrick skin types I, II, and III; history of skin cancers; and infection by human papillomavirus.[47] KEY CONCEPT Many believe that ToR inhibitors in place of CNIs in transplant recipients can reduce risk of nonmelanoma skin carcinomas.[49]

Transplant practitioners must educate their patients about excessive exposure to the sun.[47] Patients should be warned about the risk of skin cancer and advised on simple methods to limit risk:

- Wear protective clothing (ie, long-sleeved shirts, pants, dark-colored clothing).
- Apply sunscreen, sun protection factor (SPF) 30 or higher, daily to all sun-exposed skin.

The ToR inhibitors have activity against basal and squamous cell carcinoma and should be considered in patients with a history of these malignancies or those that develop these malignancies de novo posttransplant.

▶ *Posttransplant Lymphoproliferative Disorders (PTLDs)*

KEY CONCEPT PTLDs are a major complication following organ transplantation.[47] Large series of case reports have demonstrated the incidence of PTLD is 1% for renal patients, 1.8% for cardiac patients, 2.2% for liver patients, and 9.4% for heart–lung patients. The risk of developing non-Hodgkin lymphoma is nearly 50-fold higher in organ transplant recipients compared with the general population. Another risk factor is presence of EBV. Lymphomas are the most common form of PTLD.[47,48]

Disease incidence depends on certain factors including the type of organ transplanted, age of the transplant recipient, type and degree of immunosuppression, and exposure to EBV. Mortality rate in these patients is 50%, with most dying shortly after diagnosis. It has also been demonstrated that risk of developing PTLD is greater in EBV seronegative patients.[47,48] Belatacept has a black-box warning outlining an increased risk of PTLD, especially of the CNS. Patients who are EBV seronegative or have an unknown immunity to EBV should not receive belatacept. Also, immunosuppressive regimens utilizing the ALAs have been proven to increase risk of PTLD.[47,48]

Treatment KEY CONCEPT Treatment for PTLD is still controversial; however, the most common treatment options include reduction of immunosuppression, chemotherapy, and anti–B-cell monoclonal antibodies.[47,48] PTLD continues to be a long-term complication of prolonged immunosuppression. Current treatment options are all associated with certain risks. Prevention is the most effective treatment for PTLD. A better understanding of the disease process and risk factors involved will aid in prophylaxis and treatment of this disorder.[47,48]

▶ *Pregnancy*

Women of childbearing age require adequate education on family planning and preferred forms of birth control.[50] The optimal

Table 55–9

Cancer Screening Recommendations in Transplant Patients[47,48]

Cancer Type	General Populations	Transplant Populations
Breast	Mammography every 1–2 years for all women ≥ 50 years old Clinical breast examination every 3 years in women 20–39 years old, yearly after age 40 Monthly self-examination	Mammography every 1–2 years for all women ≥ 50 years old May undergo screening between 40 and 49 years old but no evidence for or against screening in this age group
Cervical	Annual Pap smear and pelvic examination once sexually active; after three or more tests with normal results, may decrease frequency of examinations	Annual Pap smear and pelvic examination once sexually active
Colorectal	Annual FOBT plus flexible sigmoidoscopy every 5 years for all patients ≥ 50 years old or colonoscopy and DRE every 10 years	Annual FOBT plus flexible sigmoidoscopy every 5 years for all transplant patients ≥ 50 years old
Prostate	Annual DRE and PSA for men ≥ 50 years old with 10-year life expectancy or younger men at high risk	Annual DRE and PSA measurement in all males ≥ 50 years old
Hepatocellular	Not recommended for average-risk individuals α-Fetoprotein and ultrasound every 6 months in high-risk patients (no firm supporting data)	α-Fetoprotein and ultrasound every 6 months in high-risk patients (no firm supporting data)
Skin	Skin examination every 3 years between ages 20 and 40, annually thereafter	Monthly self-examination Total body skin examination every 6–12 months by dermatologists
Renal	Insufficient evidence to support routine screening	No firm recommendations Regular ultrasound of native kidneys
Lung	Insufficient evidence to support routine screening	No firm recommendations
Ovarian	Insufficient evidence to support routine screening	No firm recommendations
Testicular	Insufficient evidence to support routine screening	No firm recommendations
Endometrial	Insufficient evidence to support routine screening	No firm recommendations

DRE, digital rectal examination; FOBT, fecal occult blood test; PSA, prostate-specific antigen.

method of birth control in this population is barrier method (eg, condom, diaphragm). Use of intrauterine devices and progestin-based oral contraceptives is controversial and associated risks must be considered. Intrauterine devices may be less effective in the setting of immunosuppression and predispose patients to increased risk of infection. Progestin-based contraceptives are considered a less effective form of birth control, but may be a safe option in patients without hypertension.[50]

Those considering pregnancy after transplantation should be educated extensively regarding the potential impact of pregnancy on renal function and the risks transplantation and medical immunosuppression may present a fetus.[50] Risks to the infant include premature birth (50%) and intrauterine growth restriction (20%), which may result in death or long-term complications, including cerebral palsy, blindness, deafness, and learning deficiencies. Patients should wait at least 1 year after transplantation to ensure reconstitution of gonadal function posttransplant, as well as demonstrate 1-year freedom from acute rejection.[50]

Understanding the associated risk of immunosuppressives while pregnant is paramount considering their ability to cross the placenta, as well as enter breast milk.[50] Tacrolimus and cyclosporine, both pregnancy category C, are the backbone of immunosuppressive therapy and have been used safely and effectively in pregnancy posttransplant. Side effects associated with CNIs such as hypertension, diabetes, and nephrotoxicity should be monitored closely in the pregnant population. The ToR inhibitors are also pregnancy category C and have not been associated with fetal malformation but should be used cautiously in pregnant patients. Corticosteroids, pregnancy category B, are recognized as relatively safe and have been used extensively in pregnancy after transplantation. However, they carry a risk of premature membrane rupture and newborn adrenal insufficiency. More common side effects associated with corticosteroids that may cause complications in pregnancy include hypertension, diabetes, weight gain, and poor wound healing. Due to teratogenic effects in animal studies, azathioprine is considered pregnancy category D; however, it has been used extensively as an antimetabolite in pregnant transplant patients without extensive evidence of harm to the fetus. 6-Mercaptopurine does not cross the placental barrier.[50]

Currently, the MPA derivatives, both pregnancy category D, are not considered optimal immunosuppressive agents for patients who become pregnant, and alternative therapies should be pursued.[50] These agents have a FDA-approved risk evaluation and minimization strategy to help minimize fetal exposure to MPA, prevent unplanned pregnancies in patients using MPA, collect data on MPA use in pregnancy via the Mycophenolate Pregnancy Registry, and educate patients about the risks associated with the use of this medication. A less teratogenic antimetabolite, azathioprine, should be substituted for MPA products in patients who plan on becoming pregnant. Both belatacept and everolimus are pregnancy category C but are not recommended for use in pregnant patients due to inadequate human data.[50]

▸ *Immunosuppressant Therapy Adherence*

Transplant recipients require strict adherence to medications to ensure optimal outcomes. Nonadherence in this population is attributed to the regimen's complexity, coupled with the variability in drug dosing, need for therapeutic drug monitoring, potential DDIs, infectious risks, and drug toxicities. The incidence of nonadherence to immunosuppressant therapy in the first year posttransplant has been estimated to be as high as 23%.[51] This is alarming when 35% of all graft failures are directly attributed to nonadherence. Risk factors associated with immunosuppressant therapy nonadherence include a history of substance abuse,

Patient Encounter Part 4

The patient continues to have his posttransplant care at your cardiac transplant ambulatory care clinic. He returns to your clinic 1 month after transplant.

Labs:

Na: 142 mEq/L (mmol/L)

K: 5.6 mEq/L (mmol/L)

Cl: 195 mEq/L (mmol/L)

CO_2: 18 mEq/L (mmol/L)

BUN: 24 mg/dL (8.6 mmol/L)

SCr: 0.9 mg/dL (80 μmol/L)

Glucose: 96 mg/dL (5.3 mmol/L)

Lipid panel: total cholesterol 312 mg/dL (8.07 mmol/L); LDL-C 130 mg/dL (3.36 mmol/L); HDL-C 47 mg/dL (1.22 mmol/L); triglycerides 312 mg/dL (3.53 mmol/L)

Uric Acid: 3.4 mg/dL (202 μmol/L)

Tacrolimus: 13.5 ng/mL (mcg/L; 16.7 nmol/L)

Vitals: BP 164/95 mm Hg (162/88 mm Hg repeated); HR 96

Normal EKG

Medications:

- Tacrolimus 6 mg by mouth twice daily (goal 8-12 ng/mL [mcg/L]; 9.9-14.9 nmol/L)
- Mycophenolate mofetil 1000 mg by mouth twice daily
- Prednisone 10 mg by mouth once daily
- Atovaquone 1500 mg by mouth once daily
- Valganciclovir 900 mg by mouth once daily
- Nystatin 500,000 units swish and swallow four times daily
- Aspirin 81 mg by mouth once daily
- Pravastatin 20 mg by mouth once daily
- Furosemide 20 mg by mouth twice daily
- Levothyroxine 50 mcg by mouth once daily
- Sertraline 50 mg by mouth once daily
- Allopurinol 100 mg by mouth once daily
- Insulin glargine inject subcutaneously 20 units every night
- Insulin aspart 8 units inject subcutaneously three times daily with meals

Identify why the patient is taking each agent listed.

What are some treatment options for the patient's elevated blood pressure?

What are some treatment options for the patient's elevated cholesterol?

What are some treatment options for the patient's elevated potassium?

Design a monitoring plan for the patient's therapy.

personality disorders, and lack of social support. The role of healthcare providers in educating patients on the importance of their medication regimens and stressing the need for adherence is paramount to optimize patient and allograft survival. Previous reports have suggested intervention by a pharmacist posttransplant improves adherence.[51]

OUTCOME EVALUATION

- Successful outcomes in solid-organ transplantation are measured in terms of: (a) preventing rejection, (b) preventing drug complications, and (c) improving long-term survival.
- By accomplishing the goals listed above, transplant clinicians hope to attain good allograft function to allow for improved quality of life. These goals can be achieved through appropriate use of medical immunosuppression and scrutinizing the therapeutic and toxic monitoring parameters associated with each medication employed. In addition, transplant recipients should be monitored for adverse drug reactions, DDIs, and adherence with their therapeutic regimen.
- Long-term goals after organ transplant are to maximize functionality of the allograft and prevent the complications of immunosuppression, which lead to improved patient survival. Clinicians must play multiple roles in the long-term care of transplant recipients, as not only must the patient be followed from an immunologic perspective, but practitioners must be focused on identifying and treating adverse sequelae associated with lifelong immunosuppression including cardiovascular disease, malignancy, infection, and osteoporosis, among others. Again, limiting drug misadventures and ensuring adherence with the therapeutic regimen are important and should be stressed.

Patient Care Process

Collect Information:

- Perform a pretransplant evaluation, including taking a medication history for use of prescription, nonprescription, and complementary and alternative medications. Identify allergies to medications and other substances.
- Review all available diagnostic and laboratory data, and patient history and comorbidities to evaluate patient for transplant.
- Speak with the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and adherence and other aspects of care.

Assess the Information:

- Document current medications that should be addressed prior to a surgical procedure (eg, anticoagulation, antiplatelet therapies).

(Continued)

Patient Care Process (*Continued*)

- Identify comorbidities and how they may impact patient and allograft survival, and medication adherence.
- Review relevant laboratory tests (eg, PRA, infectious serologies of the recipient and donor).
- Evaluate current medications that will be continued posttransplant such as drugs to treat concomitant disease states (eg, hypertension, DM, dyslipidemia).
- For medications likely to be continued posttransplant, assess efficacy, safety, adherence, and any significant drug interactions with potential immunosuppressants or other medications following transplant. Are there any financial issues surrounding medications or access?
- Determine whether patient is taking any substance that could adversely affect transplant outcomes.
- Based on allergy history, determine whether the patient has compelling reasons to avoid center-specific immunosuppressants (eg, macrolide antibiotic allergy and tacrolimus) or antimicrobial prophylaxis (eg, sulfa allergy and SMZ-TMP).

Develop a Care Plan:

- Develop patient-specific short-term and long-term therapeutic goals.
- Evaluate patient-specific immunogenic risk based on donor and recipient characteristics and tissue typing at the time of transplant (eg, donor-specific antibodies, crossmatch).
- Propose an immunosuppressive regimen following transplantation, including:
  - Induction therapy (see Table 55–2):
    - Determine if patient requires induction therapy based on type of organ being transplanted and patient's immunogenic or infectious risk.
    - If induction therapy is warranted, assess for appropriate drug choice, dose, and duration of therapy and develop a monitoring plan.
  - Maintenance immunosuppressive agents (see Tables 55–2, 55–3, 55–4, and 55–5, and Figure 55–2):
    - Assess for appropriate choice, dose, and duration of therapy considering center-specific maintenance immunosuppressive policies and need for individualization based on patient's immunogenic or infectious risks.
    - Assess for eligibility to utilize a steroid withdrawal regimen, or a CNI-sparing regimen considering comorbidities or medication intolerance.
    - Assess the need for therapeutic drug monitoring and allograft function surveillance.
  - Antimicrobial prophylaxis (see Table 55–6):
    - Assess suitability of chosen prophylactic agents (eg, drug allergies, CMV donor and recipient serostatus, need for antifungal prophylaxis).
  - Medications used for comorbidities:
    - Assess appropriate selection of medications for pharmacokinetic and pharmacodynamic DDIs, need, efficacy, and side effects.
    - Determine if patient has insurance coverage and what agents are on formulary.

Implement the Care Plan:

- Educate the patient and caregiver about the organ transplant, complications associated with transplantation, need for lifestyle modifications to reduce risk of complications (eg, wear sunscreen, low-sodium diet, precautions to prevent contracting infection), drug therapy (including importance of adherence to therapeutic regimen and insurance/payer information), changes in drug therapy, medication administration, potential adverse effects, and how to manage and report adverse effects that occur.
- Address patient concerns about management of comorbidities, including medication adherence and lifestyle modifications.
- Determine whether the patient has insurance coverage or whether recommended agents are included on the institution's formulary.

Follow-up: Monitor and Evaluate:

- General therapeutic monitoring parameters based on organ transplanted and toxic monitoring parameters for medications prescribed.
- Continually evaluate the patient for presence of adverse drug reactions, drug allergies, or DDIs.
- In outpatient transplant clinic:
  - Monitor therapeutic parameters for allograft function and signs and symptoms of over- or under-immunosuppression by reviewing physical examination, lab tests, and results of other diagnostic tests.
  - Obtain a thorough history of prescription, nonprescription, and complementary and alternative medication use.
  - Monitor the patient's maintenance immunosuppression, including adherence.
  - Assess for appropriate dose, duration of therapy, and toxic monitoring parameters for all prescribed medications.
- Antimicrobial prophylaxis:
  - How long does the patient need to continue prophylaxis therapy?
- Medications used for comorbidities:
  - Assess appropriate selection of medications for pharmacokinetic and pharmacodynamic DDIs, need, and efficacy.
  - Assess for new or worsening comorbid disease and whether new medications are needed for existing comorbidities or new diagnoses.
- Reassess patient-specific short- and long-term therapeutic goals.
- Continue with patient education regarding complications associated with transplantation, need for lifestyle modifications to reduce risk of complications (eg, wear sunscreen, low-sodium diet), and drug therapy.
- Reemphasize the importance of adherence with therapeutic regimen.
- Assess improvement in quality-of-life measures such as physical, psychological, and social functioning, and well-being.

Abbreviations Introduced in This Chapter

6-MP	6-Mercaptopurine
ACE	Angiotensin-converting enzyme
aHUS	Atypical hemolytic uremic syndrome
ALA	Antilymphocyte antibodies
AMR	Antibody-mediated rejection
APC	Antigen-presenting cell
ARB	Angiotensin receptor blocker
AUC	Area under the curve
BKV	BK virus
BMI	Body mass index
BUN	Blood urea nitrogen
C_0	Trough concentration
CCB	Calcium channel blocker
$CD4^+$	Helper T-cells
$CD8^+$	Cytotoxic T-cells
CKD	Chronic kidney disease
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CNS	Central nervous system
CXR	Chest x-ray
CYP	Cytochrome P-450
DC	Dendritic cell
DDI	Drug–drug interaction
DM	Diabetes mellitus
DOE	Dyspnea on exertion
DRE	Digital rectal examination
DS	Double strength
DSA	Donor-specific antibody
e-ATG	Antithymocyte globulin equine
EBV	Epstein-Barr virus
ESRD	End-stage renal disease
FBS	Fasting blood sugar
FDA	Food and Drug Administration
FEV	Forced expiratory volume
FOBT	Fecal occult blood test
G6PD	Glucose-6-phosphate-dehydrogenase
GFR	Glomerular filtration rate
GI	Gastrointestinal
HDL-C	High-density lipoprotein cholesterol
HLA	Human leukocyte antigen
HMG-CoA	3-Hydroxy-3-methylglutaryl coenzyme A
Ig	Immunoglobulin (A, G, etc.)
IL-2	Interleukin-2
IV	Intravenous
IVIG	Intravenous immunoglobulin
LC-MS/MS	Liquid chromatography coupled to tandem mass spectrometry
LDL-C	Low-density lipoprotein cholesterol
LFT	Liver function test
MAC	Membrane attack complex
MACE	Major adverse cardiac events
MHC	Major histocompatibility complex
MPA	Mycophenolic acid
MPAG	MPA-glucurinide
NK	Natural killer
NODAT	New-onset diabetes mellitus after transplantation
NYHA	New York Heart Association
P-gp	P-glycoprotein
PRA	Panel-reactive antibodies
PSA	prostate-specific antigen
PTLD	Posttransplant lymphoproliferative disorders
PyVAN	Polyomavirus-associated nephropathy
r-ATG (RATG)	Antithymocyte globulin rabbit
SCr	Serum creatinine
SL	Sublingual
SMZ-TMP	Sulfamethoxazole-trimethoprim
SOB	Shortness of breath
SOT	Solid organ transplant
SPF	Sun protection factor
SPK	Simultaneous pancreas-kidney
SS	Single strength
TCR	T-cell receptor
TDaP	Tetanus, diphtheria, and pertussis
ToR	Target of rapamycin
TPMT	Thiopurine methyltransferase
UV	Ultraviolet

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56 Systemic Lupus Erythematosus

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader should be able to:

1. Discuss the incidence and risk factors for systemic lupus erythematosus (SLE).
2. Describe key events in the pathogenesis of SLE including contributions of genetics, hormonal, and environmental factors to the immune dysfunction.
3. Explain symptoms and signs of the disease and tissue damage associated with SLE.
4. List diagnostic criteria for SLE.
5. Recommend nonpharmacologic therapies including cognitive behavioral therapy, sun protection and smoking cessation.
6. Compare and contrast pharmacologic treatment options for SLE by their mechanisms of action, side effects, contraindications, and effectiveness.
7. Discuss the clinical manifestations and appropriate therapy used to treat the corresponding disease manifestations associated with SLE.
8. Provide a counseling plan for adjunct therapies used to treat clinical manifestations of SLE.

INTRODUCTION

Often difficult to diagnose, systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease in which the immune system attacks the body's own tissue, causing inflammation and tissue damage. A delay in definitive diagnosis can lead to delays in organ-saving treatment. SLE often involves multiple organs and is characterized by flares and periods of quiescence.

EPIDEMIOLOGY AND ETIOLOGY

The incidence and prevalence of SLE is highest in North America, with estimates at 23.2 per 100,000 person-years, and 241 cases per 100,000 people.[1] Known risk factors for SLE include demographics, genetics, and interactions with environmental triggers. **KEY CONCEPT** The strongest risk factor for SLE is gender. Nine of 10 people living with a lupus diagnosis are women,[2] and women of color are disproportionately affected. On average, women of color are two to three times more likely to have SLE and more severe disease.[2] Women of childbearing age are also most likely to be affected, with most diagnoses occurring between 15 and 44 years of age.[2] Genetics may predispose some individuals to the development of SLE after interactions with certain triggers. Normal variations in a variety of genes can increase the risk of developing SLE, and in most cases, multiple genes are involved. Environmental triggers include exposure to sunlight, infections, or exposure to certain medications (see Table 56–1).[3-5]

Lupus Phenotypes

Lupus can be characterized by three major phenotypes: chronic cutaneous lupus, SLE, and drug-induced lupus. Nearly 70% of lupus cases are categorized as SLE, a condition in which symptoms may affect any organ. Approximately 10% of persons living with lupus have chronic cutaneous lupus erythematosus, a type of lupus that only involves the skin. Another 10% of lupus cases can be characterized as drug-induced lupus, which typically resolves after withdrawal of the offending agent. Finally, the remaining 10% of cases are characterized as neonatal lupus. Neonatal lupus is often a term used to describe neonates born to mothers with SLE due to exposure to antibodies in utero and is not considered a true type of lupus. Symptoms of neonatal lupus often resolve in 6 months after birth. The term "lupus" most often refers to SLE, which is the main focus of this chapter.

PATHOPHYSIOLOGY

SLE is a chronic autoimmune disease characterized by a dysfunctional immune system as the result of autoantibody production leading to a systemic inflammatory response.[4] Autoantibodies are produced by B-cells that have lost self-tolerance and may be driven by T-cell dysfunction. Autoantibodies can form immune complexes, which are deposited into tissues causing inflammation and subsequent damage (Figure 56–1). These deposits can also be comprised of immunoglobulin (Ig) M, IgG, IgA, and complement (C). Of autoantibodies identified in patients with autoimmune diseases, antinuclear antibodies (ANA) are the most characteristic of SLE and are found in more than 95% of patients. While a positive ANA can occur in healthy individuals, titers and patterns can be used to identify various types of autoimmune conditions. SLE-specific antibodies include double-stranded DNA (dsDNA), Sjögren syndrome antigen A (SSA; Ro), Sjögren syndrome antigen B (SSB; La), Sm, DNA-histone and

Table 56–1

Medications Associated with Drug-Induced Lupus[3-5]

Definite (> 1% incidence)	Procainamide, hydralazine, D-penicillamine, minocycline, quinidine, isoniazid, methyldopa, TNFi, interferon-alpha, diltiazem (subacute cutaneous lupus rash), chlorpromazine, and practolol
Probable (incidence < 1% or > 4 case reports)	Anticonvulsants (phenytoin, carbamazepine, valproic acid, others), ethosuximide, captopril, propylthiouracil (PTU), β-adrenergic blocking agents, sulfasalazine, antimicrobials (sulfonamides, nitrofurantoin), lithium, docetaxel, hydrochlorothiazide, glyburide, amiodarone, interferon gamma, simvastatin, terbinafine, oral contraceptives, acebutolol
Possible (3–4 case reports)	Statins, clozapine, griseofulvin, mesalazine, methimazole, ticlopidine, gemfibrozil
Case reports	Aminoglutethimide, aminosalicylic acid, cefuroxime, celiprolol, chlorprothixene, cimetidine, cinnarizine, clonidine, danazol, dapsone, diclofenac, efalizumab, enalapril, futamide, fluvastatin, granulocyte colony-stimulating factors, hepatitis B vaccination, hydrazine, ibuprofen, interleukin-11, labetalol, lamotrigine, levodopa, mephenytoin, minoxidil, nafcillin, nalidixic acid, nifedipine, olanzapine, olsalazine, paclitaxel, phenelzine, phenobarbital, primidone, propafenone, quinine, rifamycin, streptomycin, sulindac, tamoxifen, verapamil, zafirlukast

TNFi, tumor necrosis factor inhibitors.

ribonucleoprotein (RNP). Autoantibody titers can fluctuate with disease activity and may be present for many years prior to clinical symptoms.

The pathologic findings of SLE can affect every organ system and manifest as inflammation, blood vessel abnormalities, and the autoantibody/immune complex deposition. Genetic predispositions paired with environmental exposures lead to immune dysregulation and subsequent autoantibody formation and deposits, along with cytokine release resulting in a chronic inflammatory state ultimately leading to irreversible organ damage over time. Inflammation can affect and damage many organs, particularly the kidneys, blood vessels, and joints, and also the heart and lungs.

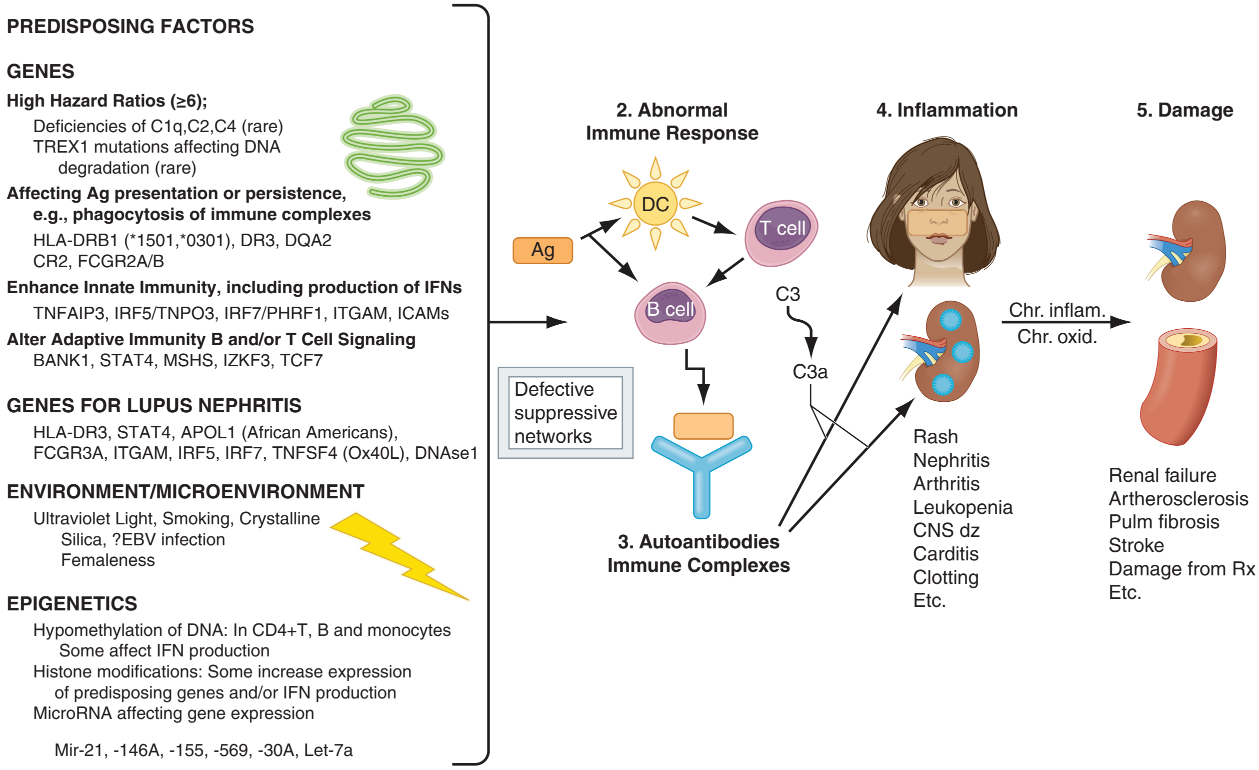

PREDISPOSING FACTORS
GENES
High Hazard Ratios (≥6);
Deficiencies of C1q,C2,C4 (rare)
TREX1 mutations affecting DNA degradation (rare)
Affecting Ag presentation or persistence, e.g., phagocytosis of immune complexes
HLA-DRB1 (*1501,*0301), DR3, DQA2
CR2, FCGR2A/B
Enhance Innate Immunity, including production of IFNs
TNFAIP3, IRF5/TNPO3, IRF7/PHRF1, ITGAM, ICAMs
Alter Adaptive Immunity B and/or T Cell Signaling
BANK1, STAT4, MSHS, IZKF3, TCF7
GENES FOR LUPUS NEPHRITIS
HLA-DR3, STAT4, APOL1 (African Americans), FCGR3A, ITGAM, IRF5, IRF7, TNFSF4 (Ox40L), DNAse1
ENVIRONMENT/MICROENVIRONMENT
Ultraviolet Light, Smoking, Crystalline Silica, ?EBV infection
Femaleness
EPIGENETICS
Hypomethylation of DNA: In CD4+T, B and monocytes
Some affect IFN production
Histone modifications: Some increase expression of predisposing genes and/or IFN production
MicroRNA affecting gene expression
Mir-21, -146A, -155, -569, -30A, Let-7a
2. Abnormal Immune Response
Ag
DC
T cell
B cell
Defective suppressive networks
C3
C3a
3. Autoantibodies Immune Complexes
4. Inflammation
Rash
Nephritis
Arthritis
Leukopenia
CNS dz
Carditis
Clotting
Etc.
Chr. inflam.
Chr. oxid.
5. Damage
Renal failure
Artherosclerosis
Pulm fibrosis
Stroke
Damage from Rx
Etc.

FIGURE 56–1. Pathogenesis of Systemic Lupus Erythematosus. Pathogenesis is related in large part to production of increased quantities and immunogenic forms of nucleic acids and other self-antigens, which drive autoimmune-inducing activation of innate immunity, autoantibodies, and T-cells. Interactions between genes, environment, and epigenetic changes drive increased autophagy, Ag presentation, neutrophil NETosis, autoantibody formation with increased plasma cells, and production of pathogenic effector T-cells in Th1, Th17, and Tfh subsets, with ineffective regulatory networks. (Ag, antigen; C1q, complement system; C3, complement component; chr, chronic; CNS, central nervous system; DC, dendritic cell; dz, disease; EBV, Epstein-Barr virus; HLA, human leukocyte antigen; IFN, interferon; inflam, inflammation; oxid, oxidation; Pulm, pulmonary; Rx, medications.) With permission from Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 20th ed. New York, NY: McGraw-Hill; 2019; and Resman-Targof BH. Systemic Lupus Erythematosus. In: DiPiro JT, Yee GC, Posey M, Haines ST, Nolin TD, Ellingrod V, eds. Pharmacotherapy: a pathophysiologic approach. 11th ed. New York: McGraw-Hill; c2020.

CLINICAL PRESENTATION AND DIAGNOSIS

SLE is a multi-organ, multi-system heterogeneous (meaning symptoms vary by patient) disease. The variability in clinical presentation and onset of symptoms often results in a delay in diagnosis. The "Clinical Presentation by Organ System and Diagnosis of SLE" textbox outlines a multitude of symptoms commonly seen as part of the clinical presentation in SLE.

Diagnosis

KEY CONCEPT Diagnosis is often difficult, as there is not one specific test for SLE. Diagnosis is made based on clinical signs and symptoms, immunologic signs and symptoms, and laboratory and other tests. The 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) Classification Criteria for SLE are outlined in Table 56–2.[6] While this

Table 56–2

Comparison of EULAR/ACR 2019 and SLICC 2012 SLE Classification Criteria

EULAR/ACR 2019 Criteria[6]		SLICC Criteria[7]
Entry criterion: ANA at a titer of ≥ 1:80 on HEp-2[a] cells or an equivalent positive test; if present, apply additive criteria		**Immunological Criteria** 1. ANA above laboratory reference range 2. Anti-dsDNA above laboratory reference range, except ELISA: twice the laboratory reference range 3. Anti-Sm 4. Antiphospholipid antibody: any of the following: lupus anticoagulant, false-positive RPR, medium or high titer anticardiolipin (IgA, IgG, or IgM), anti-β2 glycoprotein (IgA, IgG, or IgM) 5. Low complement (C): low C3, low C4, low CH50 6. Direct Coombs test in the absence of hemolytic anemia
Additive Criteria	Score	Clinical Criteria
Constitutional		N/A
Fever	2	
Hematologic		1. Hemolytic anemia
Leukopenia	3	2. Leukopenia (< 4000/mm^3 [4 × 10^9/L] at least once), or Lymphopenia (< 1000/mm^3 [1 × 10^9/L] at least once) in the absence of other causes
Thrombocytopenia	4	
Autoimmune hemolysis	4	3. Thrombocytopenia (< 100,000/mm^3 [100 × 10^9/L] at least once), in the absence of other causes
Neuropsychiatric		4. Neurologic: seizures, psychosis, mononeuritis multiplex in the absence of other causes, myelitis, peripheral or cranial neuropathy in the absence of other causes, acute confusional state
Delirium	2	
Psychosis	3	
Seizure	5	
Mucocutaneous		5. Acute cutaneous lupus including lupus malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, photosensitive rash, or subacute cutaneous lupus
Nonscarring alopecia	2	
Oral ulcers	2	6. Chronic cutaneous lupus including classical discoid rash, localized or generalized, hypertrophic lupus, lupus panniculitis, mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/lichen planus overlap
Subacute cutaneous or discoid lupus	4	
Acute cutaneous lupus	6	7. Oral ulcers: palate, buccal, tongue, or nasal ulcers in the absence of other causes 8. Nonscarring alopecia
Serosal		9. Serositis: typical pleurisy for more than 1 day, or pleural effusions, or pleural rub; typical pericardial pain for more than 1 day, or pericardial effusion, or pericardial rub, or pericarditis by ECG in the absence of other causes
Pleural or pericardial effusion	5	
Acute pericarditis	6	
Musculoskeletal		10. Synovitis involving two or more joints, characterized by swelling or effusion OR tenderness in two or more joints and 30 minutes or more of morning stiffness
Joint involvement	6	
Renal		11. Renal: urine protein/creatinine (or 24-hour urine protein) representing 500 mg protein/24 hours, or red blood cell casts
Proteinuria > 0.5 g/24 hours	4	
Renal biopsy class II or V lupus nephritis	8	
Renal biopsy class III or IV lupus nephritis	10	
Total Score	A score of 10 or more plus fulfilling the entry criterion meets a classification of SLE	Meets four of the above criteria, including at least one clinical and one immunologic criterion, OR biopsy-proven nephritis compatible with SLE and with ANA or anti-dsDNA antibodies

ACR, American College of Rheumatology; ANA, antinuclear antibody; dsDNA, double-stranded DNA; ELISA, enzyme-linked immunoassay; ECG, electrocardiogram; EULAR, European League Against Rheumatism; Ig, immunoglobulin; RPR, rapid plasma reagin; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics

[a] HEp-2: a cell that is a substrate for ANA testing that aids in the detection of ANA; ANA screening using HEp-2 cells is considered the gold standard for screening.

Clinical Presentation by Organ System and Diagnosis of SLE[6]

Constitutional	fever, fatigue, weight loss, nausea
Hematologic	thrombocytopenia, leukopenia, hemolytic anemia
Dermatologic	malar rash ("butterfly"), alopecia, oral/nasal ulcers, photosensitivity
Musculoskeletal	joint swelling, tenderness, effusions
Central nervous system	vasculitis, psychosis, seizures, memory impairment
Pulmonary	pleurisy, diffuse alveolar hemorrhage
Cardiovascular	pericarditis, endocarditis, myocarditis, Raynaud disease, vasculitis
Renal	proteinuria, nephritis

DIAGNOSIS: refer to Table 56–2 for 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) Classification Criteria for Systemic Lupus Erythematosus as well as the classification system of the Systemic Lupus International Collaborating Clinics (SLICC).[6,7]

classification criteria provide a guide for clinicians, they are designed for research purposes and may not be sensitive enough for diagnosis in mild cases. An additional classification system exists, the Systemic Lupus International Collaborating Clinics (SLICC); however, this system is often used in clinical trials and less commonly used to guide routine patient care.[7] For each system, the criteria need not be present concurrently. Renal biopsies are often done to aid in diagnosis of renal involvement.

Differentiating SLE from other rheumatologic conditions can be difficult, and overlap with other conditions may occur. This may delay diagnosis and therefore treatment. A stepwise approach may assist with applying symptoms, laboratory tests, and diagnostic criteria (Figure 56–2).

TREATMENT

Desired Outcomes

There is no cure for SLE. KEY CONCEPT Goals of therapy include reducing or eliminating flares, preventing and reducing organ damage, minimizing treatment-related adverse events, and maintaining and improving quality of life.

Nonpharmacologic Therapy

Nonpharmacologic treatments for SLE include sun protection, smoking cessation, exercise, and minimization of environmental risk factors including exposure to sunlight, infection risk, and predisposing medications. SLE causes an increase in sensitivity to ultraviolet exposure, which may worsen skin manifestations of the disease. Avoidance of exposure is ideal, although not always feasible. Sunscreen with at least 30 sun protection factor (SPF) is recommended,

Patient Encounter Part 1

A 34-year-old African American woman presents to the rheumatology clinic as a new patient consult with a chief complaint of intermittent bilateral hand pain accompanied with swelling, morning stiffness lasting an average of 45 minutes to an hour and a malar/butterfly rash. She reports working as a software engineer in a high stress environment where she sits at a desk for extended periods of time.

PMH: Hypertension, hyperlipidemia, anemia, anxiety

FH: Mother (age 62): chronic anemia secondary to ulcerative colitis, major depressive disorder; father (age 68): osteoarthritis of knees, osteoporosis, and rheumatoid arthritis; paternal aunt (age 57): SLE

SH: Married w/no children, denied alcohol and illicit drug use, current smoker (less than 1 pack per day), sedentary lifestyle

Allergies: NKDA

Medications: Lisinopril 10 mg daily, nifedipine ER 60 mg daily, atorvastatin 10 mg daily, women's multivitamin 1 tab daily

Vitals: Height 65.5 in (166.4 cm), weight 180 lb (82 kg), pulse rate 77 bpm, blood pressure (BP) 132/82 mm Hg, body mass index (BMI) 29.5 kg/m^2

Relevant Labs:

Complete blood count (CBC): WNL

Comprehensive metabolic panel (CMP): WNL (SCr 0.67 mg/dL [59 μmol/L])

Urinalysis: Protein urine levels WNL

Thyroid-stimulating hormone (TSH), triiodothyronine (T$_3$), thyroxine (T$_4$): WNL

Low C3, Low C4

(+) anti SSA/B, high titer ANA (1:160 speckled pattern), rheumatoid factor (RF), antiphospholipid antibodies, anti-dsDNA 3x upper limit of normal (ULN)

ROS:

Constitutional: (+) Fatigue

Integumentary: (+) Hair loss, photosensitivity, malar rash, skin lesion / (–) hives, nail changes, pruritus, psoriasis, and scalp tenderness

Musculoskeletal (MSK): (+) Joint pain, joint tenderness, morning stiffness, neck pain

Physical Examination:

MSK: Shoulders/elbows/knees/hips/feet, and ankles—no tenderness, swelling, effusion, or limited range of motion

Hands—Tenderness, effusion and limited range of motion in the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints

What risk factors does the patient have for SLE?

Are there any medications the patient is taking associated with drug-induced lupus? What is the incidence of drug-induced lupus associated with any identified agent(s) (definite, probable, possible, or case reports)?

What clinical manifestations presented meet SLICC Criteria for Classification of SLE versus what clinical manifestations presented meet ACR/EULAR Criteria for Classification SLE?

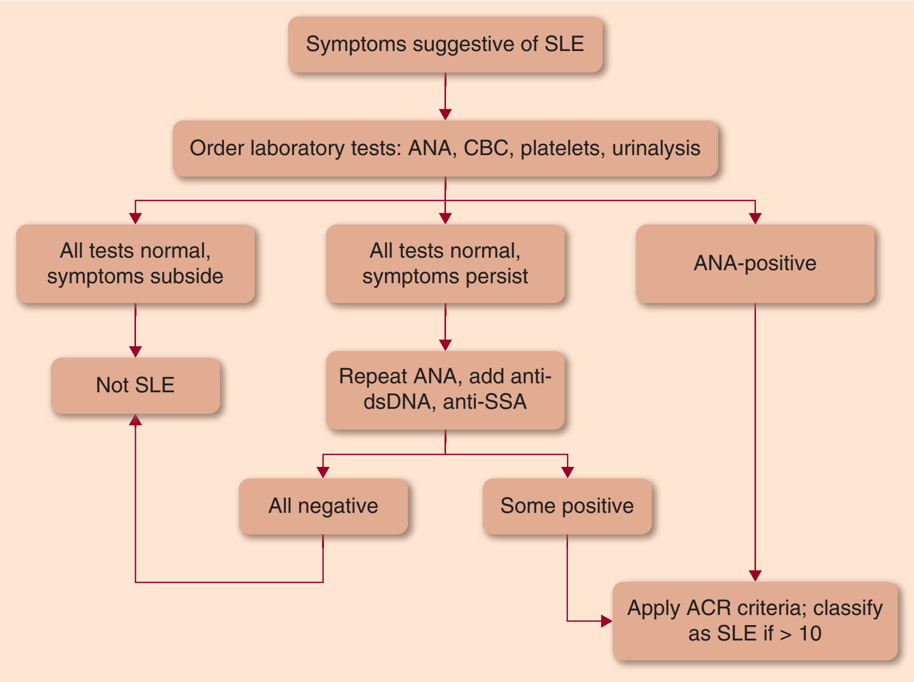

Symptoms suggestive of SLE
Order laboratory tests: ANA, CBC, platelets, urinalysis
All tests normal, symptoms subside
All tests normal, symptoms persist
ANA-positive
Not SLE
Repeat ANA, add anti-dsDNA, anti-SSA
All negative
Some positive
Apply ACR criteria; classify as SLE if > 10

FIGURE 56–2. Decision Assistance for Diagnosing SLE. (ACR, American College of Rheumatology; anti-dsDNA, antibody directed against double-stranded DNA; ANA, antinuclear antibody; CBC, complete blood count; SLE, systemic lupus erythematosus; SSA, Sjögren syndrome antigen A). Adapted from Hahn BH. Systemic lupus erythematosus. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 20th ed. New York: McGraw-Hill; 2018; and Aringer at al. 2019 EULAR/ACR classification criteria for SLE. Arthritis Rheumatol. 2019;17(9):1400-1412.

along with lip balm with at least 15 SPF.[8] Smoking has been shown to increase the risk of developing SLE,[9] and is also associated with a twofold decrease in the proportion of patients achieving improvement with antimalarials with cutaneous lupus.[10] Therefore, smoking cessation interventions should be offered to all patients with SLE. Additionally, exercise has been shown to reduce fatigue in patients with SLE[11] and has also been shown to not induce disease flares.

SLE can affect all aspects of daily life. Persons living with SLE often experience significant economic and social burdens. This can include absenteeism from work, complete inability to work, higher rates of disability, higher rates of anxiety and depression, and chronic pain.[12] Further, the impact of SLE on mental health is often overlooked. Persons with SLE are much more likely to experience depression, anxiety, and psychological impacts, and should be screened and appropriately treated for anxiety and depression as part of a multifaceted approach to care. For example, cognitive behavioral therapy has been shown to reduce daily stress, psychological symptoms, and improve quality of life.[13] Patient education and connecting patients to support groups are important aspects of nonpharmacologic treatment in SLE.

Pharmacologic Therapy

KEY CONCEPT In general, treatment of SLE is guided by organ involvement, disease severity, and childbearing potential. Fatigue is a very common symptom in SLE; however, it is important to identify and address comorbidities and/or overlapping conditions that can contribute to fatigue such as hypothyroidism, depression, and fibromyalgia. Infections are common in patients with SLE due to immune dysfunction and immunosuppressive therapies, and therefore staying up to date on immunizations such as influenza and pneumococcal can help minimize risk. Due to the increased risk of premature cardiovascular disease (CVD) in patients with SLE, reducing modifiable risk factors such as hypertension (see Chapter 6, "Hypertension"), dyslipidemia (see Chapter 13, "Dyslipidemias"), and obesity is a vital part of the treatment plan.

▶ *Acute Treatment*

Glucocorticoids are the mainstay of treatment for acute symptoms due to fast onset of anti-inflammatory action and are used in times of organ-threatening disease. Glucocorticoids exert anti-inflammatory effects by reduction of B and T lymphocyte proliferation and activation, immunoglobulin production, mononuclear cell and neutrophil migration and adhesion, and reduction of proinflammatory prostaglandins.[14] Typically oral or intravenous glucocorticoids are utilized depending on the severity of the flare, characterized by worsening of symptoms (flares can range from mild to severe and life-threatening). Intravenous steroids are the mainstay of treatment for severe, life-threatening disease flares; however, they should not be used chronically due to negative effects of long-term therapy.[15]

Adverse effects of acute glucocorticoid use include elevated blood glucose and neuropsychiatric events (insomnia, psychosis), while chronic exposure can increase the risk of osteoporosis, elevated blood pressure, weight gain, cataract development, and increased infection risk.[14] Long-term glucocorticoid use in SLE has also been associated with irreversible organ damage; prednisone daily dosages above 6 mg have been shown to increase the risk of future organ damage by 50%.[14] The optimal formulation and dose has not been identified. The lowest effective dose and duration should be used. Patients on glucocorticoids should be continually monitored for toxicities.

▶ *Nonrenal SLE*

Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)[16] is a validated assessment tool used to measure SLE

Table 56–3

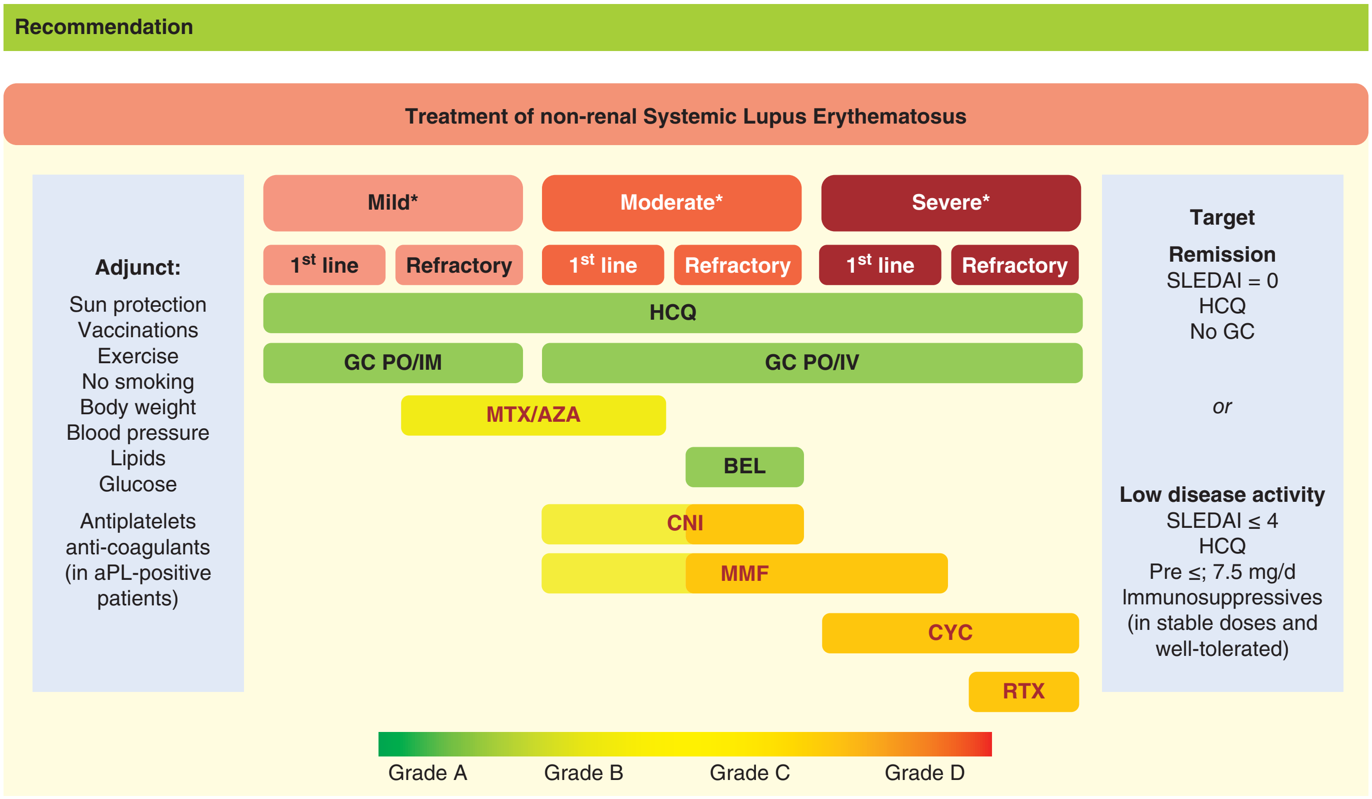
Classification of Nonrenal SLE[15-17]

	Clinical Presentation	Disease Activity Score
Mild	Constitutional symptoms, mild arthritis, rash covering ≤ 9% of BSA, platelets 50,000 to 100,000 cells/mm^3 (50 × 10^9/L to 100 × 10^9/L)	SLEDAI-2K score ≤ 6; BILAG C or ≤ 1 BILAG B manifestation
Moderate	RA-like arthritis, rash covering 9% to 18% of BSA, cutaneous vasculitis ≤ 18% of BSA, platelets 20,000 to 50,000 cells/mm^3 (20 × 10^9/L to 50 × 10^9/L), serositis	SLEDAI-2K score 7–12, or ≥ 2 BILAG B manifestations
Severe	Major organ threatening disease (nephritis, cerebritis, myelitis, pneumonitis, mesenteric vasculitis, platelets < 20,000 cells/mm^3 [20 × 10^9/L], TTP-like disease or acute hemophagocytic syndrome)	SLEDAI-2K score > 12, or ≥ 1 BILAG A manifestation

BILAG, British Isles Lupus Assessment Group; BSA, body surface area; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE disease activity index 2000; TTP, thrombotic thrombocytopenic purpura.

disease activity. Additionally, the British Isles Lupus Assessment Group (BILAG)[17] disease activity index assesses disease activity in a single organ and also provides information on multiple systems and therefore can be used as a composite score. These scoring indices are used to aid in classification of SLE disease activity as mild, moderate, and severe (Table 56–3).[15-17]

KEY CONCEPT First-line treatment of nonrenal SLE regardless of disease severity includes hydroxychloroquine with or without glucocorticoids. See Figure 56–3. Decision between the agents is based on side effect profile, comorbidities, and childbearing potential. First-line treatment for moderate nonrenal SLE may also include methotrexate or azathioprine. If refractory to the


Recommendation
Treatment of non-renal Systemic Lupus Erythematosus
Adjunct:
Sun protection
Vaccinations
Exercise
No smoking
Body weight
Blood pressure
Lipids
Glucose
Antiplatelets
anti-coagulants
(in aPL-positive patients)
Mild*
Moderate*
Severe*
1st line
Refractory
1st line
Refractory
1st line
Refractory
HCQ
GC PO/IM
GC PO/IV
MTX/AZA
BEL
CNI
MMF
CYC
RTX
Target
Remission
SLEDAI = 0
HCQ
No GC
or
Low disease activity
SLEDAI ≤ 4
HCQ
Pre ≤; 7.5 mg/d
Immunosuppressives
(in stable doses and well-tolerated)
Grade A
Grade B
Grade C
Grade D

Mild: constitutional symptoms/mild arthritis/rash ≤ 9% BSA/PLTs 50–100 × 10^3/mm^3; SLEDAI ≤ 6: BILAG C or ≤ 1 BILAG B manifestation
Moderate: RA-like arthritis/rash 9–18% BSA/cutaneous vasculitis ≤ 18% BSA; PLTs 20–50 × 10^3/mm^3/serositis; SLEDAI 7–12; ≥ 2 BILAG B manifestations
Severe: major organ threatening disease (nephritis, cerebritis, myelitis, pneumonitis, mesenteric vasculitis; thrombocytopenia with platelets < 20 × 10^3/mm^3; TTP-like disease or acute hemophagocytic syndrome; SLEDAI > 12; ≥ 1 BILAG A manifestations

FIGURE 56–3. Treatment of Nonrenal SLE. Platelet concentrations of 50 × 10^3 to 100 × 10^3/mm^3 are equivalent to 50 × 10^9 to 100 × 10^9/L; platelet concentrations of 20 × 10^3 to 50 × 10^3/mm^3 are equivalent to 20 × 10^9 to 50 × 10^9/L; and platelet concentrations less than 20 × 10^3/mm^3 are equivalent to less than 20 × 10^9 to 50 × 10^9/L. (aPL, antiphospholipid antibodies; AZA, azathioprine; BEL, belimumab; BILAG, British Isles Lupus Assessment Group; BSA, body surface area; CNI, calcineurin inhibitor; CYC, cyclophosphamide; GC, glucocorticoid; HCQ, hydroxychloroquine; IM, intramuscular; IV, intravenous; MMF, mycophenolate mofetil; MTX, methotrexate; PLT, platelet; Pre, prednisone; PO, per oral route; RA, rheumatoid arthritis; RTX, rituximab; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; TTP, thrombotic thrombocytopenic purpura). (Reproduced from Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 Update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis. 2019 Jun;78(6):736–745, with permission from BMJ Publishing Group Ltd.)

Patient Encounter Part 2

After receiving the official diagnosis of SLE during her initial visit, the patient was prescribed hydroxychloroquine 200 mg twice daily which she has been taking consistently since then. Today, she presents 11 months later for routine follow up. Her chief complaint is right elbow pain, and she is requesting a steroid joint injection. She also complains of fatigue, dry mouth, worsening arthralgias, anxiety, and stiffness. She is not interested in having children at this time, but may consider it in the next few years.

PMH: Hypertension, hyperlipidemia, anemia, anxiety

Medications: Lisinopril 10 mg daily, nifedipine ER 60 mg daily, atorvastatin 10 mg daily, women's multivitamin 1 tab daily, hydroxychloroquine 200 mg twice daily

Allergies: NKDA

Physical Examination: All normal except MSK mild swelling right elbow. Hands—Worsened tenderness, effusion and limited range of motion in the MCP and PIP joints

Vitals: Weight 185 lb (84 kg), pulse rate 73 bpm, BP 127/75 mm Hg, BMI 30.3 kg/m^2

Relevant Labs:

CBC: WNL

CMP: WNL (SCr 0.67 mg/dL [59 µmol/L])

Liver function tests (LFTs): WNL

Urinalysis: Protein urine levels 650 mg/24 hours

TSH, T_3, T_4: WNL

Low C3, low C4

Elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and RF

Intermediate thiopurine S-methyltransferase (TPMT) activity

What are the goals of therapy for this patient? What are the targets for remission and low disease activity?

What nonpharmacological lifestyle modifications can the patient be counseled on?

Develop an immunomodulator-specific treatment plan for first-line therapy for moderate nonrenal refractory SLE. Identify appropriate dosing, including considerations for renal or hepatic function, laboratory monitoring, and patient counseling regarding common side effects?

What form(s) of contraception should be considered?

combination of hydroxychloroquine plus methotrexate or azathioprine, belimumab may be added. Third-line options include a calcineurin inhibitor or mycophenolate mofetil. First-line treatment for severe nonrenal SLE includes hydroxychloroquine plus oral or intravenous (IV) glucocorticoids, mycophenolate mofetil, or cyclophosphamide. If refractory to mycophenolate mofetil, second-line treatment includes cyclophosphamide. If refractory to cyclophosphamide, third-line treatment includes rituximab.

▶ *Lupus Nephritis*

Lupus nephritis (LN) is defined as persistent proteinuria greater than 0.5 g/day or greater than 3+ by urine dipstick, and/or cellular casts including red blood cells (RBCs), hemoglobin, granular, tubular, or mixed.[18] LN is categorized into six classifications, depending on the location and degree of nephron involvement, according to the International Society of Nephrology/Renal Pathology Society (Table 56–4).[18] Class of LN guides treatment.

According to the 2012 ACR lupus nephritis guidelines,[18] treatment of LN is separated into induction therapy and maintenance therapy. Induction typically involves cyclophosphamide or mycophenolate mofetil, with or without steroids. Maintenance typically involves azathioprine, mycophenolate mofetil, or rituximab.

Classes I and II generally do not require immunosuppressive treatment. Treatment includes hydroxychloroquine with glucocorticoids at doses required to suppress activity.[18] Hydroxychloroquine is recommended for all classes of LN unless contraindicated. For classes III or IV LN (Figure 56–4), if improvements are made with induction therapy of mycophenolate mofetil, it is then continued for maintenance therapy. If improvement is not seen with mycophenolate mofetil induction, cyclophosphamide induction may be attempted. If cyclophosphamide induction leads to clinical improvement, mycophenolate mofetil or azathioprine are used for maintenance therapy. If these options do not result in clinical improvement, glucocorticoids plus rituximab or a calcineurin inhibitor may be utilized.

For class V LN (Figure 56–5), induction is first attempted with mycophenolate mofetil. If clinical improvement results, then mycophenolate mofetil or azathioprine is utilized for maintenance therapy. If improvement does not occur, then cyclophosphamide induction is attempted.

▶ *Immunomodulators*

Immunomodulators are almost always required for management of SLE. Applicable immunomodulators include antimalarial agents, immunosuppressants, and biologic agents. Choice of agent is guided by organ involvement and disease severity. Currently, the only agents that are Food and Drug Administration (FDA) approved for

Table 56–4

Lupus Nephritis (LN) Classifications[18]

Class I	Minimal mesangial LN[a]
Class II	Mesangial proliferative LN[b]
Class III	Focal LN involving < 50% of glomeruli; further subcategorized based on presence of active and/or chronic lesions
Class IV	Diffuse LN involving 50% or more of glomeruli; further subcategorized based on presence of active and/or chronic lesions
Class V	Membranous LN; may occur in combination with class III or IV
Class VI	Advanced sclerosing LN with 90% or more globally sclerosed glomeruli without residual activity

[a] Mesangial LN, mesangial cells are specialized cells that make up the mesangium of the glomerulus.

[b] Mesangial proliferative LN, also called mesangial proliferative glomerulonephritis; a form of glomerulonephritis associated primarily with the mesangium portion of the kidney.

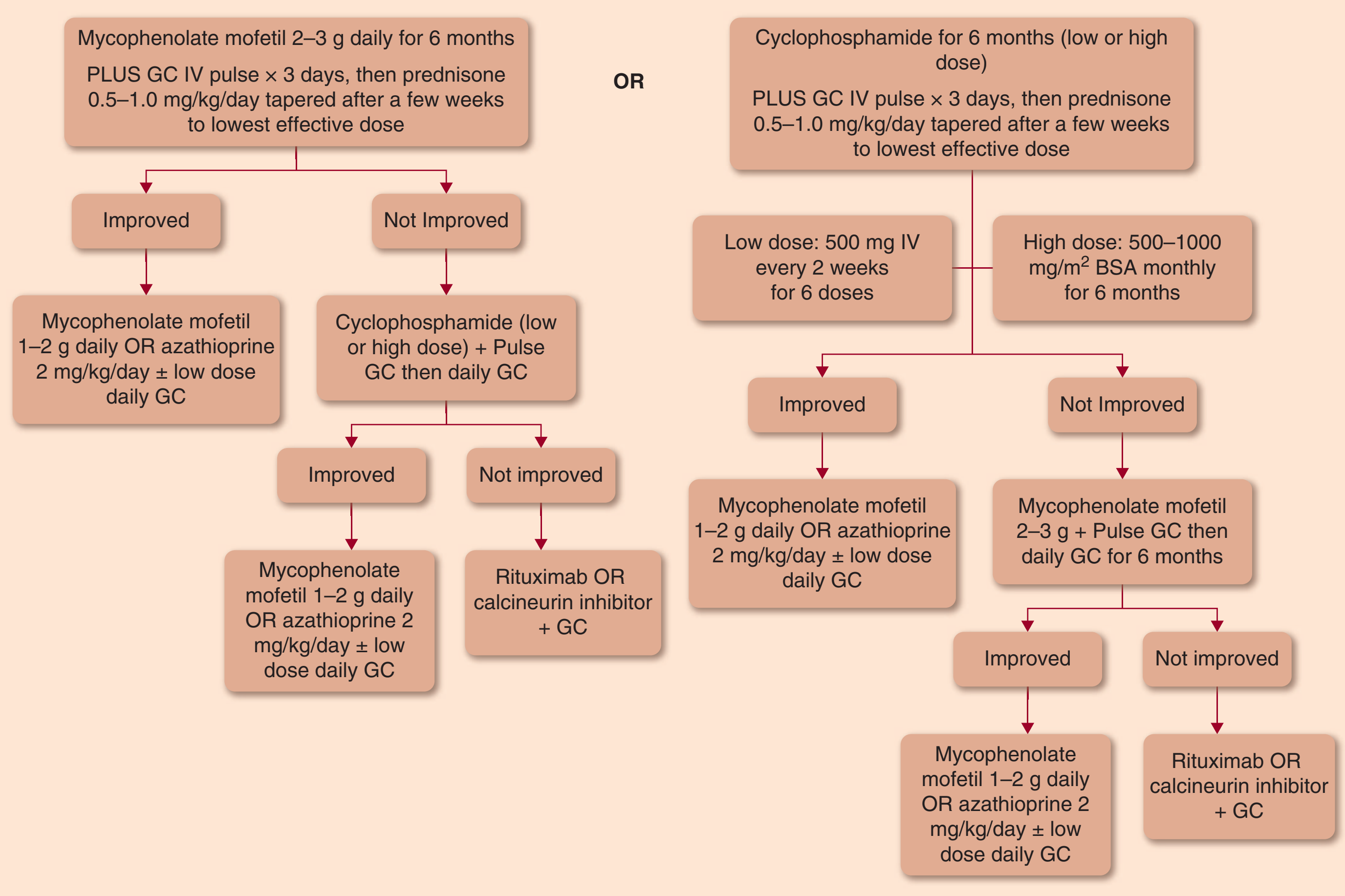

Mycophenolate mofetil 2–3 g daily for 6 months
PLUS GC IV pulse × 3 days, then prednisone 0.5–1.0 mg/kg/day tapered after a few weeks to lowest effective dose
OR
Cyclophosphamide for 6 months (low or high dose)
PLUS GC IV pulse × 3 days, then prednisone 0.5–1.0 mg/kg/day tapered after a few weeks to lowest effective dose
Improved
Not Improved
Mycophenolate mofetil 1–2 g daily OR azathioprine 2 mg/kg/day ± low dose daily GC
Cyclophosphamide (low or high dose) + Pulse GC then daily GC
Improved
Not improved
Mycophenolate mofetil 1–2 g daily OR azathioprine 2 mg/kg/day ± low dose daily GC
Rituximab OR calcineurin inhibitor + GC
Low dose: 500 mg IV every 2 weeks for 6 doses
High dose: 500–1000 mg/m2 BSA monthly for 6 months
Improved
Not Improved
Mycophenolate mofetil 1–2 g daily OR azathioprine 2 mg/kg/day ± low dose daily GC
Mycophenolate mofetil 2–3 g + Pulse GC then daily GC for 6 months
Improved
Not improved
Mycophenolate mofetil 1–2 g daily OR azathioprine 2 mg/kg/day ± low dose daily GC
Rituximab OR calcineurin inhibitor + GC

FIGURE 56–4. Induction treatment for class III or IV Lupus Nephritis. (BSA, body surface area; GC, glucocorticoid; IV, intravenous). (Adapted from Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012 Jun;64(6):797–808.)

treatment of SLE are hydroxychloroquine and belimumab. Duration of therapy varies depending on disease severity, but most patients require chronic immunomodulator therapy. Table 56–5 includes dosing and administration considerations, adverse drug reactions, contraindications, interactions, pharmacogenomics, and monitoring parameters for immunomodulators used for SLE.

Hydroxychloroquine The mechanism of hydroxychloroquine in inflammatory diseases differs from its antimalarial properties. Hydroxychloroquine accumulates in lysosomes and increases the pH, inhibiting the enzymatic degradation of proteins and organelles obtained via endocytosis, phagocytosis, or autophagy.[19] This prevents downstream presentation of autoantigens by class II major histocompatibility complexes (MHC) seen in autoinflammatory diseases. Further, hydroxychloroquine accumulates in endosomes and alters the pH of endosomes causing inhibition of Toll-like receptor (TLR) signaling, and inhibits activity of the

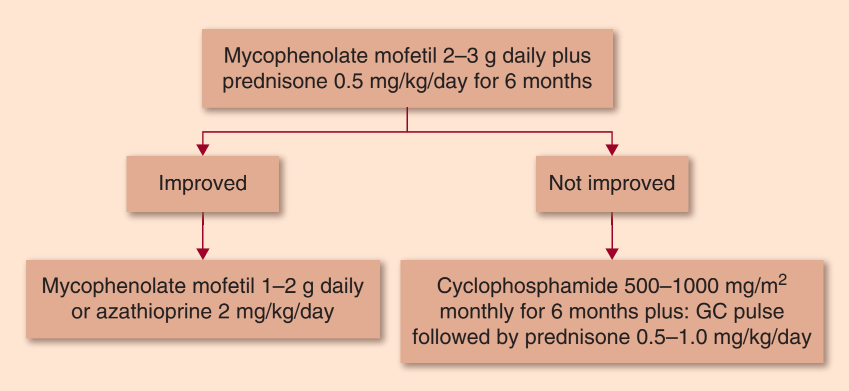

Mycophenolate mofetil 2–3 g daily plus prednisone 0.5 mg/kg/day for 6 months
Improved
Not improved
Mycophenolate mofetil 1–2 g daily or azathioprine 2 mg/kg/day
Cyclophosphamide 500–1000 mg/m2 monthly for 6 months plus: GC pulse followed by prednisone 0.5–1.0 mg/kg/day

FIGURE 56–5. Treatment of class V Lupus Nephritis. (GC, glucocorticoid). (Adapted from Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012 Jun;64(6):797–808.)

Table 56–5

Immunomodulators Used in Treatment of SLE[21-22]

Drug Name	Dosing/ Administration	Dose Adjustments for Renal or Hepatic Impairment	Adverse Drug Reactions	Contraindications	Select Drug–Drug, Drug–Food Interactions	Pharmacogenomics	Monitoring
Hydroxychloroquine	Weight Based–5 mg/kg/day actual body weight 200 mg to 400 mg PO daily; may take in divided doses	N/A	Common: retinal toxicity, N/V/D, exacerbation of psoriasis Less common/rare: hypoglycemia, QTc prolongation, abnormal LFTs, hemolysis in G6PD deficiency	Hypersensitivity	Consider therapy modification with: citalopram, cyclosporine, dapsone, digoxin, antiepileptics, haloperidol, tamoxifen Avoid concomitant use with: artemether, lumefantrine, mefloquine, remdesivir	G6PD	Retinal examination at baseline or within first year, then annually after 5 years of use, CBC, LFTs, renal function, blood glucose, ECG if at risk for Torsades de Pointes
Chloroquine	Weight-based Maximum dose of 2.3 mg/kg/day actual body weight	GFR < 10 mL/min (0.17 mL/s): administer 50% of dose	Common: retinal toxicity, hypotension, alopecia, exacerbation of psoriasis, N/V/D, pancytopenia Less common/rare: AV block, cardiac arrhythmias and failure, cardiomyopathy, Torsades de Pointes, hypoglycemia, agranulocytosis, aplastic anemia, hemolytic anemia in G6PD deficiency, hepatitis, hearing loss, tinnitus, visual disturbances	Hypersensitivity	Consider therapy modification with: ampicillin, antacids, bacampicillin, digoxin, cyclosporine, dapsone, domperidone, haloperidol, kaolin, lanthanum, QT prolonging agents Avoid concomitant use with: agalsifase, artemether, cimetidine, fexinidazole, lumefantrine, mefloquine, pimozide, remdesivir, strong CYP 3A4 inhibitors	G6PD; Substrate of CYP2C8, CYP2D6, CYP3A4	Retinal examination at baseline or within first year, then annually after 5 years of use, ECG, cardiomyopathy, blood glucose
Quinacrine	100 mg daily No longer commercially available	Unknown	Common: yellowish skin discoloration, rash, N/V/D, psychosis, restlessness, insomnia Less common/rare: hepatotoxicity, cardiac toxicity, mutagenicity, carcinogenicity, aplastic anemia, porphyria, retinopathy	Pregnancy	Unknown	N/A	CBC, LFTs, ECG, pregnancy status

(Continued)

Table 56–5

Immunomodulators Used in Treatment of SLE[21-22] (*Continued*)

Drug Name	Dosing/ Administration	Dose Adjustments for Renal or Hepatic Impairment	Adverse Drug Reactions	Contraindications	Select Drug–Drug, Drug–Food Interactions	Pharmacogenomics	Monitoring
Mycophenolate Mofetil	Induction: 2–3 g/day orally for 6 months in combination with IV pulse glucocorticoid for 3 days followed by oral prednisone Maintenance: 1–2 g/day orally	Lower doses may be required in renal impairment, though no specific adjustments have been identified Increased monitoring may be necessary in patients with hyperbilirubinemia and/or hypoalbuminemia Reduce or interrupt dose for ANC $< 1.3 \times 10^3/\text{mm}^3$ (1.3×10^9/L)	Common: hypertension, edema, hypotension, tachycardia, hyperglycemia, hypercholesterolemia, hypomagnesemia, hypokalemia, hypocalcemia, hyperkalemia, increased LFTs, infections, pain, constipation, N/V/D, dyspepsia, flatulence, cytopenias, leukocytosis, headache, insomnia, dizziness, rash, increased serum creatinine and BUN Less common/rare: thrombosis, fatigue, acne vulgaris, pruritis, gingival hyperplasia, urinary retention, malignancy, myalgias, renal insufficiency	Hypersensitivity to any mycophenolate formulation; pregnancy	Consider therapy modification with: antacids, other immunosuppressants, echinacea, estrogens, metronidazole, penicillins, probenecid, progestins, PPIs, quinolones, roflumilast, sevelamer, tolvaptan Avoid concomitant use with: BCG, bile acid sequestrants, cholestyramine, cladribine, pimecrolimus, rifamycin derivatives, upadacitinib	HPRT1; Substrate of OAT1/3, OATP1B1/1B3 (SLCO1B1/1B3), UGT1A10, UGT1A8, UGT1A9, UGT2B7	CBC, renal function, LFTs, s/sx infection, pregnancy status
Azathioprine	1.5 to 2 mg/kg/day orally in 2–3 divided doses.	CrCl 10–50 mL/min (0.17–0.83 mL/s): administer 75% of normal dose; CrCl <10 mL/min (0.17 mL/s): administer 50% of normal dose; hemodialysis: administer 50% of normal dose and supplement 0.25 mg/kg; CRRT: administer 75% of normal dose No adjustments for hepatic impairment Consider 50% dose reduction or discontinuation for persistent cytopenias	Common: N/V/D, leukopenia, thrombocytopenia, stomatitis, myalgias, hepatotoxicity, fever, infection Less common/rare: anemia, alopecia, pancreatitis, malignancy, rash, hypotension, bone marrow suppression	Hypersensitivity; concurrent use of alkylating agents	Consider therapy modification with: allopurinol, other immunosuppressants, baricitinib, echinacea, leflunomide, ribavirin, roflumilast, sulfamethoxazole, tofacitinib, warfarin Avoid concomitant use with: BCG, cladribine, febuxostat, mercaptopurine, natalizumab, pimecrolimus, upadacitinib	TPMT; NUDT15	CBC with differential weekly during first month, twice monthly for months 2–3, and monthly thereafter; T Bili, CrCl, LFTs, s/sx infection and malignancy

Cyclophosphamide	High dose: 500–1000 mg/m^2 BSA IV monthly × 6 months Low Dose: 500 mg IV every 2 weeks × 6 doses *cycles can be repeated every 3 months at provider discretion	No adjustments noted in the product labeling; however, alternative sources suggest adjustments	Common: alopecia, abdominal pain, N/V/D, anorexia, stomatitis, amenorrhea, oligospermia, sterility, cytopenias, bone marrow suppression, infection Less common/rare: confusion, blurred vision, dizziness, rash, hemorrhagic cystitis	Hypersensitivity, urinary outflow obstruction	Consider therapy modification with: allopurinol, amiodarone, anthracyclines, azathioprine, baricitinib, clozapine, other immunosuppressants, dabrafenib, deferiprone, echinacea, filgrastim, fingolimod, leflunomide, lenograstim, lipegfilgrastim, palifermin, roflumilast, succinylcholine, tofacitinib Avoid concomitant use with: abametapir, BCG, belimumab, cladribine, dipyrone, etanercept, natalizumab, pimecrolimus, tacrolimus, upadacitinib	Substrate of CYP2A6, CYP 2B6, CYP 2C19, CYP 2C9, CYP 3A4	CBC with differential, BUN, urinalysis, BMP, pregnancy status, s/sx hemorrhagic cystitis, toxicities
Methotrexate	Initial: 7.5 mg once weekly, can be increased by 2.5 mg every 2–4 weeks to a maximum of 25 mg weekly. Take with daily folic acid	No dose modifications for renal or hepatic impairment recommended in manufacturer labeling; alternative sources suggest dose reductions in patients with renal dysfunction	Common: increased liver enzymes, alopecia, skin photosensitivity, rash, N/V/D, stomatitis, oligospermia, thrombocytopenia, infection Less common/rare: leukopenia, pancytopenia, dizziness, headache, blurred vision, tinnitus	Hypersensitivity; breastfeeding; pregnancy; alcoholism; chronic liver disease; preexisting bone marrow suppression, leukopenia, thrombocytopenia, or anemia	Consider therapy modification with: alcohol, baricitinib, clozapine, other immunosuppressants, deferiprone, dexketoprofen, echinacea, fingolimod, lenograstin, levetiracetam, lipegfilgrastim, loop diuretics, nivolumab, palifermin, penicillins, probenecid, PPIs, roflumilast, salicylates, sulfonamide antibiotics, tofacitinib, tolvaptan, trimethoprim Avoid concomitant use with: acitretin, BCG, cladribine, dichlorphenamide, dipyrone, foscarnet, natalizumab, nitrous oxide, pimecrolimus, tacrolimus	Substrate of BCRP/ ABCG2, OAT1/3, OATP1B1, Pg-P	Pregnancy status, CBC with differential, serum creatinine, BUN, LFTs, Hepatitis B and C serology, TB testing

(*Continued*)

Table 56–5

Immunomodulators Used in Treatment of SLE[21-22] (*Continued*)

Drug Name	Dosing/ Administration	Dose Adjustments for Renal or Hepatic Impairment	Adverse Drug Reactions	Contraindications	Select Drug–Drug, Drug–Food Interactions	Pharmacogenomics	Monitoring
Tacrolimus	2–8 mg/day, may be taken once or twice daily Take with or without food, just be consistent	N/A Lower starting doses may be required in severe hepatic impairment	Common: cardiac arrhythmias, DVT, ECG abnormalities, flushing, hypertension, hypotension, orthostatic hypotension, edema, agitation, anxiety, depression, fatigue, headache, hallucination, psychosis, alopecia, rash, pruritus, acne vulgaris, urticaria, photosensitivity, hyperglycemia, altered electrolytes, new onset diabetes mellitus, weight gain, N/V/D, GERD, cystitis, anemia, cytopenias, hepatotoxicity, infections, myalgias, tremor Less common/rare: hemorrhage, hot flashes, skin hyperpigmentation, neuropathy, pancreatitis, cardiomyopathy, weight loss	Hypersensitivity	Consider therapy modification with: alcohol, ACE inhibitors, ARBs, baricitinib, chloramphenicol, clozapine, colchicine, CYP3A4 inducers, CYP3A4 inhibitors, dabratenib, deferiprone, dronedarone, echinacea, enzalutamide, fingolimod, fluconazole, haloperidol, itraconazole, ketoconazole, leflunomide, mitotane, nivolumab, posaconazole, PPIs, ritonavir, roflumilast, St John's wort, stiripentol, tofacitinib Avoid concomitant use with: abametapir, BCG, cladribine, conivaptan, cyclosporine, dipyrone, eplerenone, foscarnet, fusidic acid, grapefruit juice, idelalisib, lasmiditan, mifamurtide, mifepristone, natalizumab, nelfinavir, protease inhibitors, pimecrolimus, saquinavir, sirolimus, temsirolimus, upadacitinib	Substrate of CYP 3A4 and P-gp	Renal function, LFTs, serum magnesium, BMP, BP; Trough whole blood concentrations (optimal level for SLE unknown)
Belimumab	Initial: 10 mg/kg IV every 2 weeks × 3 doses, or 200 mg SC weekly Maintenance: 10 mg/kg IV every 4 weeks, or 200 mg SC weekly	N/A	Common: N/V/D, hypersensitivity reaction, infection, psychiatric disturbances, infusion reactions, injection site reactions, anxiety, depression, headache, insomnia, leukopenia, fever Less common/rare: bradycardia, myalgia, angioedema, anaphylaxis	Hypersensitivity	Consider therapy modification with: echinacea, fingolimod, leflunomide, nivolumab, roflumilast Avoid concomitant use with: BCG, biologic DMARDs, cladribine, cyclophosphamide, natalizumab, pimecrolimus, tacrolimus, upadacitinib	N/A	s/sx hypersensitivity and infusion reactions; s/sx infections; mood changes, worsening of depression, suicidal thoughts

Rituximab	375 mg/m^2 BSA IV weekly × 4 doses OR 1000 mg IV on days 0 and 15 OR 500–1000 mg IV on days 1 and 15	N/A	Common: flushing, hypertension, peripheral edema, night sweats, pruritis, rash, hypophosphatemia, weight gain, N/V/D, pain, cytopenias, increased LFTs, angioedema, infections, fatigue, headache, insomnia, neuropathy, arthralgia, asthenia, cough, epistaxis, pulmonary toxicity, fever, PML, infusion reactions (premedicate with acetaminophen and antihistamine) Less common/rare: anemia, hepatotoxicity, hypogammaglobulinemia	None listed in labeling	Consider therapy modification with: clozapine, deferiprone, echinacea, fingolimod, leflunomide, nivolumab, roflumilast Avoid concomitant use with: BCG, belimumab, biologic DMARDs, cladribine, dipyrone, natalizumab, pimecrolimus, tacrolimus	MS4A1 (CD20 antigen)	CBC with differential, BMP, renal function, BP, fluid/hydration status, s/sx hypersensitivity and infusion reactions, HBV and HCV screening prior to initiation

ACE, angiotensin-converting enzyme; ANC, absolute neutrophil count ; ARB, angiotensin receptor blocker; AV, atrioventricular; BCG, Bacille Calmette Guerin; BMP, basic metabolic panel; BP, blood pressure; BSA, body surface area; BUN, blood urea nitrogen; CBC, complete blood count; CrCl, creatinine clearance; CRRT, complete renal replacement therapy; CYP, cytochrome P450; DMARD, disease-modifying antirheumatic drugs; DVT, deep vein thrombosis; ECG, electrocardiogram; G6PD: glucose 6 phosphate dehydrogenase; GERD, gastroesophageal reflux disease; GFR, glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; IV, intravenous; LFT, liver function test; NUDT15, nucleotide diphosphatase; N/V/D, nausea/vomiting/diarrhea; PO, per oral; P-gp, P-glycoprotein; PML, progressive multifocal leukoencephalopathy; PPI, proton pump inhibitor; QTc, corrected QT interval; SC, subcutaneous; SLE, systemic lupus erythematosus; s/sx, signs and symptoms; TB, tuberculosis; T Bili, bilirubin test; TPMT, thiopurine S-methyltransferase.

nucleic acid sensor cGMP-AMP synthase (cGAS) by interfering with its binding to cytosolic DNA. By preventing TLR signaling and inhibiting cGAS-stimulator of interferon genes signaling, the production of proinflammatory cytokines is reduced.

Hydroxychloroquine is considered first-line for all degrees of SLE disease severity. It has been shown to significantly reduce disease activity, prevent flares, and allows for reduction of corticosteroid doses.[20] Notably, hydroxychloroquine also is the only therapy that has been shown to prolong survival. It may also protect against irreversible organ damage, although evidence is not definitive. It is also safe to use during pregnancy, and has been shown to reduce transmission of autoantibodies to the fetus, therefore reducing risk of neonatal heart block. It is well tolerated with the most common adverse event being nausea and mild gastrointestinal upset which usually subsides after a few weeks of therapy.

Long-term (> 20 years) and high-dose hydroxychloroquine use may be limited by risk of retinal toxicity, which may lead to permanent vision loss (Table 56–5).[21,22] The mechanism of retinopathy is thought to be due to impaired lysosomal degradation of photoreceptor outer segments by the retinal pigment epithelium.[23] Predictors of retinopathy from hydroxychloroquine include doses above 5 mg/kg of actual body weight, long-term use, concurrent tamoxifen use, and preexisting kidney disease.[23,24] In one study, the risk of retinal toxicity remained less than 2% within the first 10 years of use, but rose to almost 20% after 20 years of use.[24] Baseline fundal examinations and annual visual field testing with spectral domain optical coherence tomography (SD-OCT) after 5 years of use are recommended for patients using hydroxychloroquine.[25] If definitive signs of retinopathy are found, hydroxychloroquine should be discontinued.

In patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, use of hydroxychloroquine is cautioned due to risk of hemolytic anemia.[21] Strong evidence for this association, however, is lacking. Screening for G6PD deficiency is not routinely completed prior to hydroxychloroquine initiation.

Chloroquine Chloroquine, also an antimalarial, is a 4-aminoquinoline.[21] The exact mechanism of action in SLE is unknown; however, it may exert its effect by lowering the production of proinflammatory cytokines, specifically interleukin (IL)-6, IL-18, and tumor necrosis factor (TNF)-α, significantly after 4 months of use.[26] It has been shown to reduce required prednisone doses and prevent disease flares by approximately 4.6 times compared to prednisone alone.[27]

Chloroquine use is limited by retinal and cardiovascular toxicities and has largely been replaced by hydroxychloroquine due to superior safety profile. It is associated with more retinal toxicities than hydroxychloroquine. In a study comparing retinopathy in users of chloroquine versus hydroxychloroquine, six of 31 (19%) persons on chloroquine developed retinopathy while none of the 66 hydroxychloroquine users did.[28] Risk factors identified for retinal toxicity in chloroquine use include renal impairment, age, and chloroquine dose.[28,29] As with hydroxychloroquine, patients using chloroquine should undergo baseline fundal examinations and annual visual field testing with SD-OCT after 5 years of use.[25] If definitive signs of retinopathy are identified, chloroquine should be permanently discontinued.

Long-term use of chloroquine is also known to cause cardiac toxicities, including cardiomyopathy and conduction disorders.[21] Chloroquine use is cautioned in persons with G6PD deficiency due to risk of hemolytic anemia.

Quinacrine Quinacrine, also known as mepacrine, is an acridine derivative with a long history of treatment for malaria. The exact mechanism of action in SLE is unknown. Quinacrine has shown some benefit in treating SLE, but is no longer commercially available in the United States. In rare cases, it is compounded. Given its use is limited by availability, quinacrine is replaced by other commercially available antimalarials. However, it may be used at 100 mg per day as add-on therapy to lower doses of hydroxychloroquine or chloroquine to maximize effect of antimalarial drugs while minimizing the risks of retinopathy, particularly in skin manifestations of lupus.[22]

Quinacrine is not without toxicities. No formal pharmacologic safety studies have been performed, although quinacrine has shown possible cardiac and hepatic toxicities in rats, and cancers of the female reproductive tract when used intrauterinely for female sterilization.[22] It is also known to cause fetal demise, aplastic anemia, and psychosis. Quinacrine has been associated with yellow discoloration of the skin.

Mycophenolate Mofetil Mycophenolate inhibits inosine monophosphate dehydrogenase, which inhibits de novo guanosine nucleotide synthesis.[21] B and T lymphocytes are dependent on this pathway for proliferation. Mycophenolate is available as mycophenolate mofetil (trade name: CellCept) and mycophenolate sodium (trade name: Myfortic). These formulations are not equivalent and are not interchangeable. Mycophenolate mofetil is more commonly used and studied in SLE compared to mycophenolate sodium. However, better gastrointestinal tolerability is seen with mycophenolate sodium compared to mycophenolate mofetil.

Mycophenolate mofetil is useful as induction therapy or maintenance in LN, subacute cutaneous disease, and disease refractory to other agents, although has not shown benefit in neuropsychiatric disease. Comparative data of mycophenolate mofetil and azathioprine are conflicting. Mycophenolate has been shown to be superior to azathioprine at reducing flares and achieving remission with lower rates of adverse events.[30] Despite these differences, another trial found no significant differences in time to renal flare.[31] Azathioprine, however, is often preferred in women of childbearing age due to the risk of teratogenicity with mycophenolate mofetil. Mycophenolate mofetil is preferred over cyclophosphamide due to its safety profile and ease of administration. Mycophenolate mofetil has lower incidence of anemias compared to cyclophosphamide; however, mycophenolate mofetil requires dose titration due to gastrointestinal tolerability, specifically diarrhea.

Rates of response to LN induction therapy with mycophenolate mofetil or IV cyclophosphamide were compared based on race.[32] Response rates were similar in Asian and White patients, but differed in Black and Hispanic groups. Black and Hispanic patients had better treatment response to induction with mycophenolate mofetil compared to IV cyclophosphamide.

Azathioprine Azathioprine is an imidazolyl derivative of mercaptopurine; metabolites are incorporated into replicating DNA, halting DNA replication, and blocking the pathway for purine synthesis.[21] Azathioprine is a prodrug that is metabolized to 6-mercaptopurine (6-MP). Activation of 6-MP occurs via hypoxanthine-guanine phosphoribosyltransferase (HGPRT) and a series of processes involving kinases to form 6-thioguanine nucleotides (6-TGN) as major metabolites. 6-TGN incorporation into DNA is at least partly responsible for azathioprine's cytotoxicity. 6-MP is inactivated by two major routes: methylation by thiopurine S-methyltransferase (TPMT) to form an inactive metabolite methyl-6-MP, and oxidation by xanthine oxidase (XO) to form 6-thiouric acid (6-TG). The nucleotide diphosphatase (NUDT15) enzyme converts 6-TGN to inactive monophosphates.

Genetic polymorphisms in TPMT and NUDT15 causing reduced activity may lead to significant exposure to 6-TGN, and therefore increased risk of toxicities at usual doses of azathioprine or mercaptopurine. Pharmacogenomic testing is available to determine TPMT and NUDT15 activity. Patients with low or intermediate TPMT activity are at risk for significant bone marrow suppression due to potentially toxic 6-TGN levels on standard doses of azathioprine or mercaptopurine; lower doses or alternative therapies may be required. Prior to use of azathioprine, testing of TPMT and NUDT15 activity should be considered to guide dosing and treatment decision making.

Inhibition of XO may cause increased plasma concentration of azathioprine and metabolites. If a patient does not have detectable levels of the active metabolites, a xanthine oxidase inhibitor may be added to drive metabolism of 6-MP through the HGPRT and TPMT pathways. Alternatively, xanthine oxidase inhibitor use may potentiate toxicities. Historically, it was recommended to decrease the azathioprine dose by half or one-third when used in combination with a xanthine oxidase inhibitor; however, this may not be necessary with close monitoring of metabolites and symptoms of toxicities (hematologic toxicities, nausea, and vomiting). Once metabolite levels are stable, periodic monitoring of CBC to identify myelosuppression should occur.

Azathioprine is often considered for use in SLE patients with poor symptomatic control with glucocorticoids and hydroxychloroquine, or when hydroxychloroquine alone is unlikely to be sufficient. It can also be used to treat severe disease in pregnancy. Azathioprine is used for maintenance treatment of nephritis after induction with cyclophosphamide or mycophenolate mofetil.

Cyclophosphamide Cyclophosphamide is an alkylating agent that prevents cell division by cross-linking DNA strands and decreasing DNA synthesis, leading to cell death.[21] Cyclophosphamide is administered by IV infusion for SLE. Cyclophosphamide is typically reserved for use in severe organ-threatening disease or as rescue therapy for refractory nonmajor organ manifestations due to toxicities. Toxicities include hemorrhagic cystitis, bone marrow suppression, gonadal toxicities causing male and female infertility, teratogenicity, hyponatremia, and increased risk of malignancy.

Hydration before, during, and after IV infusion of cyclophosphamide, and use of mesna may help lower the risk of hemorrhagic cystitis. Shorter courses of cyclophosphamide may not cause infertility. A major risk factor for toxicities is the cumulative dose. Dosing approaches have been developed to minimize overall exposure.

A multicenter, prospective, randomized trial (Euro-Lupus Nephritis Trial) compared outcomes after low- and high-dose cyclophosphamide induction dosing in 90 patients with SLE and glomerulonephritis.[33] Patients assigned to the high-dose group received monthly infusions of cyclophosphamide for 6 months followed by two quarterly infusions. The initial dose was 0.5 g/m^2 body surface area (BSA), and was increased to a maximum of 1500 mg per dose depending on white blood cell (WBC) nadir (lowest point) on day 14. Patients assigned to the low-dose group received fixed-dose infusions of 500 mg every 2 weeks for a cumulative dose of 3 g. In both treatment arms, azathioprine was initiated 2 weeks after the last cyclophosphamide dose for maintenance treatment. After a median of 41 months, 20% of patients in the high-dose group and 16% in the low-dose group experienced treatment failure. Reasons for failure were defined as an absence of primary response, emergence of a glucocorticoid-resistant flare, and doubling of the serum creatinine level. Outcomes were comparable between groups, while rates of infection were lower in the low-dose group, although not statistically significant. Based on this trial and concerns with toxicities, some clinicians prefer to use low-dose cyclophosphamide.

Methotrexate Methotrexate irreversibly binds to and inhibits dihydrofolate reductase and thymidylate synthestase, inhibiting the formation of reduced folates, purine, and thymidylic acid, resulting in inhibition DNA synthesis, repair, and cellular replication.[21] Methotrexate use is often limited to joint or mucocutaneous involvement, as it is not particularly helpful for SLE with major organ involvement. A systematic review found that methotrexate has been shown to reduce disease activity and average dose of corticosteroids.[34] Similar to utilization in other rheumatic diseases, methotrexate is administered once weekly either orally or subcutaneously, along with daily folic acid supplementation to minimize toxicities, such as anemia, elevated liver function test, nausea, and mucositis.

Tacrolimus Tacrolimus inhibits T lymphocyte activation, although the exact mechanism in SLE is unknown.[21] Use of tacrolimus is typically reserved for patients with LN that is refractory to mycophenolate and cyclosporine. When added to prednisolone for induction therapy, response to tacrolimus was noninferior to mycophenolate mofetil.[35] Over time, the tacrolimus group had numerical trends toward more renal flares and renal function decline. Tacrolimus requires frequent laboratory monitoring due to adverse events, such as electrolyte disturbances, anemia, hyperglycemia, renal abnormalities, and hepatotoxicity.

Belimumab Belimumab is an IgG1-lambda monoclonal antibody that prevents the survival of B lymphocytes by blocking the binding of soluble B lymphocyte stimulator protein (BLyS) to receptors on B lymphocytes. This reduces the activity of B-cell–mediated immunity and the autoimmune response.[21] It was FDA approved for treatment of SLE in 2011, and in 2021 for treatment of LN. Belimumab is indicated for use in seropositive SLE in combination with other immunomodulatory medications. Belimumab is well tolerated as an infusion or injection therapy with the most common side effects being mild leukopenia and risk of worsening depression.

Belimumab was studied as add-on therapy to stable immunosuppressive or antimalarial treatment in a randomized, multicenter, placebo-controlled, phase 3 trial and a corresponding continuation study in patients with anti-ANA or anti-dsDNA positivity.[36,37] Patients who received belimumab had improvements in disease severity, reduction in flares, and improvement in physician global assessment compared to placebo. Rates of severe adverse events were comparable. Notably, LN patients who were pregnant were excluded from these studies. Additionally, Black Americans represented only about 4% of study participants.

Subsequently, belimumab was studied as add-on therapy specifically in patients with autoantibody positive, biopsy-confirmed active LN.[38] Significantly more patients in the belimumab group met the primary endpoint of primary efficacy renal response, a composite defined as estimated glomerular filtration rate (eGFR) greater than or equal to 60 mL/min/1.73 m^2 BSA or no decrease in eGFR from preflare of greater than 20%, urinary protein to creatinine ratio of greater than or equal to 0.7, and not defined as a treatment failure.[38] Adverse events were similar between groups.

Finally, due to previous underrepresentation of Black Americans in belimumab trials, a randomized, multicenter, double-blind, placebo-controlled trial was conducted in adults with SLE who self-identified as Black.[39] Patients received standard of care plus either belimumab or placebo. Numerical trends favoring belimumab, although not statistically significant, were observed in disease response. When stratified by disease activity, a significant improvement was seen in patients with high disease activity. Adverse events and study withdrawals were similar between groups.

Rituximab Rituximab is a monoclonal antibody that binds to the CD20 antigen on B-lymphocyte cell surface, activating complement-dependent B-cell cytotoxicity, and to human Fc receptors, mediating cell killing through an antibody-dependent cellular toxicity.[21] Rituximab is not FDA approved for SLE and has shown conflicting results in clinical trials. A trial comparing add-on therapy with rituximab versus placebo in patients with moderate to severe SLE already receiving prednisone plus azathioprine, mycophenolate mofetil, or methotrexate was conducted.[40] No differences were seen between the treatment arms in clinical response. Safety and tolerability were similar between groups. A subgroup analysis comparing pooled African American and Hispanic patients to other ethnic groups found an improvement in clinical response in this group.

Rituximab increases the risk of hypogammaglobulinemia and subsequent infections. In one study, 19.3% of patients who had normal IgG levels prior to rituximab treatment developed mild to severe hypogammaglobulinemia after rituximab, while 22.4% of patients with preexisting mild to moderate hypogammaglobulinemia worsened after rituximab.[41] Additional therapy-limiting safety issues include immunosuppression, progressive multifocal leukoencephalopathy (PML), and infusion reactions. Due to conflicting results and safety issues, rituximab is therefore often reserved for persons refractory or intolerant to conventional therapies.

Dihydroepiandrosterone Dihydroepiandrosterone (DHEA) is an androgenic adrenal steroid available as a supplement and not evaluated by the FDA. Evidence in SLE is conflicting. A multicenter, randomized, double-blind and placebo-controlled trial in adult women with mild to moderate SLE found no significant difference in disease activity scores, but did show a significant difference in numbers of patients that experienced a flare during treatment, and patient global assessment.[42] Adverse events of DHEA included increased testosterone levels and acne. A small, open-label, noncontrolled trial of patients with mild to moderate SLE reported significant improvements in disease activity, patient global assessment, physician global assessment, and reductions in prednisone doses as compared to baseline.[43] Similar adverse events were observed in this trial.

▶ *Drugs in the Pipeline*

Multiple therapies are currently being studied for SLE treatment. Treatment targets include janus kinase, type 1 interferon, BLyS, antiproliferating-inducing ligand (APRIL), CD20, and CD22. In April 2020, the FDA granted fast-track designation to telitacicept, a recombinant transmembrane activator, calcium modulator, and cyclophilin ligand interactor fusion protein that operates by targeting and neutralizing BLyS and APRIL. In July 2020, a New Drug Application was filed for voclosporin, a potential treatment for LN. It was FDA approved for treatment of LN under the trade name Lupkynis in January 2021.

Treatment of Complications

Due to multi-organ involvement, complications of SLE frequently occur. Common complications include cardiovascular, pregnancy, renal impairment, pulmonary, and musculoskeletal. Persons with SLE also experience social and economic complications.

▶ *Cardiovascular Complications*

KEY CONCEPT Approximately 10% to 15% of people diagnosed with lupus will die prematurely due to cardiovascular complications of SLE.[44] Inflammation as well as treatments for SLE contribute to cardiovascular risk factors, including hypertension, hyperlipidemia, elevated blood glucose, and thromboembolic risk.

Treatment targeted to minimize atherosclerotic and cardiovascular complications in SLE are the same as treating that disease state. Interventions are targeted at meeting and maintaining blood pressure and lipid goals, according to the applicable guidelines (refer to Chapter 6, "Hypertension," and Chapter 13, "Dyslipidemias"). Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) may be particularly useful in the setting of hypertension or proteinuria. Hydroxychloroquine has been shown to reduce total cholesterol, very-low-density lipoprotein (VLDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, and increase high-density lipoprotein (HDL) cholesterol, even in patients on corticosteroid therapy.[20]

Antiphospholipid syndrome (APS) is the association of thrombosis and/or pregnancy morbidity with antiphospholipid antibodies (aPL). Approximately 30% to 40% of persons with SLE are positive for aPL.[45] This increases the risk of thromboembolism by twofold compared to persons with SLE without aPL. Warfarin is the recommended treatment of acute venous thromboembolism in SLE patients with APS. When compared to warfarin, rivaroxaban was associated with higher rates of thromboembolism and major bleeding.[46] Exposure to hydroxychloroquine has been associated with the prevention thrombotic events.[20]

Primary thromboprophylaxis in patients with SLE and positive lupus anticoagulant or isolated persistent aPL at medium to high titers receive hydroxychloroquine and low-dose aspirin.[47] Patients with definite APS and a first venous event are recommended to receive oral anticoagulation with warfarin with a target INR of 2 to 3. Consensus on recommendations for patients with definite APS and a first arterial event were not reached. Indefinite anticoagulation therapy is recommended in patients with definite APS and thrombosis. Anticoagulation limited to a duration of 3 to 6 months may be considered in patients with a low-risk aPL profile and a known transient cause.

▶ *Pregnancy Complications*

KEY CONCEPT Women with SLE are at a higher risk of experiencing difficulty conceiving, miscarriage, stillbirth, and preeclampsia. Women who are aPL-positive are more likely to experience thromboemboli during pregnancy that can be life-threatening to the mother and the fetus. Due to fluctuating hormone levels, women often experience a disease flare during pregnancy. It is imperative that high-risk obstetric specialists are involved early and throughout the pregnancy. It is recommended that women work with their rheumatologist and obstetrician to plan pregnancies. Due to risk of teratogenicity and adverse effects on pregnancy associated with some medications used in SLE, careful selection of immunomodulators may need to be considered prior to conception. Pregnancy outcomes are best when conception occurs during a period of remission. Pregnancy morbidity is more common in women with SLE, particularly those with aPL positivity. This makes contraception and pregnancy planning of particular importance.

Contraception Estrogen use is an independent risk factor for cardiovascular events. Use of estrogen-containing

Table 56–6

Effectiveness and Safety of Contraceptive Options in Women with SLE[48]

	Method	Safety in SLE
Highly effective	Copper IUD Progestin IUD	Safe in all women with SLE
	Progestin Implant	Limited data but likely safe in all women with SLE
Effective	Progestin-only pill	Safe in all women with SLE
	Depo medroxyprogesterone acetate	Avoid in positive aPL, or high risk of osteoporosis
	Combined estrogen and progestin pill	Avoid in moderate to severe SLE, or positive aPL
	Transdermal patch Estrogen ring	Avoid in SLE or positive aPL
Less effective	Diaphragm Condom Fertility-awareness tracking Spermicide	Safe in all women with SLE

aPL, antiphospholipid antibody; IUD, intrauterine device; SLE, systemic lupus erythematosus

contraceptives may increase the risk of thromboembolism in an already vulnerable population. Intrauterine devices (IUDs) are the preferred method of contraception in women with SLE, regardless of aPL status. Estrogen should be avoided in aPL-positive women, leaving the alternative options of the progestin-only pill, progestin implant, and IUDs. In women with SLE and negative aPL tests, alternative options are presented in Table 56–6.[48]

Combined oral contraceptives such as ethinyl estradiol and levonorgestrel have drug interactions with mycophenolate mofetil, cyclosporine, and glucocorticoids. Mycophenolate mofetil can decrease the effectiveness of oral contraceptives, while the combined contraceptives may increase the serum concentrations of cyclosporine and glucocorticoids.

Treatment of SLE During Pregnancy KEY CONCEPT Hydroxychloroquine is safe for use during pregnancy and should continue throughout gestation. Hydroxychloroquine is not teratogenic, and does not increase the risk of miscarriage, stillbirth, pregnancy loss, or fetal abnormalities.[21] It has also been shown to reduce the risk of anti-SSA–associated cardiac manifestations of neonatal lupus.

While azathioprine has been shown to cause fetal abnormalities in some case reports, updated guidelines support its use in LN and other rheumatic diseases during pregnancy.[48] It may be used for a severe nephritis flare if benefits outweigh the potential risks. Treatment of LN during pregnancy may include glucocorticoids, with the possibility of adding azathioprine not to exceed 2 mg/kg/day if needed to reduce glucocorticoid doses or maintain disease control.[18] KEY CONCEPT Cyclophosphamide, mycophenolate mofetil, methotrexate, and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided during pregnancy due to association with fetal harm.

Tacrolimus crosses the placenta.[21] Miscarriage, preterm delivery, low birth weight, birth defects, renal dysfunction, transient neonatal hyperkalemia, and fetal distress have been reported following in utero exposure to tacrolimus in infants of organ transplant recipients. Pharmacokinetics are also altered during pregnancy. Whole blood concentrations decrease as pregnancy progresses; however, unbound concentrations increase. Measuring unbound concentrations may be preferred, especially in women with anemia or hypoalbuminemia. If unbound concentration measurement is not available, interpretation of whole blood concentrations should account for RBC count and serum albumin concentration. The risk of infection, hypertension, and preeclampsia may be increased in pregnant women who have had a kidney transplant.

KEY CONCEPT Treatment of thromboembolism during pregnancy should include low molecular weight heparins. Warfarin should be avoided in pregnancy. Low-dose aspirin may be considered in low-risk aPL-positive patients without previous venous thromboembolism, while high-risk patients should receive low molecular weight heparin.

Ideally, pregnancies should be planned for conception to occur during periods of disease remission. Pregnancies in patients with SLE are considered high risk.

▶ *Other Complications*

KEY CONCEPT Additional noncardiovascular complications in SLE include renal, pulmonary, musculoskeletal involvement, and glandular involvement. Uncontrolled LN may result in the need for dialysis and/or a renal transplant. A less common pulmonary complication of SLE includes pulmonary hypertension (PH). Osteopenia or osteoporosis may develop as a result of chronic steroid use or due to lack of vitamin D due to sunscreen/sun avoidance. Sjögren syndrome and hypothyroidism often coexist with SLE. Treatment of SLE complications, including PH,

Patient Encounter Part 3

The patient returns to the clinic a year and half later currently flaring with thrombocytopenia, anemia, and rash (burning, pruritus). She has 3+ protein and 2+ blood in the urine and is diagnosed with active LN. Her most recent labs of hemoglobin (9.8 g/dL [98 g/L; 6.1 mmol/L]), hematocrit (29.8% [0.298]), and platelets (31,000/mm^3 [31×10^9/L]) support this diagnosis. She is currently being treated with belimumab and hydroxychloroquine. Methotrexate was previously utilized; however, she did not tolerate treatment due to significant gastrointestinal side effects and continuous fatigue. To treat the flare, she began taking prednisone 60 mg daily 5 days ago. She mentions that she wants to have children this year and wants to discuss prepregnancy planning during this visit.

What pregnancy planning counseling points should be considered regarding preconception planning and assessment of associated risk?

During pregnancy, what pharmacological therapy is considered mainstay treatment if not otherwise contraindicated versus what is absolutely contraindicated?

If prednisone is continued long term, what side effects should she be educated on?

What modifications, if any, need to be made to this patient's pharmacological therapy plan leading up to conception and pregnancy?

Patient Care Process

Collect Information:

- Perform a comprehensive medication reconciliation including prescription, over-the-counter and supplement use.
  - Review for medications associated with drug-induced lupus (see Table 56–1).
  - If applicable, identify both failed and successful SLE pharmacological treatments, noting side effects, adverse effects and therapeutic response in the past.
- Review patient's clinical history and physical assessment findings (see Table 56–2):
  - Joint pain
  - Skin involvement
  - Hematologic abnormalities
  - Constitutional symptoms (eg, fatigue)
  - Cardiovascular involvement
  - Lung involvement
  - Central nervous system involvement
- Review laboratory data in correlation and context to clinical history findings and organ involvement (see Table 56–2).

Assess the Information:

- Identify clinically relevant drug–drug interactions, any patient reported allergies and presence of adverse reactions.
- Classify severity of disease activity (see Table 56–3):
  - Mild
  - Moderate
  - Severe
- Assess frequency of flares, organ involvement, and severity of organ involvement to determine appropriate recommendations for therapeutic intervention(s) (see Table 56–3):
  - Intermittent disease flares
  - Chronic disease flare related to organ involvement
  - Quiescent disease
- Assess use of intravenous "pulse" versus daily oral systemic glucocorticoids (see **Acute Treatment** section).
  - Methylprednisolone versus prednisone
- Screen for presence of comorbid conditions; the following conditions are commonly associated with SLE:
  - Accelerated atherosclerosis
  - Pulmonary hypertension
  - APS
  - Osteopenia or osteoporosis
  - Depression and anxiety
- Assess contraception and pregnancy planning in patients of childbearing age (see **Pregnancy Complications, Contraception, and Treatment of SLE During Pregnancy** sections).
- Based on the following baseline laboratory findings, determine if any findings need to be brought to the attention of supervising rheumatology provider when collaborating on initiating, modifying, or stopping pharmacological therapy:
  - ESR/CRP
  - CBC/CMP
  - TSH
  - Hepatitis B virus (HBV) and hepatitis C virus (HCV) testing
  - Infection (eg, tuberculosis)

Develop a Care Plan:

- Considering disease activity, organ involvement, severity of organ involvement, and laboratory findings, determine appropriate pharmacological treatment.
  - Determine insurance authorization, if applicable.
- Establish personalized monitoring frequency of laboratory findings and therapeutic response based on disease activity, medication(s) selected, and severity of organ involvement.
  - CRP, ESR, C4, C3
  - Additional testing dependent on symptoms and organ involvement which may include ECG, lung function testing, chest x-ray, renal or skin biopsies, CT scan
- Determine necessity of steroid treatment.
- If appropriate, address preconception planning and assessment of associated risk.

Implement the Care Plan: (See Treatment section)

- Counsel patient on significance of reporting side effects and therapeutic response to pharmacological treatment.
  - Adherence is dependent on the safety, effectiveness, and tolerability of medications
- Provide education on:
  - Modifiable risk factors, lifestyle modifications, and nonpharmacologic interventions
  - Drug therapy including mechanism of action, benefits of medication, common and serious adverse effects, expected time to response

Follow-up: Monitor and Evaluate: (See Outcome Evaluation section)

- Follow up approximately every 3 to 4 months on patient's response to medication, disease activity, and nonpharmacological modifiable risk factors.
- Follow up on patient reported disease flares.
- Reverify insurance coverage in case of modification of therapy.
- If applicable, follow up on long-term steroid treatment side effects.
- Assess for comorbidities, such as cardiovascular complications.

hypothyroidism, Sjögren syndrome, and osteopenia and osteoporosis, follows the same treatment recommendations for non-SLE patients who have these disease states (refer to Chapter 45, “Thyroid Disorders,” and Chapter 57, “Osteoporosis”).

Pulmonary hypertension due to SLE is treated as World Health Organization group I PH, also called pulmonary arterial hypertension (PAH). Therapy options aimed at inducing vasodilation of the pulmonary vasculature include prostacyclin analogues and agonists, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and soluble guanylate cyclase stimulators.[49] Sjögren syndrome is a chronic autoimmune condition characterized by antibodies directed against salivary and lacrimal glands, although other organs may be affected. Common symptoms include dry eyes, dry mouth, and poor salivation. Although there is no cure, treatments are aimed at symptomatic improvement. Nonpharmacologic treatments include increased fluid intake, artificial saliva and tears, and plugging lacrimal ducts with collagen plugs. Topical pharmacologic treatments include cyclosporine and lifitegrast. Lastly, systemic pharmacologic treatments include corticosteroids and cholinergic agonists such as pilocarpine or cevimeline.

OUTCOME EVALUATION

- Multiple disease activity indices exist (SLEDAI-2K, BILAG), but are rarely used outside of clinical trials.
- In practice, assess disease activity and severity with history taking, physical examination, and laboratory testing. Laboratory evaluation is typically done every 3 to 6 months, but can be done more frequently if a patient had a recent flare.
- Complete additional testing as symptoms arise and organ involvement is suspected. This may include electrocardiogram (ECG), lung function testing, chest x-ray, renal or skin biopsies, computed tomography (CT) scan.
- Appropriately monitor drug-induced adverse effects and toxicities (Table 56–5).

Abbreviations

6-MP	6-Mercaptopurine
6-TG	6-Thiouric acid
6-TGN	6-Thioguanine nucleotides
ACE	Angiotensin-converting enzyme
ACR	American College of Rheumatology
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
aPL	Antiphospholipid antibody
APRIL	Antiproliferating-inducing ligand
APS	Antiphospholipid syndrome
ARB	Angiotensin receptor blocker
AV	Atrioventricular
BCG	Bacille Calmette Guerin
BILAG	British Isles Lupus Assessment Group
BLyS	B lymphocyte stimulator protein
BMI	Body mass index
BMP	Basic metabolic panel
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
C (C3, C4)	Complement
CBC	Complete blood count
cGAS	Cyclic GMP-AMP synthase
CMP	Comprehensive metabolic panel
CrCl	Creatinine clearance
CRP	C-reactive protein
CRRT	Complete renal replacement therapy
CT	Computed tomography
CVD	Cardiovascular disease
CYP	Cytochrome P450
DHEA	Dihydroepiandrosterone
DMARD	Disease-modifying antirheumatic drugs
dsDNA	Double-stranded DNA
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eGFR	Estimate glomerular filtration rate
ELISA	Enzyme-linked immunoassay
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
G6PD	Glucose-6-phosphate dehydrogenase
GERD	Gastroesophageal reflux disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HGPRT	Hypoxanthine-guanine phosphoribosyltransferase
Ig	Immunoglobulin
IL	Interleukin
IUD	Intrauterine device
IV	Intravenous
LDL	Low-density lipoprotein
LN	Lupus nephritis
LFT	Liver function test
MCP	Metacarpophalangeal
MHC	Major histocompatibility complex
MSK	Musculoskeletal
NSAID	Nonsteroidal anti-inflammatory drug
NUDT15	Nucleotide diphosphatase
N/V/D	Nausea/vomiting/diarrhea
P-gp	P-glycoprotein
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
PIP	Proximal interphalangeal
PML	Progressive multifocal leukoencephalopathy
PPI	Proton pump inhibitor
PTU	Propylthiouracil
QTc	Corrected QT interval
RA	Rheumatoid arthritis
RBC	Red blood cell
RF	Rheumatoid factor
RNP	Ribonucleoprotein
RPR	Rapid plasma reagin
SC	Subcutaneous
SD-OCT	Spectral domain optical coherence tomography
SLE	Systemic lupus erythematosus
SLEDAI-2K	SLE disease activity index 2000
SLICC	Systemic Lupus International Collaborating Clinics
SPF	Sun protection factor
SSA	Sjögren syndrome antigen A
SSB	Sjögren syndrome antigen B
T_3	Triiodothyronine
T_4	Thyroxine
TB	Tuberculosis
T Bili	Bilirubin test
TLR	Toll-like receptor
TNFi	Tumor necrosis factor inhibitors
TPMT	Thiopurine S-methyltransferase
TSH	Thyroid-stimulating hormone
TTP	Thrombotic thrombocytopenic purpura
ULN	Upper limit of normal
VLDL	Very-low-density lipoprotein
WBC	White blood cell
XO	Xanthine oxidase

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Osteoporosis

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the association between osteoporosis and morbidity and mortality.
2. Identify risk factors that predispose patients to osteoporosis.
3. Describe the pathogenesis of fractures in patients with osteoporosis.
4. List the criteria for diagnosis and screening of osteoporosis.
5. Recommend appropriate lifestyle modifications to prevent bone loss.
6. Compare and contrast the effect of available treatment options on reducing fracture risk.
7. Recommend an appropriate treatment regimen for a patient with osteoporosis, and develop a monitoring plan for the selected regimen.
8. Educate patients about osteoporosis and drug treatment, including appropriate use, administration, and adverse effects.

INTRODUCTION

Osteoporosis is a common and often silent disorder causing significant morbidity and mortality and reduced quality of life. It is characterized by low bone density and loss of strength in bone tissue resulting in an increased risk and rate of bone fracture. Osteoporosis is responsible for more than 2 million fractures in the United States annually. Approximately 10 million Americans have osteoporosis, and an additional 43 million are classified as having low bone density.[1,2] The cost of care is expected to rise to $25.3 billion by 2025. The risk of developing an osteoporosis-related fracture varies according to age, sex, and race/ethnicity.[1] Common sites of fracture include the spine, hip, and wrist, although almost all sites can be affected.

The fractures associated with osteoporosis have an enormous impact on individual patients, not only causing initial pain, but also chronic pain, loss of mobility, depression, nursing home placement, and death. Patients with vertebral fractures may also experience height loss, kyphosis, and decreased mobility due to limitations in bending and reaching. These patients are also at greater risk of having a future vertebral fracture. Multiple vertebral fractures may lead to restrictive lung disease and altered abdominal anatomy, while patients with hip fractures have added risks associated with surgical intervention to repair the fracture. More than 50% of patients never fully recover or regain preinjury independence, and death may occur in up to 20% of patients within 2 years after fracture.[2]

EPIDEMIOLOGY AND ETIOLOGY

Osteoporosis is the most common skeletal disorder, but only a fraction of patients are evaluated and diagnosed, and less than one in four receives treatment after a fracture.[2,3] Osteoporosis can be classified as either primary (no known cause) or secondary (caused by drugs or other diseases). Primary osteoporosis is most often found in postmenopausal women and aging men, but it can occur in other age groups as well.[1,2]

The prevalence of osteoporosis varies by age, sex, and race/ethnicity and increases exponentially after age 50.[4] As a group, African Americans have the highest BMD, while Asian Americans have the lowest.[4] In the United States most hip fractures occur in postmenopausal White women, who also have the highest incidence of fracture when adjusted for age. The frequency of fracture in African American and Hispanic women trail far behind that of Caucasians, although hip fracture-related mortality may be higher.[5] Although both men and women lose bone as they age, postmenopausal women have accelerated bone loss due to loss of estrogen. Men have some protection from osteoporosis due to their larger initial bone mass and size and lack of accelerated bone loss associated with menopause.[6] Secondary causes of osteoporosis, such as hypogonadism, are found more commonly in men with low trauma fractures.[6]

PATHOPHYSIOLOGY

The human skeleton contains both cortical and trabecular bone. Cortical bone comprises approximately 80% of the skeleton, and its density and compactness account for much of bone strength. It is generally found on the surfaces of long and flat bones. Trabecular (or cancellous) bone has a sponge-like appearance and is found along the inner surfaces of long bones and throughout the vertebrae, pelvis, and ribs. This type of bone is more susceptible to osteoporotic fractures.

Under normal circumstances, the skeleton undergoes a dynamic and constant process of bone remodeling, responding to stress and injury through continuous replacement and repair. This process is completed by the basic multicellular unit, including both osteoblasts and osteoclasts. Osteoclasts are involved with

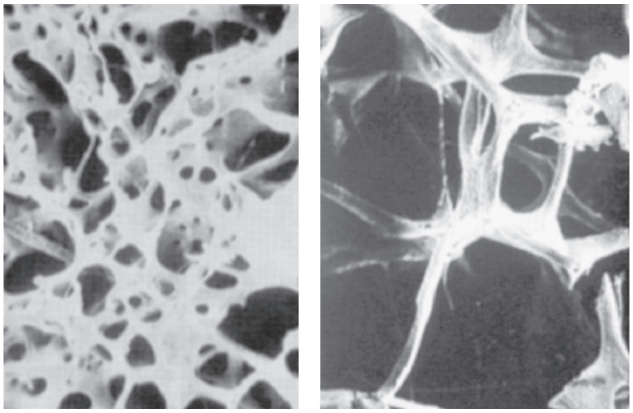


FIGURE 57–1. Normal trabecular bone (*left*) compared with trabecular bone from a patient with osteoporosis (*right*). The loss of mass in osteoporosis leaves bones more susceptible to breakage. (From Barrett KE, Barman SM, Brooks HL, Yuan JJ, eds. Ganong's Review of Medical Physiology, 26e. New York: McGraw-Hill; 2016: Figure 21–12; with permission. http://www.accesspharmacy.com.)

Table 57–1

Risk Factors for Osteoporosis and Osteoporotic Fractures[1,2]

Risk Factors for Osteoporosis	Risk Factors for Falling and Fractures
Low bone mineral density	Poor health/frailty
Female sex[a]	Impaired gait or balance
Age 65 and over	Recent falls
Race/ethnicity[a]	Cognitive impairment
History of previous low trauma (fragility) fracture after age 50	Impaired vision
Osteoporotic fracture in a first-degree relative (especially parental hip fracture)[a]	Environmental factors (eg, stairs, throw rugs, pets, poor lighting)
Low BMI or body weight (under 57.6 kg)	Medications (eg, opioids, psychotropics, anticonvulsants)
Premature menopause (before 45 years old)	
Secondary osteoporosis[b]	
Rheumatoid arthritis[a]	
Oral glucocorticoid therapy[a]	
Current cigarette smoking[a]	
Alcohol intake (three or more drinks daily)	
Loss of height	

[a] Risk factors included in FRAX risk assessment calculator.

[b] Secondary causes in the FRAX tool: type 1 diabetes, adult osteogenesis imperfecta, longstanding untreated hyperthyroidism, hypogonadism, premature menopause (before age 45), chronic malnutrition, malabsorption, and chronic liver disease.

BMI, body mass index.

resorption or breakdown of bone and continuously create microscopic cavities in bone tissue. Osteoblasts are involved in bone formation and continuously mineralize new bone in the cavities created by osteoclasts. Until peak bone mass is achieved between the ages of 25 and 35, bone formation exceeds bone resorption for an overall increase in bone mass. Figure 57–1 illustrates the difference between normal and osteoporotic bone.

In osteoporosis, an imbalance in bone remodeling occurs. Most commonly, osteoclastic activity is enhanced, resulting in overall bone loss. However, a reduction in osteoblastic activity and bone formation also occurs in certain types of osteoporosis. Due to a decrease in endogenous estrogen, bone remodeling accelerates during menopause, and a substantial amount of bone is lost during the first 5 years after menopause compared to men of the same age. The resultant bone loss and change in bone quality predispose patients to low impact (or low trauma) fractures.

CLINICAL PRESENTATION AND DIAGNOSIS

See accompanying text box for the clinical presentation of osteoporosis.

KEY CONCEPT All postmenopausal women and men older than 50 years should be evaluated for osteoporosis risk and need for further diagnostic assessment.[1,2] Many risk factors for osteoporosis and osteoporotic fractures are predictors of low bone mineral density (BMD) (Table 57–1). The risk for osteoporosis generally increases as the number of risk factors increases, and the risk of fractures increases as BMD decreases. Because osteoporosis is commonly caused by secondary factors (Table 57–2), medical history, medication history, and laboratory values should be evaluated to determine if further workup is needed.

Clinical Presentation of Osteoporosis

General

Many patients with osteoporosis are asymptomatic unless they experience a low trauma fracture.

Symptoms of Low Trauma Fracture

Pain at the site of the fracture or immobility.

Signs

Height loss (> 2 cm), spinal kyphosis ("dowager's hump"), low trauma fracture especially of the hip or spine.

Diagnostic Assessment

The diagnostic assessment for osteoporosis may include an assessment of BMD, vertebral imaging, laboratory workup, and other factors for secondary causes of osteoporosis, and biochemical markers of bone turnover. **KEY CONCEPT** Osteoporosis may be diagnosed by low bone density as determined by BMD or established history of low-trauma hip or vertebral fracture (resulting from a fall from standing height or less) in adulthood.[1]

▶ *Measurement of Bone Mineral Density*

Osteoporosis is characterized by weakened bone tissue, and BMD is the best measure of bone strength, predicting approximately 70% of bone strength.[7] Low BMD is associated with an increased risk of fractures. BMD can be measured at various sites throughout the skeletal system and by various methods. Dual-energy x-ray absorptiometry (DXA) can be used to measure central (hip and/or spine) and peripheral (heel, forearm, or hand) sites. Quantitative ultrasound, peripheral quantitative computed

Table 57–2

Medical Conditions and Drugs Associated with Osteoporosis or Low Bone Mass (Secondary Osteoporosis)[1,2]

Medical Conditions	Drugs
Alcoholism	Anticoagulants (heparin, warfarin)
Chronic kidney disease	Anticonvulsants (phenytoin, phenobarbital, primidone, valproate, carbamazepine)
Chronic obstructive pulmonary disease	Aromatase inhibitors (anastrozole, exemestane, letrozole)
Cushing syndrome	Cytotoxic drugs (eg, methotrexate, cisplatin)
Cystic fibrosis	Glucocorticoids (5 mg or more of prednisone daily or equivalent for at least 3 months)
Diabetes mellitus	Gonadotropin-releasing hormone analogs (leuprolide acetate, nafarelin, goserelin)
Eating disorders	Immunosuppressants (eg, tacrolimus)
GI disorders (eg, gastrectomy, malabsorption syndromes)	Lithium
Hematologic disorders (eg, hemophilia)	Medroxyprogesterone acetate
Hyperparathyroidism	Proton pump inhibitors
Hyperthyroidism	Selective serotonin reuptake inhibitors
Hypogonadal states	Sodium-glucose cotransporter 2 (SGLT2) inhibitors
Immunologic Diseases (eg, AIDS/HIV, rheumatoid arthritis)	Thiazolidinediones
Organ transplantation	Thyroid supplements (due to over-replacement)
Renal failure	Total parenteral nutrition
Skeletal cancer (eg, myeloma)	
Vitamin D deficiency	

Table 57–3

World Health Organization (WHO) Definition of Osteoporosis

Classification	T-Score[a]
Normal	–1 or greater
Osteopenia	Between –1 to –2.5
Osteoporosis	Less than –2.5

[a] *T*-score is the number of standard deviations above or below the mean bone mineral density in young adults.

tomography, radiographic absorptiometry, and single-energy x-ray absorptiometry are used to measure peripheral sites.

The World Health Organization (WHO) recommends a standardized approach to measuring BMD for diagnosis of osteoporosis using central measurement of BMD by DXA.[2] Preferred sites for central measurement include the total hip, femoral neck, and lumbar spine. Additionally, the American Association of Clinical Endocrinologists (AACE) states that the mid-third radius (also called 33% or 1/3 radius) of the forearm may be used when other data are not available.[2] Some instruments used for peripheral bone densitometry are portable, allowing bone density to be measured in pharmacies and health-fair screening booths. In addition to accessibility, peripheral measurement of BMD is generally less expensive than central DXA, making it an attractive option for many patients. Peripheral BMD testing is useful in identifying patients who are candidates for central DXA and who are at increased risk of fracture, but it should not be used for diagnosis.

Once the BMD report is available, *T*-scores and *Z*-scores are used to interpret the data. The *T*-score is the number of standard deviations from the mean BMD in healthy, young, White women. Osteoporosis is defined as a *T*-score more than –2.5 standard deviations below the mean BMD in young adults (Table 57–3). Osteopenia, or low bone mass, is defined as a *T*-score between –2.5 and –1.0. The *Z*-score, defined as the number of standard deviations from the mean BMD of age- and sex-matched controls, is similar to the *T*-score but is corrected for both age and sex of the patient. *Z*-scores may be more clinically relevant in evaluating BMD in premenopausal women, men younger than the age of 50, and patients who may have secondary causes for low BMD.

▶ *Screening and Risk Factor Assessment*

The National Osteoporosis Foundation (NOF) and AACE recommend BMD measurements in the following groups: women age 65 and older, men age 70 and older, perimenopausal women and men age 50 to 69 with risk factors, anyone with a fracture after age 50, and adults with a secondary cause for osteoporosis.[1,2]

FRAX (see *www.shef.ac.uk/FRAX*) is an additional tool developed by the WHO to evaluate an individual's 10-year probability of developing hip and major osteoporotic fractures based on femoral neck BMD *T*-score, age, and other risk factors.[1] The intended use is for men and women older than 40 years. The FRAX tool has not been validated for patients with previous or current use of pharmacotherapy to treat osteoporosis. Although the *T*-score is helpful in calculating risk of fracture with FRAX, fracture risk may be calculated without it.

▶ *Vertebral Imaging*

Vertebral fractures cause significant morbidity and mortality among patients with osteoporosis. They are often clinically silent, widespread, frequently recur, and commonly go undiagnosed. For these reasons, vertebral imaging is recommended in patients with a central T-score –1.0 or less and at least one other factor: (a) women age 70 and older and men age 80 and older; (b) reported decrease in height of 4 or more centimeters; (c) reported or documented prior vertebral fracture; and (d) glucocorticoid therapy of at least 5 mg daily of prednisone (or equivalent) for at least 3 months.[2]

▶ *Laboratory Evaluation*

Laboratory assessment has little value in diagnosing osteoporosis but can be beneficial in identifying or excluding secondary causes of bone loss, or for monitoring drug therapy. Screening laboratory tests for the most common causes of secondary osteoporosis include complete blood cell count, serum chemistries (electrolytes with calcium, phosphorus, and liver enzymes), vitamin D, and urinalysis. For monitoring, bone turnover markers (BTMs) may be used: C-terminal telopeptide (CTX) for bone resorption, and serum carboxy-terminal propeptide of type I collagen (PINP) for bone formation. CTX should be drawn in the fasting state and at the same time in the morning due to potential variability. The clinical utility of BTMs include a more rapid measure of drug therapy response (3–6 months) compared to DXA (1–2 years), detecting presence of drug malabsorption or nonadherence, and assisting in determining length of a bisphosphonate drug holiday.[2] Other considerations for use of BTMs include high cost and lack of reliable results in patients with chronic kidney disease.[2,8]

Patient Encounter Part 1: Patient History

HPI: A 76 -year-old White woman presents to the clinic with her daughter for follow-up on her bone mineral density test results. She currently takes no prescription medication to prevent osteoporotic fracture. She takes calcium carbonate (Tums) approximately once a week for heartburn in addition to omeprazole daily. Milk upsets her stomach, so she usually drinks tea or diet soda (occasionally fruit juice), and she is unable to eat much cheese or dairy products. She reports occasional gardening for exercise. She has longstanding uncontrolled diabetes, although it has been under good control after her hospitalization 6 months ago. She has thought about quitting smoking but is not ready to do so at this time. She reports tolerating her medications well and reports no problems. She lives alone in her own home in a rural community.

PMH: DM type 2, HTN, hyperlipidemia, coronary heart disease S/P myocardial infarction with stent placement 6 months ago, CKD stage IV, GERD, lactose intolerance, osteoarthritis.

FH: Father died at age 76 with Alzheimer disease; mother died at age 92 with history of breast cancer and osteoporotic fracture of the hip; sister alive and well at age 69

SH: Homemaker; smoked 2 packs a day for 40 years, now smokes ½ pack daily; denies alcohol use

Meds: Acetaminophen 1000 mg 3 times daily as needed for joint pain, insulin glargine 40 units at bedtime, lisinopril 10 mg daily, atorvastatin 40 mg daily, omeprazole 20 mg daily, calcium carbonate (Tums) 500 mg as needed, aspirin 81 mg daily, clopidogrel 75 mg daily

Do any symptoms suggest the presence of osteoporosis?

What risk factors for osteoporosis does this patient have as defined by the World Health Organization?

What diseases or medications could contribute to osteoporosis in this patient?

What are the recommended daily intakes for calcium and vitamin D?

How could she incorporate more calcium into her diet?

TREATMENT

Desired Outcomes

KEY CONCEPT Treatment goals for osteoporosis include: (a) preventing fractures; (b) maintaining or increasing BMD; (c) preventing secondary causes of bone loss; and (d) reducing morbidity and mortality associated with osteoporosis. Strategies to prevent fractures include maximizing peak bone mass, reducing bone loss, and using precautions to prevent falls leading to low trauma fractures.

Nonpharmacologic Therapy

▸ *Modification of Risk Factors*

Some osteoporosis risk factors (see Tables 57–1 and 57–2) are nonmodifiable, including family history, age, ethnicity, sex, and concomitant disease states. Other risk factors for bone loss may be minimized by early intervention, including smoking, low calcium intake, poor nutrition, inactivity, heavy alcohol use, and vitamin D deficiency. To avoid certain risk factors and maximize peak bone mass, efforts must be directed toward osteoporosis prevention at an early age.

▸ *Nutrition*

A healthy diet is essential to ensure sufficient nutrient intake and appropriate weight maintenance. Dietary calcium intake is important for achieving peak bone mass and maintaining bone density. Good dietary sources of calcium include dairy products, fortified juice, cruciferous vegetables (eg, broccoli, kale), salmon, and sardines (Table 57–4). Dietary intake generally provides 600 to 700 mg/day of calcium for men and women 50 and older. Supplementation to achieve recommended intake not attained by diet alone is important for primary prevention, as well as for those with a diagnosis of osteoporosis.

Adequate dietary intake of vitamin D is essential for calcium absorption. The most common source of vitamin D comes from exposure to sunlight. Ultraviolet rays from the sun promote synthesis of vitamin D_3 (cholecalciferol) in the skin, generally occurring within 15 minutes of direct sunlight exposure to bare skin without sunscreen. Ideally, individuals should receive twice weekly sun exposure to ensure optimal synthesis, but adequate exposure may not be possible during winter months in northern climates. Vitamin D may also be found in some dietary sources, including fortified milk, egg yolks, saltwater fish, and liver.

Table 57–4

Foods Containing Approximately 300 mg of Elemental Calcium

1 cup[a] skim milk
1 cup soy milk (calcium-fortified)
1 cup yogurt
1½ oz[b] cheddar cheese
1½ oz jack cheese
1½ oz Swiss cheese
1½ oz part-skim mozzarella
4 tablespoonfuls[c] grated Parmesan cheese
8 oz tofu
1 cup greens (collards, kale)
2 cups broccoli
4 oz almonds
2 cups low-fat cottage cheese
3 oz sardines with bones
5 oz canned salmon
1 cup orange juice (calcium-fortified)

[a] One cup = 240 mL.

[b] One ounce (1 oz) = 28 g.

[c] One tablespoon ≈ 15 mL.

▶ *Exercise*

Exercise can help prevent low trauma fractures. Weight-bearing exercise such as walking, jogging, dancing, and climbing stairs can help build and maintain bone strength. Muscle-strengthening or resistance exercises can help improve and maintain strength, agility, and balance, which can reduce falls.[1] It is important to develop and maintain a lifelong routine of weight-bearing and resistance exercise, because the benefits on bone can be lost after cessation of the exercise program.[1]

▶ *Falls Prevention*

The threshold at which individual patients develop a fracture varies, and other factors, such as fall risk, may play a role in fracture susceptibility. For this reason, fall history and evaluation of risk factors for falling should also be included in the initial evaluation. Patients with frailty, poor vision, hearing loss, or those taking medications affecting balance are at higher risk for falling and subsequent low trauma fractures.[1,2]

Many medications are associated with an increased risk of falling, such as antipsychotics, benzodiazepines, tricyclic antidepressants, sedative/hypnotics, anticholinergics, and glucocorticoids. Some cardiovascular and antihypertensive drugs can also contribute to falls, especially those causing orthostatic hypotension.[1] Efforts to decrease the risk of falling include balance training, muscle strengthening, removal of hazards in the home, installation of fall reduction measures such as handrails, and discontinuation of predisposing medications.[1,2] Patients with underlying physical and functional deficits may also benefit from physical and occupational therapy intervention to augment fall prevention strategies.[1,2]

Pharmacologic Treatment

KEY CONCEPT All men and women older than 50 years should be considered for pharmacologic treatment if they meet **any** of these criteria: (a) history of hip or vertebral fracture, (b) *T*-score –2.5 or less at femoral neck or spine, or (c) osteopenia and at least a 3% 10-year probability of hip fracture or at least a 20% 10-year probability of major osteoporosis-related fracture as determined by FRAX.[1,2]

▶ *Pharmacologic Therapy Guideline Recommendations*

Several guidelines for treating osteoporosis in men and women have been published.[1,2,4,9-11] The AACE guidelines provide the most comprehensive approach to evaluation and treatment of postmenopausal women.[2] The Endocrine Society's recommendations for treating postmenopausal women differ in some areas from the AACE guidelines. A treatment algorithm for managing osteoporosis referencing the guidelines is provided in Figure 57-2.

▶ *Calcium and Vitamin D*

KEY CONCEPT Calcium and vitamin D supplements to meet requirements should be added to all drug therapy regimens for osteoporosis to increase BMD and decrease the risk of hip and vertebral fractures.

Calcium plays an important role in maximizing peak bone mass and decreasing bone turnover, thereby slowing bone loss. When the calcium supply is insufficient, calcium is taken from bone stores to maintain the serum calcium level. Adequate calcium consumption is proposed to prevent this from occurring and may also correct secondary hyperparathyroidism in older adults.

The NOF recommends a daily calcium intake of 1000 mg for men between the ages of 51 and 70 and a higher intake of 1200 mg for women older than age 51 and men older than age 71.[1] When these requirements cannot be achieved by diet alone, appropriate calcium supplementation is recommended. Intakes over 1200 to 1500 mg/day may increase the risk of developing kidney stones,[1] and supplementation greater than 2500 mg/day may lead to hypercalciuria and hypercalcemia. Additionally, excessive calcium supplementation may be associated with an increased risk of cardiovascular events.[12,13]

Calcium supplements are available in a variety of calcium salts and dosage forms. Daily calcium requirements are reported as elemental calcium. However, many product labels list calcium content in the salt form, so the percentage of elemental calcium must be known to calculate the elemental calcium content per tablet. There is a lack of data supporting one salt form over another for reducing fracture risk or BMD stabilization.[2] However, a number of factors, including a single large intake of calcium, can limit calcium absorption, and special consideration must be given to calcium dosing to maximize absorption. Supplement doses should be limited to 500 to 600 mg of elemental calcium per dose, and absorption parameters, elemental calcium content, and adherence should be considered when choosing an appropriate supplement. Similar to other over-the-counter (OTC) products, various formulations may be included under the same general brand name (eg, Tums), so product labeling is very important in determining the amount of calcium in the product. Table 57–5 lists several common OTC products with their calcium and vitamin D content.

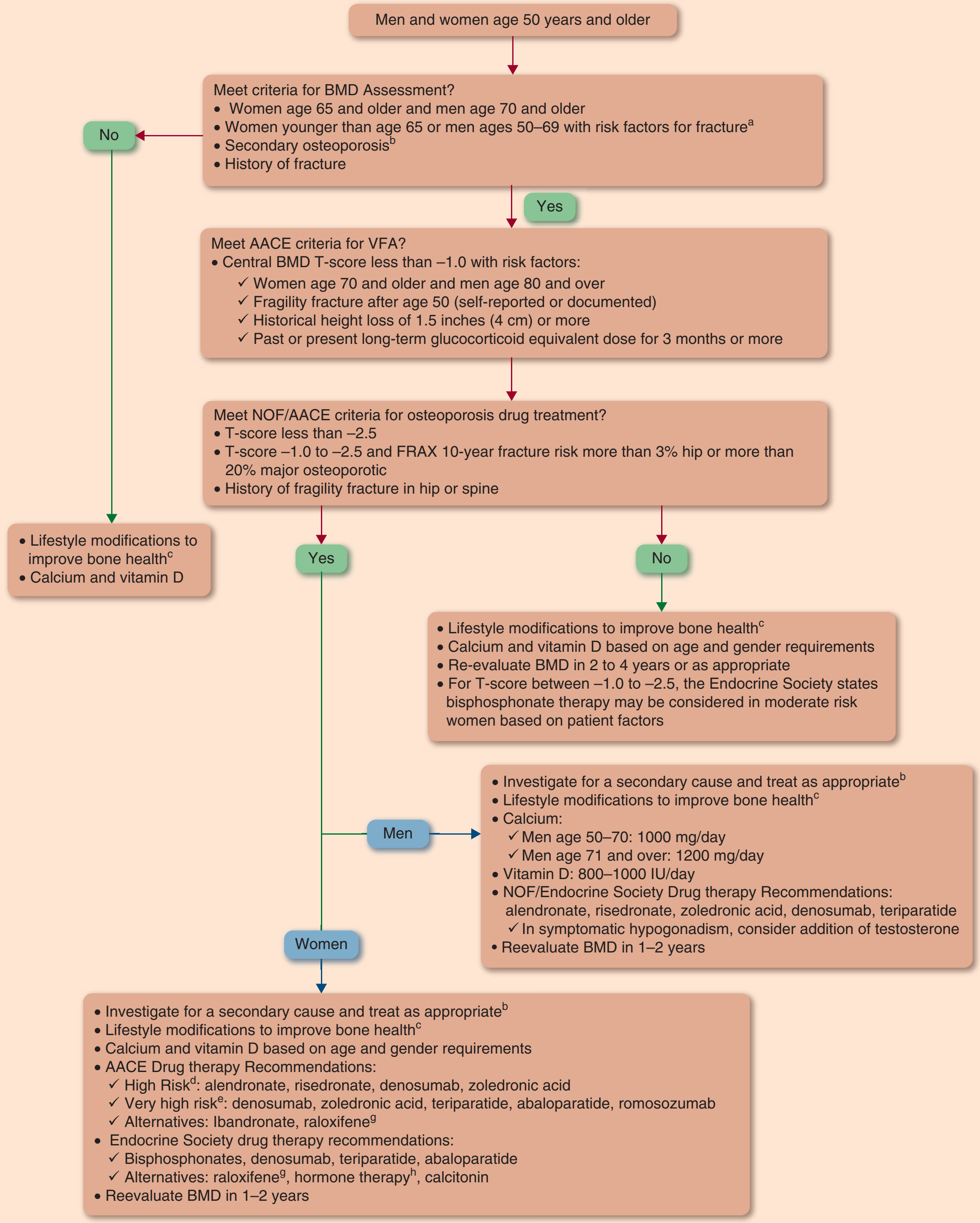
Calcium carbonate should be taken with food to maximize absorption. Older adults or patients receiving proton pump inhibitors or H_2-receptor antagonists may have difficulty absorbing calcium supplements due to reduced stomach acidity. Calcium citrate may be better absorbed in these situations because an acid environment is not needed for absorption; it may be taken with or without food.

Common adverse effects include constipation, bloating, cramps, and flatulence, especially with calcium carbonate. Changing to a different salt form may alleviate symptoms for some patients. Calcium salts may reduce the absorption of iron and some antibiotics, such as tetracycline and fluoroquinolones. To mitigate absorption issues, calcium supplements should be administered 2 hours prior to or 4 hours after antibiotic or iron therapy.

Vitamin D is crucial for bone health. It is needed for calcium absorption and may aid in balance and reduce fall risk, enhance bisphosphonate efficacy, improve BMD, and reduce fracture risk.[2] The NOF recommends a daily vitamin D intake of 800 to 1000 IU daily for all adults age 50 and older.[1] Vitamin D is available as a single entity, in combination with varying amounts of calcium salts, and in many multivitamin preparations. To avoid hypercalciuria and hypercalcemia, the maximum recommended dose for chronic use in most patients is 4000 IU/day.[14]

Patients at risk for vitamin D deficiency include older adults with malabsorption syndromes, chronic renal insufficiency, other chronic diseases, and those with limited sun exposure.[1] Frail, older adults in particular are at increased risk of deficiency due to decreased exposure to sunlight and subsequent decreased vitamin D synthesis in the skin, decreased GI absorption of vitamin D, and reduction in vitamin D_3 synthesis.

Many adults have low vitamin D levels, and vitamin D deficiency is an important secondary cause of osteoporosis.[2] Although vitamin levels should only be drawn in patients at risk for deficiency, patients with osteoporosis meet this criterion.[15] Laboratory determination of 25-hydroxyvitamin D



Men and women age 50 years and older

Meet criteria for BMD Assessment?
- Women age 65 and older and men age 70 and older
- Women younger than age 65 or men ages 50–69 with risk factors for fracture[a]
- Secondary osteoporosis[b]
- History of fracture

Meet AACE criteria for VFA?
- Central BMD T-score less than –1.0 with risk factors:
  - ✓ Women age 70 and older and men age 80 and over
  - ✓ Fragility fracture after age 50 (self-reported or documented)
  - ✓ Historical height loss of 1.5 inches (4 cm) or more
  - ✓ Past or present long-term glucocorticoid equivalent dose for 3 months or more

Meet NOF/AACE criteria for osteoporosis drug treatment?
- T-score less than –2.5
- T-score –1.0 to –2.5 and FRAX 10-year fracture risk more than 3% hip or more than 20% major osteoporotic
- History of fragility fracture in hip or spine

- Lifestyle modifications to improve bone health[c]
- Calcium and vitamin D

- Lifestyle modifications to improve bone health[c]
- Calcium and vitamin D based on age and gender requirements
- Re-evaluate BMD in 2 to 4 years or as appropriate
- For T-score between –1.0 to –2.5, the Endocrine Society states bisphosphonate therapy may be considered in moderate risk women based on patient factors

- Investigate for a secondary cause and treat as appropriate[b]
- Lifestyle modifications to improve bone health[c]
- Calcium:
  - ✓ Men age 50–70: 1000 mg/day
  - ✓ Men age 71 and over: 1200 mg/day
- Vitamin D: 800–1000 IU/day
- NOF/Endocrine Society Drug therapy Recommendations: alendronate, risedronate, zoledronic acid, denosumab, teriparatide
  - ✓ In symptomatic hypogonadism, consider addition of testosterone
- Reevaluate BMD in 1–2 years

- Investigate for a secondary cause and treat as appropriate[b]
- Lifestyle modifications to improve bone health[c]
- Calcium and vitamin D based on age and gender requirements
- AACE Drug therapy Recommendations:
  - ✓ High Risk[d]: alendronate, risedronate, denosumab, zoledronic acid
  - ✓ Very high risk[e]: denosumab, zoledronic acid, teriparatide, abaloparatide, romosozumab
  - ✓ Alternatives: Ibandronate, raloxifene[g]
- Endocrine Society drug therapy recommendations:
  - ✓ Bisphosphonates, denosumab, teriparatide, abaloparatide
  - ✓ Alternatives: raloxifene[g], hormone therapy[h], calcitonin
- Reevaluate BMD in 1–2 years

[a] Risk factors: Current smoker, personal history of fracture (after age 50), history of low-trauma fracture in a first-degree relative, low BMD, low body weight/body mass index, excessive alcohol use, early menopause, chronic glucocorticoid use (3 months or longer).

[b] See Table 56–2.

[c] Lifestyle modifications to improve bone health: Tobacco avoidance, weight-bearing/resistance exercise, fall prevention, good nutrition, and limiting alcohol.

[d] High Risk: No history of fragility fracture or meet any of the other criteria listed in “very high risk” category.

[e] Very high risk: Fracture within the past 12 months, fractures while on osteoporosis therapy, multiple fractures, fractures while on glucocorticoid therapy, T-score less than –3.0, high risk of falls or history of falls with injury, or FRAX 10-year fracture risk greater than 4.5% for hip or greater than 30% for major osteoporotic.

[f] Romosozumab: Consider after using more established therapies first.

[g] Raloxifene: Consider for women at high breast cancer risk who are not appropriate for other therapies.

[h] Hormone therapy: Consider for women with a history of hysterectomy who are not appropriate for other therapies.

(AACE, American Association of Clinical Endocrinologists; BMD, bone mineral density; NOF, National Osteoporosis Foundation; VFA, vertebral fracture assessment.)

FIGURE 57–2. Algorithm for the management of osteoporosis in postmenopausal women and men ages 50 and older.

Table 57–5

Calcium and Vitamin D Content of Common Supplements

Product (% Elemental Calcium)	Elemental Calcium per Tablet (mg)	Vitamin D per Tablet (IU)
Calcium Carbonate (40%)		
Tums 500 mg	200	—
Tums E-X 750 mg	300	—
Tums ULTRA 1000 mg	400	—
Os-Cal 500	500	—
Os-Cal 500 + D	500	200
Os-Cal Ultra	600	200
Caltrate 600	600	—
Caltrate 600 + D	600	200
Caltrate 600 + Soy	600	200
One-A-Day Women's Multivitamin	450	400
Rolaids 550 mg	220	—
Viactiv	500	100
Calcium Citrate (24%)		
Citracal	200	—
Citracal 250 mg + D	250	62.5
Citracal + D	315	200
Calcium Phosphate, Tribasic (39%)		
Posture – D	600	125
Calcium Lactate (13%)	85	—
Calcium Gluconate (9%)	60	—

levels should occur prior to the start of pharmacotherapy to determine whether supplementation is adequate or whether treatment of deficiency is needed. The AACE guidelines recommend treatment with vitamin D$_3$ (cholecalciferol, readily available over-the-counter) 5000 IU daily for 8 to 12 weeks.[2] After 25-hydroxyvitamin D levels have risen above 30 ng/mL (75 nmol/L), cholecalciferol doses of 1500 to 2000 IU or more may be needed to maintain 25-hydroxyvitamin D levels between 30 and 60 ng/mL (75–150 nmol/L).[2,15] The AACE no longer recommends high-dose vitamin D$_2$ (ergocalciferol, prescription only) as a preferred option for replacement due to variability in current 25-hydroxyvitamin D assays. These assays have unequal cross-reactivity for vitamin D$_2$, causing inaccurately low total amounts of vitamin D$_2$ to be reported.[2]

▸ *Bisphosphonates*

KEY CONCEPT Bisphosphonates are a first-line option for many men and women due to established efficacy in preventing osteoporotic fractures. They decrease bone resorption by rapidly binding to the bone matrix and inhibiting osteoclast activity. Once attached to bone tissue, bisphosphonates are released very slowly over several years, with alendronate and zoledronic acid having the highest binding affinity to bone.[2] Three of the four available agents (alendronate, risedronate, and zoledronic acid) are considered to be "broad spectrum" due to efficacy in decreasing hip, vertebral and nonvertebral fractures.[2] Alendronate, risedronate, and zoledronic acid are approved for use in men and women, whereas ibandronate is only approved for postmenopausal osteoporosis. Ibandronate is generally considered a second-line bisphosphonate due to lack of documented efficacy in nonvertebral fractures in prospective trials.[2,16] Table 57–6 contains comparative dosing for the bisphosphonates.

Bisphosphonates cause initial increases in BMD by up to 5% to 8% in the lumbar spine and up to 3% to 6% in the hip.[17,18] BMD continues to increase with long-term bisphosphonate therapy of 7 to 10 years.[19,20] Although increases in BMD have been reported at other sites, most of the clinically significant increases occur in the hip or spine and are an important marker of treatment effects. Bisphosphonate therapy can also prevent vertebral and nonvertebral fractures, decreasing the vertebral fracture risk by as much as 40% to 50% with oral bisphosphonates and up to 70% with zoledronic acid.[1,21] IV zoledronic acid has also shown a 28% decrease in mortality associated with hip fracture.[22] Upon discontinuation of therapy, clinical trials with alendronate and zoledronic acid showed sustained benefits in fracture risk reduction up to 5 years after therapy is stopped.[2] Long-term administration of bisphosphonates is considered beneficial in patients at high risk for fracture. However, for women who must discontinue bisphosphonate therapy due to intolerance or adverse events, improvements in BMD may be sustained.[20]

Patients may experience bone, muscle, or joint pain that resolves upon bisphosphonate discontinuation. Upper GI adverse effects occur in up to 20% of patients receiving oral bisphosphonates and are often related to inappropriate administration. These adverse effects range from relatively mild nausea, vomiting, and diarrhea to more severe esophageal irritation and esophagitis. Other common adverse reactions include dyspepsia, abdominal pain, nausea, and esophageal reflux. Esophageal ulceration, erosions with bleeding, perforation, stricture, and esophagitis may also occur. Advanced age, previous upper GI tract disease, and use of nonsteroidal anti-inflammatory drugs also increase the risk for GI adverse events, whereas once-weekly administration of oral bisphosphonates may decrease the risk.

IV zoledronic acid is associated with acute-phase reactions (flu-like symptoms) that can last for days, such as headache, arthralgia, myalgia, and fever.[1,2,22] Acetaminophen may be given to prevent and treat these symptoms.[2] Patients with moderate to severe renal impairment, severe dehydration, or taking concomitant diuretics or nephrotoxic drugs may be at higher risk of developing acute renal failure with zoledronic acid. Laboratory monitoring, including serum creatinine, alkaline phosphatase, phosphate, magnesium, and calcium, is recommended prior to administration of each zoledronic acid dose.

Serious but rare adverse events associated with long-term bisphosphonate use include osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF).[23,24] These events may be related to oversuppression of bone turnover causing weakening of bone structure related to inhibition of osteoclastic activity. The incidence of developing ONJ with bisphosphonate therapy ranges from 1/10,000 to 1/100,000 patient treatment years.[25-27] ONJ is less common in patients receiving bisphosphonates for osteoporosis than other indications. Patients should complete major dental work prior to initiation of bisphosphonate therapy.[27,28] The rate of AFF increases with duration of bisphosphonate use, and the risk appears to decline upon discontinuation of therapy.[27,29,30] Patients may experience thigh or groin pain prior to the fracture.

Due to the potential risks of long-term bisphosphonate use and residual beneficial effects after stopping therapy, the AACE recommends a bisphosphonate drug holiday based on initial risk assessment.[2,27] For patients initially at very high risk for fractures (see Figure 57-2), bisphosphonates should be discontinued after 10 years of oral therapy or after 6 years of IV bisphosphonate use. In patients who were initially at high risk for fracture, a drug holiday should be considered after 5 years of oral or 3 years of IV bisphosphonate use.[2] The optimal duration of the drug holiday is unknown, but reinitiation of the same or alternative therapy may be considered in patients who have experienced a fracture,

Table 57–6

Prescription Drug Therapy for Osteoporosis

Drug	Product Size	Indication/Usual Dose	Administration
Bisphosphonates			
Alendronate (Fosamax)	5-, 10-, 35-, 70-mg tablets; 70-mg with cholecalciferol 2800 IU; 70-mg with cholecalciferol 5600 IU; 70-mg oral solution	Prevention of PM osteoporosis: 5 mg orally daily or 35 mg orally once weekly Osteoporosis (men and women): 10 mg orally once daily or 70 mg orally once weekly Glucocorticoid-induced osteoporosis: 10 mg once daily Avoid when CrCl < 35 mL/min (0.58 mL/s)	Take after an overnight fast with 6–8 oz (180–240 mL) plain water while sitting or standing upright at least 30 minutes prior to morning meal. Do not lie down for 30 minutes after administration. Do not take with other medications or fluids. Do not crush, chew, or suck on the tablet.
Ibandronate (Boniva)	150-mg tablets; 3-mg/3 mL injection	PM osteoporosis: 150 mg orally once monthly; 3 mg IV push over 15–30 seconds every 3 months Avoid when CrCl < 30 mL/min (0.5 mL/s)	Same as alendronate except administer at least 1 hour prior to morning meal and refrain from lying down for 1 hour after administration.
Risedronate (Actonel, Atelvia)	5-, 30-, 35-, 75-, 150-mg tablets; 35-mg delayed release tablets	PM osteoporosis: 5 mg orally daily, 35 mg orally once weekly, 75 mg on 2 consecutive days each month, or 150 mg once monthly Male osteoporosis: 35 mg orally weekly or 150 mg orally monthly Glucocorticoid-induced osteoporosis: 5 mg orally daily Avoid when CrCl < 30 mL/min (0.50 mL/s)	Same as alendronate. Delayed release tablets may be taken with food.
Zoledronic acid (Reclast)	5 mg/100 mL IV infusion	Prevention of PM osteoporosis: 5 mg infused IV over 15 minutes or longer every 24 months Treatment of osteoporosis (men and women), glucocorticoid-induced osteoporosis: 5 mg infused IV over 15 minutes or longer every 12 months Avoid when CrCl < 35 mL/min (0.58 mL/s)	Infuse over at least 15 minutes. May premedicate with acetaminophen.
Monoclonal Antibody			
Denosumab (Prolia)	60 mg/mL SC prefilled syringe	PM or male osteoporosis, glucocorticoid-induced osteoporosis: 60 mg SC every 6 months	Inject in the upper arm, upper thigh, or abdomen. Keep refrigerated.
Parathyroid Hormone Analogs			
Abaloparatide (Tymlos)	3120 mcg/1.56 mL pen injector (30 doses)	PM osteoporosis: 80 mcg SC daily	Inject into abdomen. Keep refrigerated.
Teriparatide (Forteo)	250 mcg/mL, 2.4-mL prefilled pen	Osteoporosis (men and women), glucocorticoid-induced osteoporosis: 20 mcg SC daily	Inject into thigh or abdominal wall. Keep pen refrigerated.
Antisclerostin Antibody			
Romosozumab (Evenity)	105 mg/1.17 mL prefilled syringes	PM osteoporosis: 210 mg (two 105-mg prefilled syringes) SC once monthly	Inject into the abdomen, thigh, or upper arm. Keep refrigerated.
Estrogen Agonists/Antagonists			
Raloxifene (Evista)	60-mg tablets	PM osteoporosis: 60 mg daily	May be taken with or without food.
Bazedoxifene/conjugated estrogens (Duavee)	20 mg/0.45 mg	PM osteoporosis + menopausal symptoms: one tablet daily	Only for short duration.
Calcitonin			
Calcitonin salmon (Miacalcin)	200 IU/0.9 mL, 3.7-mL nasal spray	PM osteoporosis: Nasal spray: 200 IU daily	Nasal spray: Alternate nostrils on a daily basis.

CrCl, creatinine clearance; PM, postmenopausal; SC, subcutaneously.

significant BMD loss, or possibly a rise in CTX to pretreatment values. One strategy suggests that for women at low risk of fracture who have been maintained on bisphosphonate therapy for 3 to 5 years, a drug holiday of 2 to 3 years may be considered.[27]

Oral bisphosphonates are poorly absorbed, and administration with food or calcium supplementation further reduces absorption. Proper drug administration is important for adequate absorption and prevention of adverse effects. See Table 57–6 for

Patient Encounter Part 2: Physical Examination and Diagnostic Tests

ROS: 4 cm height loss since middle age; (+) back and knee pain; weight decrease of 7 lb (3.2 kg) in last 6 months

PE:

Gen: Well-developed White woman in no acute distress

VS: BP 134/76 mm Hg, P 76 beats/min, RR 18 breaths/min, T 36.3°C (97.3°F), Wt 64.1 kg (141 lb), Ht 64 in (163 cm), BMI 24.2 kg/m^2

Chest: No crackles or rhonchi

CV: RRR, normal S_1, S_2; no murmurs, rubs, or gallops

Spine: Mild kyphosis present, nontender

Abd: Soft, nontender, nondistended; normal bowel sounds, no hepatosplenomegaly

Ext: No clubbing, cyanosis, or edema

Labs:

Na 139 mEq/L (139 mmol/L)
K 4.0 mEq/L (4.0 mmol/L)
Cl 105 mEq/L (105 mmol/L)
CO_2 26 mEq/L (26 mmol/L)
25(OH)D 21 ng/mL (52 nmol/L)
A1C 6.9% (0.069; 52 mmol/mol Hb)
WBC 4.5 × 10^3/µL (4.5 × 10^9/L)
RBC 4.3 × 10^6/µL (4.3 × 10^{12}/L)
BUN 29 mg/dL (10.4 mmol/L)
SCr 1.86 mg/dL (164 µmol/L)
eGFR 26 mL/min/1.73 m^2
Calcium 8.8 mg/dL (2.2 mmol/L)
Hemoglobin 12.6 g/dL (126 g/L; 7.82 mmol/L)
Hematocrit 37.1% (0.371)
Platelets 298 × 10^3/µL (298 × 10^9/L)

Bone Densitometry by DXA

- BMD of femoral neck: T-score = −1.8
- BMD of lumbar spine: T-score = −2.4

Vertebral Fracture Assessment (VFA): No fracture present

What additional risk factors and signs of osteoporosis are present in this patient?

What are the goals of pharmacologic and nonpharmacologic therapy?

List at least three nonpharmacologic interventions important in her treatment plan.

What factors support pharmacotherapy for osteoporosis in this patient?

What type of supplement(s) would you recommend for this patient to meet her calcium and vitamin D requirements? Why?

recommended administration. Contraindications to bisphosphonates include hypersensitivity, hypocalcemia, pregnancy, and renal impairment (creatinine clearance less than 30–35 mL/min [0.50–0.58 mL/s]), or failure. Patients with esophageal abnormalities delaying swallowing (eg, achalasia, stricture), GI malabsorption (eg, celiac disease, Crohn disease, or gastric bypass), or who cannot remain upright for 30 minutes should avoid oral bisphosphonates; consider IV bisphosphonates for these patients.

▶ *Denosumab*

Denosumab is a broad-spectrum, twice-yearly injectable human monoclonal antibody that prevents nuclear factor-kappa B ligand (RANKL) from binding to its receptor, thereby decreasing osteoclast maturity, function, and survival.[2] It has proven benefit in reducing hip, vertebral, and nonvertebral fractures through its antiresorptive effects.[2] Denosumab decreases hip, vertebral, and nonvertebral fracture risk by up to 40%, 68%, and 20%, respectively.[31] Its use for up to 10 years has been associated with continued increases in lumbar spine and hip BMD as well as sustained reductions in fracture risk.[32] It is a first-line therapy for many women and men, and it can also be considered in patients unable to tolerate bisphosphonates due to GI contraindications or side effects and for patients with malabsorption or adherence issues.[2] In contrast to bisphosphonates, the antiresorptive effects of denosumab are reversible, and decreases in BMD may be seen within months of discontinuation of therapy.[2,9]

Common adverse effects include back pain, arthralgias, fatigue, headache, dermatologic reactions, diarrhea, and nausea. Serious adverse reactions, including hypophosphatemia, hypocalcemia, dyspnea, and skin and other infections, can also occur. Patients should seek medical attention if they experience any signs or symptoms of infection. Denosumab can worsen hypocalcemia, and preexisting hypocalcemia should be corrected before initiating therapy. Suppression of bone turnover has been associated with denosumab therapy, and although rare, ONJ and AFF have occurred.[32] Drug holidays are not recommended because of the rapid reversal of fracture risk reduction after discontinuation of therapy.[2] In patients unable to tolerate denosumab or who experience treatment failure, alternative therapy should be started when the next scheduled dose of denosumab is due.[2,9] Denosumab therapy should not be followed with an anabolic agent (eg, teriparatide) due to potential loss of hip BMD.[2]

Denosumab has a risk evaluation and mitigation strategy (REMS) program, in which the manufacturer is required by the FDA to inform patients and healthcare providers of the risks associated with its use.[33] Denosumab is administered as a subcutaneous injection once every 6 months by a healthcare provider and should be stored in the refrigerator until administration. Once at room temperature, the vial or prefilled syringe must be used within 14 days. Doses can be administered within 1 month of the scheduled dose.[9] Denosumab can be used in chronic kidney disease, but the risk of developing hypocalcemia is higher compared to patients with normal kidney function.[2]

▶ *Parathyroid Hormone Analogs*

Teriparatide (recombinant human PTH [1–34]) and abaloparatide (a synthetic analog of PTH-related protein [PTHrP]) are anabolic therapies that exert beneficial effects on bone through stimulation of the parathyroid hormone (PTH) type 1 receptor. Activation of this receptor promotes osteoblastic activity and bone formation but may also enhance bone resorption.[34] The overall net effect is an increase in BMD. They produced large decreases in vertebral and nonvertebral fractures by up to 86% and 43%, respectively,[35-37] but reduction in hip fractures has not been demonstrated.[2,9] Teriparatide is FDA-approved for treatment of postmenopausal and male osteoporosis, but abaloparatide is approved for treatment of postmenopausal women only. The AACE and Endocrine Society recommend these drugs as a first-line option in patients with prior fractures or those deemed very high risk.[2,9] Both agents are available for self-injection as prefilled pens and administered as daily subcutaneous injections.

Common adverse effects of both drugs include nausea, headache, leg cramps, dizziness, orthostatic hypotension, injection site discomfort, hypercalciuria, and hypercalcemia.[2] Abaloparatide may also be associated with palpitations.[37] Neither drug should be used in patients with preexisting hypercalcemia, hyperparathyroidism, or patients at risk of osteosarcoma including Paget disease, and history of skeletal radiation. Observations of osteosarcoma in animal studies led to the inclusion of a black box warning in product labeling for both drugs, but the risk has not been confirmed in humans.[2]

Patient-related concerns include cost of therapy and need for daily subcutaneous injections. Treatment is not recommended beyond 2 years due to unestablished safety and efficacy with long-term treatment. BMD declines once treatment is stopped, although sustained benefits in fracture reduction may persist for 1 to 2 years after discontinuation.[2] Once the maximum treatment duration has been reached, the patient should be switched to a bisphosphonate or denosumab to prevent these losses and maintain or provide further reduction in fracture risk.[2,9]

▶ *Antisclerostin Antibody*

Romosozumab is a monoclonal antibody that promotes bone formation and reduces resorption by binding to and inhibiting sclerostin, thereby increasing production of mature osteoblasts.[2,38] It has demonstrated reductions in vertebral fracture by as much as 73% when compared to placebo at 1 year.[39] Additionally, romosozumab has demonstrated a greater reduction in vertebral fracture risk than alendronate and denosumab.[38,39] It is indicated for treatment of osteoporosis in postmenopausal women at high risk of fracture (history of fracture or multiple risk factors for fracture) who have failed or are intolerant to other treatment options.[38,39]

Romosozumab 210 mg is administered as two subcutaneous injections once monthly by a healthcare provider and should be stored in the refrigerator until administration. Once at room temperature, the prefilled syringes must be used within 30 days.[38] The effect of romosozumab wanes after 1 year; therefore, treatment is only recommended for a total of 12 months. Upon discontinuation of therapy, a bisphosphonate or denosumab should be started to prevent the loss of benefit, including gains in BMD and reduction in fracture risk.

Common adverse effects include injection site reactions, arthralgias, headache, and skin-related hypersensitivity reactions. ONJ and AFF also occurred in clinical trials. Because of increased cardiovascular events compared to alendronate in a clinical trial, romosozumab carries a black box warning for increased risk of myocardial infarction, stroke, or cardiovascular death.[38] Patients should not take the drug if they have had a stroke or myocardial infarction in the past year.

▶ *Estrogen Agonists/Antagonists*

Raloxifene has estrogen-like activity on bones and cholesterol metabolism and estrogen antagonist activity in breast and endometrium. It reduces bone resorption and decreases overall bone turnover. Raloxifene has demonstrated reductions in vertebral fractures but not hip or nonvertebral fractures.[40] It has been shown to decrease breast cancer risk in patients at risk for osteoporosis.[41] Due to availability of other more effective therapies, its use is generally recommended only in select women with a high risk of breast cancer and inability to take other agents.[2,9]

Adverse effects of raloxifene include hot flushes, leg cramps, and increased risk of venous thromboembolism.[41] A previous history of venous thromboembolism is a contraindication to therapy. Hot flushes are very common and may be intolerable in postmenopausal women who are already predisposed to experiencing them.

Bazedoxifene, a third-generation estrogen agonist/antagonist, has similar effects to raloxifene. It is available in the United States only as a combination product with conjugated estrogens (Duavee) for treatment of moderate to severe vasomotor symptoms associated with menopause and for prevention of postmenopausal osteoporosis.[1] Other therapies should be considered for women who meet criteria for osteoporosis treatment.

▶ *Calcitonin*

Calcitonin is a naturally occurring mammalian hormone that plays a major role in regulating calcium levels. It inhibits bone resorption by binding to osteoclast receptors. Calcitonin reduces vertebral fracture risk by up to 30%, but no benefit has been demonstrated in reducing hip or nonvertebral fractures.[2,42] Only the nasal formulation has demonstrated fracture benefit. This drug is generally reserved for patients unable to tolerate or take other agents. However, it is sometimes used for short-term relief of back pain from vertebral fractures due to data suggesting benefit for this purpose.[2,9]

Adverse effects associated with the intranasal formulation include rhinitis, nasal irritation, and dryness. The safety and effectiveness of calcitonin has been studied for up to 5 years. Once discontinued, benefits of drug therapy are lost within 1 to 2 years.[2]

▶ *Hormone Therapy*

Estrogen, either alone or in combination with a progestin as hormone replacement therapy (HRT), has a long history as an effective treatment for osteoporosis. The Women's Health Initiative (WHI) trial found a 34% reduction in both vertebral and hip fractures and a 23% reduction in other fractures in postmenopausal women receiving conjugated estrogens and medroxyprogesterone.[43] However, significant risks associated with long-term HRT, including breast cancer and venous thromboembolism, limit its use as a first-line option.[2,43,44] The Endocrine Society states that hormone therapy may be considered in women with past hysterectomy intolerant to other therapies who are less than 10 years postmenopause and experiencing vasomotor symptoms.[9]

▶ *Combination Therapy*

Combination therapy is based on the premise that two more antiresorptive therapies with different mechanisms of action may provide more benefit on bone than monotherapy. However, this

Patient Encounter Part 3: Development of a Treatment Plan

Considering all of the information presented, develop a treatment plan for this patient. Include the following information:

a) Recommendations for patient-specific drug therapy including dose and frequency;

b) Patient education about the chosen regimen, including administration directions;

c) Monitoring plan for efficacy and adverse effects;

d) After the first denosumab infusion, the patient complains of intolerable back pain and arthralgias. What are some considerations for alternative treatment options?

Patient Care Process

Collect:

Subjective and objective information:

- Patient characteristics (eg, age, sex, menopausal status)
- Past medical history (eg, secondary causes of osteoporosis)
- Presence of symptoms, if applicable, past fracture history, and history of falls
- Family history (eg, presence of parental hip fracture)
- Social history (tobacco and alcohol use/history, diet, duration and type of physical activity)
- Medication history, including prescription, over-the-counter, and alternative therapies
- Physical examination (eg, signs of previous fractures)
- Laboratory tests (eg, rule out secondary causes)
- Diagnostic test results:
    - Central BMD
    - X-ray
    - Vertebral fracture assessment
- If the patient is already receiving pharmacotherapy, assess efficacy, safety, and patient adherence. How long has the patient been on each agent? Was the patient previously treated with other agents? Has the patient experienced any new fractures?

Assess the Information:

- Assess risk factors for osteoporosis and the presence of secondary causes of osteoporosis. If secondary causes are present, can any be treated or corrected?
- Determine the patient's average daily intake of calcium and sources of vitamin D, and assess whether calcium or vitamin D supplementation (or replacement) is needed.
- Assess physical activity and fall risk. Is the patient taking any medications that could increase fall risk?
- If *T*-score is between –1.0 and –2.5, use FRAX calculator to estimate 10-year fracture risk.
- Medication assessment:
    - Does the patient meet criteria for drug treatment of osteoporosis?
    - Does the patient have any indications for (eg, recent fracture) or contraindications to specific drug therapy?
    - Are there any patient-related factors that influence choice of agent (eg, patient preference, insurance coverage, ability to administer drug therapy, availability of infusion center near patient's home)?
    - Evaluate current therapy for safety, efficacy, and adherence.

Develop a Care Plan:

- Select therapy (including agent and dose) likely to be safe and effective, and consider patient-related factors (see Table 57–6).
- Ensure the regimen includes appropriate calcium and vitamin D supplementation or replacement for the patient.

Implement the Care Plan:

- If pharmacologic therapy is indicated, discuss therapeutic goals and expectations (eg, effect of fracture risk, follow-up laboratory or diagnostic tests to evaluate efficacy).
- Educate the patient on drug therapy selected, including drug name, dose, route and method of administration, common or serious adverse reactions, adherence, and monitoring.
- Educate the patient about nonpharmacologic measures to prevent osteoporotic fractures.

Follow up: Monitor and Evaluate:

- Annually review the need for continued medication. Assess appropriate drug administration, adherence, efficacy, adverse effects, and nonpharmacologic measures to prevent fractures.
- Reassess BMD every 1 to 2 years in patients on pharmacologic agents to treat osteoporosis. Vertebral imaging is appropriate if there is a documented loss in height of 2 cm or greater.

practice is not currently recommended for most patients due to high cost and lack of long-term safety and efficacy data. The AACE states that addition of a bisphosphonate or denosumab to prevent hip fracture may be reasonable in patients using raloxifene to reduce breast cancer risk.[2]

Treatment of Special Populations

▶ *Glucocorticoid-Induced Osteoporosis*

Glucocorticoids (eg, prednisone, hydrocortisone, methylprednisolone, and dexamethasone) play a significant role in bone remodeling, including increasing bone resorption, inhibiting bone formation, and changing bone quality. They promote bone resorption through reduced calcium absorption from the GI tract and increased renal calcium excretion. Bone formation is reduced through inhibition of osteoblasts and decreased estrogen and testosterone production.[45] Up to 40% of patients receiving long-term oral glucocorticoids have evidence of vertebral fracture.[46] Most bone mass is lost during the initial 3 to 6 months of therapy and continues to decline slowly thereafter.[45] Fracture risk is affected by other osteoporotic risk factors, and this risk is largely reversible once glucocorticoids are discontinued.

KEY CONCEPT The American College of Rheumatology (ACR) recommends oral bisphosphonate therapy for all patients age 40 or over at moderate to high risk of fracture (as determined by FRAX) receiving glucocorticoids (prednisone 2.5 mg or more daily or equivalent) for 3 months or longer. For patients younger than 40 years of age, a DXA with Z-score is recommended for evaluation of risk. Nonpharmacologic therapy and optimal calcium and vitamin D intake are also recommended. For patients unable to take oral bisphosphonates, alternative therapy recommendations include IV bisphosphonates, teriparatide, denosumab, and raloxifene in that order.[46] Frequent clinical fracture risk assessment with BMD testing every 1 to 3 years is recommended while receiving glucocorticoids.[46]

OUTCOME EVALUATION

- Evaluate patients for progression of osteoporosis, including signs and symptoms of new low trauma fracture (eg, localized pain), loss of height, and physical deformity (eg, kyphosis). Assess patients on an annual basis or more often if new symptoms present.
- For patients receiving drug therapy, monitor for beneficial effects on bone density. The AACE recommends a follow-up DXA scan every 1 to 2 years to monitor the effects of therapy.
- Assess patients for adverse effects of therapy:
  - Oral bisphosphonates: Dyspepsia, esophageal reflux, esophageal pain, or burning, ONJ and AFF (unusual groin, hip, or thigh pain)
  - Injectable zoledronic acid: Influenza-type symptoms related to infusion, ONJ and AFF (rare)
  - Denosumab: Arthralgias, dermatologic reactions, and hypocalcemia, ONJ and AFF (rare)
  - Abaloparatide and teriparatide: Nausea, headache, leg cramps, hypercalcemia, and orthostatic hypotension; also palpitations with abaloparatide
  - Romosozumab: Hypersensitivity, hypocalcemia (muscle cramps, numbness, seizure), ONJ and AFF (rare)
  - Raloxifene: Hot flushes, signs, or symptoms of thromboembolic disease (eg, pain, redness, or swelling in one extremity, chest pain, and shortness of breath)
  - Calcitonin salmon: Nasal irritation or burning

Abbreviations Introduced in This Chapter

AACE	American Association of Clinical Endocrinologists
ACR	American College of Rheumatology
AFF	Atypical femoral fracture
BMD	Bone mineral density
BMI	Body mass index
CTX	C-terminal telopeptide
DXA	Dual-energy x-ray absorptiometry
FDA	Food and Drug Administration
HRT	Hormone replacement therapy
NOF	National Osteoporosis Foundation
ONJ	Osteonecrosis of the jaw
WHI	Women's Health Initiative
VFA	Vertebral fracture assessment

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58

Rheumatoid Arthritis

Susan P. Bruce

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Identify risk factors for developing adult rheumatoid arthritis (RA) or juvenile idiopathic arthritis (JIA).
2. Describe the pathophysiology of RA, with emphasis on the specific immunologic components.
3. Discuss the comorbidities associated with RA.
4. Recognize the typical clinical presentation of RA or JIA.
5. Create treatment goals for a patient with RA or JIA.
6. Compare the available pharmacotherapeutic options, selecting the most appropriate regimen for a given patient.
7. Propose a patient education plan that includes nonpharmacologic and pharmacologic treatment measures.
8. Formulate a monitoring plan to evaluate the safety and efficacy of a therapeutic regimen designed for an individual patient with RA or JIA.

INTRODUCTION

Rheumatoid arthritis (RA) is a complex systemic inflammatory condition manifesting initially as symmetric swollen and tender joints of the hands and/or feet. Some patients may experience low disease activity, whereas others may present with high disease activity and/or extraarticular manifestations. The systemic inflammation of RA leads to joint destruction, disability, and premature death. Juvenile idiopathic arthritis (JIA) is the most common form of arthritis in children.

EPIDEMIOLOGY AND ETIOLOGY

RA has a prevalence of 0.5% to 1%.[1,2] RA arises from an immunologic reaction, perhaps in response to a genetic or infectious antigen. Risk factors associated with the development of RA include the following:

- Female gender (3:1 females to males)
- Increasing age (peak onset 35–50 years of age)
- Current tobacco smoking. Tobacco users are more likely to have increased disease activity. This risk is reduced when a patient has remained tobacco-free for at least 10 years.
- Family history of RA. Genetic studies demonstrate a strong correlation between RA and the presence of major histocompatibility complex class II **human leukocyte antigens** (HLA), specifically HLA-DRB1 haplotypes.[2] HLA is a molecule associated with the presentation of antigens to T lymphocytes.
- Silica dust inhalation. Occupational exposure to silica is associated with an increased risk of developing RA.[2]
- Emerging evidence suggests that stress may influence RA onset and disease activity. It appears that individual major stressful life events may increase risk of RA. Additionally, chronic presence of minor stressors (daily difficulties, work and relationship stress, financial pressures) may affect the immune response and RA disease activity.[3]
- The prevalence of JIA is approximately 1 in 1000 children.[4] There are no known risk factors for JIA.

PATHOPHYSIOLOGY

The underlying pathogenesis of RA likely begins long before a patient presents with signs and symptoms. The characteristics of a **synovium** affected by RA are: (a) the presence of a thickened, inflamed membrane lining called **pannus**; (b) development of new blood vessels; and (c) influx of inflammatory cells in the synovial fluid, predominantly T lymphocytes. The pathogenesis of RA is driven by T lymphocytes, but the initial catalyst causing this response is unknown. Understanding specific components of the immune system and their involvement in the pathogenesis of RA will facilitate understanding of current and emerging treatment options for RA. The components of most significance are T lymphocytes, cytokines, B lymphocytes, and kinases.[5,6]

T Lymphocytes

The development and activation of T lymphocytes are important to maintain protection from infection without causing harm to the host. Activation of mature T lymphocytes requires two signals. The first is the presentation of an antigen by antigen-presenting cells to the T-lymphocyte receptor. Second, a ligand-receptor complex (ie, CD80/CD86) on antigen-presenting cells binds to CD28 receptors on T lymphocytes.[5]

Once a cell successfully passes through both stages, the inflammatory cascade is activated. Activation of T lymphocytes: (a) stimulates the release of macrophages or monocytes, which

Table 58–1

Cytokines Involved in the Pathogenesis of RA[5,6]

Cytokine	Source	Activity
Proinflammatory		
TNF-α	Macrophages, monocytes, B lymphocytes, T lymphocytes, fibroblasts	Induces IL-1, IL-6, IL-8, GM-CSF; stimulates fibroblasts to release adhesion molecules
IL-1	Macrophages, monocytes, endothelial cells, B lymphocytes, activated T lymphocytes	Stimulates fibroblasts and chondrocytes to release matrix metalloproteinases
IL-6	T lymphocytes, monocytes, macrophages, synovial fibroblasts	Activates T lymphocytes, induces acute-phase response, stimulates growth and differentiation of hematopoietic precursor cells; stimulates synovial fibroblasts
IL-17	T lymphocytes in synovium	Synergistic effect with IL-1 and TNF leading to increased production of proinflammatory cytokines
Anti-Inflammatory		
IL-4	CD4+ type 2 helper T lymphocytes	Inhibits activation of type 1 helper T lymphocytes, decreases production of IL-1, TNF-α, IL-6, IL-8
IL-10	Monocytes, macrophages, B lymphocytes, T lymphocytes	Inhibits production of IL-1, TNF-α, and proliferation of T lymphocytes

subsequently causes the release of inflammatory cytokines; (b) activates osteoclasts; (c) activates release of matrix metalloproteinases or enzymes responsible for the degradation of connective tissue; and (d) stimulates B lymphocytes and the production of antibodies.[5,6]

Cytokines

Cytokines are proteins secreted by cells that serve as intercellular mediators (Table 58–1). An imbalance of proinflammatory and anti-inflammatory cytokines in the synovium leads to inflammation and joint destruction. Some of the proinflammatory cytokines are interleukin 1 (IL-1), tumor necrosis factor-α (TNF-α), IL-6, and IL-17. These proinflammatory cytokines cause activation of other cytokines and adhesion molecules responsible for recruitment of lymphocytes to the site of inflammation. Anti-inflammatory cytokines and mediators (IL-4, IL-10, and IL-1 receptor inhibitor) are present in the synovium, although concentrations are not high enough to overcome the effects of the proinflammatory cytokines.[5,6]

B Lymphocytes

In addition to serving as antigen-presenting cells to T lymphocytes, B lymphocytes may produce proinflammatory cytokines and antibodies. Antibodies of significance in RA are rheumatoid factors (antibodies reactive with the Fc region of IgG) and anticitrullinated protein antibodies (ACPA). Rheumatoid factors are not present in all patients with RA, but their presence is indicative of disease severity and structural progression. ACPA are produced early in the course of disease. High levels of ACPA are indicative of aggressive disease and a greater likelihood of poor outcomes. Monitoring RF and ACPA may be useful to match the intensity of treatment appropriately.[5,6]

Kinases

Kinases are enzymes involved in communication or signaling activities within and between cells. Activated kinases lead to cell activation and proliferation. Examples include Janus-associated kinases (JAKs) and tyrosine kinase. Research is ongoing to identify additional therapeutic targets to interrupt signaling and thereby halt the inflammatory process.[5,6]

Comorbidities Associated with RA

RA reduces a patient's average life expectancy, but RA alone rarely causes death. Instead, specific comorbidities contribute to premature death independent of safety issues surrounding the use of immunomodulating medications. KEY CONCEPT The comorbidities with the greatest impact on morbidity and mortality associated with RA are: (a) cardiovascular disease, (b) infections, (c) malignancy, and (d) osteoporosis.

▶ *Cardiovascular Disease*

More than half of all deaths in RA patients are cardiovascular related. Because a patient with RA experiences inflammation and swelling in joints, it is likely that there is inflammation elsewhere, such as in the blood vessels, termed vasculitis. C-reactive protein (CRP), a nonspecific marker of inflammation, is associated with an increased risk of cardiovascular disease; CRP is elevated in patients with RA. Traditional cardiovascular risk factors alone cannot explain the increased cardiovascular mortality in patients with RA. Increasing evidence suggests that the presence of RA is a cardiovascular risk similar to diabetes. Aggressive management of systemic inflammation and traditional cardiovascular risk factors (eg, blood pressure, cholesterol, tobacco use) may reduce cardiovascular mortality in this population.[7-9]

▶ *Infections*

Patients with RA have an increased risk of infections due to the underlying disease process. Older age, disease activity, and concomitant conditions (ie, renal failure, lung disease) may increase risk of infection. Additionally, prolonged glucocorticoid use may contribute to infection risk. Patients and clinicians must pay close attention to signs and symptoms of infection.[10]

▶ *Malignancy*

Cancer is the second most common cause of death in RA patients. There is an overall increased risk of malignancy and an increased risk of developing lymphoproliferative malignancy (eg, lymphoma, leukemia, multiple myeloma), melanoma, and lung cancer but decreased risk of developing cancer of the breast, prostate, and digestive tract. Research is underway to understand the mechanisms that increase or decrease risk of

Table 58–2

Comparison of RA and Osteoarthritis

Characteristic	RA	Osteoarthritis
Speed of onset	Rapid (weeks to months)	Slow (years)
Gender prevalence (women:men)	3:1	1:1
Usual age of onset	Juvenile or adult (35–50 years)	Greater than 50 years
Most common joints affected	Small joints of hands (MCPs, PIPs), feet	Hands (DIPs), large weight-bearing joints (hips, knees)
Joint symptoms	Pain, swelling, warmth, stiffness	Pain, bony enlargement
Presence of inflammation	Local and systemic	None or mild, local
Duration of morning joint stiffness	Usually 60 minutes or longer	Usually less than 30 minutes
Joint pattern	Symmetric	Symmetric or asymmetric
ESR	Elevated	Normal
Synovial fluid	Leukocytosis, slightly cloudy	Mild leukocytosis
Systemic manifestations	Yes	No

DIPs, distal interphalangeal joints; ESR, erythrocyte sedimentation rate; MCPs, metacarpophalangeal joints; PIPs, proximal interphalangeal joints.

specific cancers, and how medication use independently contributes to individual risk.[11]

▶ *Osteoporosis*

Every patient with RA is at risk for developing osteoporosis. Cytokines involved in the inflammatory process directly stimulate osteoclast and inhibit osteoblast activity. Additionally, arthritis medications such as glucocorticoids can lead to increased bone loss. Bone mineral density should be evaluated at baseline and routinely using dual-energy x-ray absorptiometry.[12]

CLINICAL PRESENTATION AND DIAGNOSIS

See the box on next page for the clinical presentation of RA.

Diagnosis

Both osteoarthritis and RA are prevalent in the US population, but they differ in presentation (Table 58–2). Because management of the two conditions differs significantly, early evaluation and diagnosis are essential to maximize an individual's care.

In 2010, The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) released classification criteria for RA (Table 58–3).[1] The goal was to identify a subset of patients with undifferentiated synovitis who were at high risk for chronic and erosive disease. The criteria are intended to help identify patients earlier in the course of disease. This will allow researchers to determine whether earlier introduction of medications alters the disease process. The criteria were developed as a tool for research purposes, but they are also helpful to guide clinical diagnosis. Patients with at least one joint with definite clinical synovitis that is not explained by another disease should be evaluated for RA.

Certain clinical features of RA are considered in diagnosis and treatment decisions because they may be related to rapid disease progression. **KEY CONCEPT** The most clinically important features associated with poor long-term outcomes include: (a) high disease activity, (b) positive autoantibodies (RF or ACPA), and (c) early presence of bony erosions by radiography.[13]

▶ *Diagnosis of Juvenile Idiopathic Arthritis*

Diagnostic criteria for JIA include: (a) age less than 16 years at disease onset, (b) arthritis in one or more joints for more than 6 weeks, and (c) exclusion of other types of arthritis. JIA can be divided into three main types:

1. *Systemic (10%–20% of cases)*: Occurs equally in girls and boys at any age. There are characteristic fever spikes twice daily (> 38.3°C or 101°F) and the presence of a pale, pink, transient rash.
2. *Polyarticular (approximately 35% of cases)*: More likely to affect girls than boys (3:1). Arthritis is present in five or more joints. The disorder resembles adult RA more than the other types of JIA.

Table 58–3

ACR/EULAR 2010 Classification Criteria for Rheumatoid Arthritis1

Criteria	Score
Joint involvement	
1 large joint (hips, knees, ankles, elbows, shoulders)	0
2–10 large joints	1
1–3 small joints (MCPs, PIPs, MTPs, wrists)	2
4–10 small joints	3
More than 10 joints (at least one small joint)	5
Serology (need at least one result for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
Acute-phase reactants (need at least one result for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of symptoms	
Less than 6 weeks	0
More than 6 weeks	1
TOTAL:	6 or greater indicates definite RA

ACPA, anticitrullinated protein antibodies; ACR, American College of Rheumatology; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; MCPs, metacarpophalangeal joints; MTPs, metatarsophalangeal joints; PIPs, proximal interphalangeal joints; RA, rheumatoid arthritis; RF, rheumatoid factor.

Clinical Presentation of RA

General

- About 60% of patients develop symptoms gradually over several weeks to months.
- Patients may present with systemic findings, joint findings, or both.

Symptoms

- Nonspecific systemic symptoms may include fatigue, weakness, anorexia, and diffuse musculoskeletal pain.
- Patients complain of pain in involved joints and prolonged morning joint stiffness.

Signs

- The metacarpophalangeal (MCP), proximal interphalangeal (PIP), metatarsophalangeal (MTP), and wrist joints are involved frequently.
- Joint involvement is usually symmetric.
- There is often limited joint function.
- **Swan neck** and/or **boutonniere deformities** may be present (see **Figure 58–1**).
- Signs of joint inflammation are present (tenderness, warmth, swelling, and erythema).
- Low-grade fever may be present.
- Extraarticular manifestations:
- *Skin:* Subcutaneous **nodules**
- *Ocular:* **Keratoconjunctivitis sicca**, **scleritis**
- *Pulmonary:* Interstitial fibrosis, pulmonary nodules, **pleuritis**, pleural effusions
- *Vasculitis:* Ischemic ulcers, skin lesions, **leukocytoclastic vasculitis**
- *Neurologic:* Peripheral neuropathy, **Felty syndrome**
- *Hematologic:* Anemia, **thrombocytosis**

Laboratory Tests

- Positive rheumatoid factor (RF) (the test is negative in up to 30% of patients)
- Elevated ESR (Westergren ESR: > 20 mm/hour in men; > 30 mm/hour in women)
- Elevated C-reactive protein (CRP) (> 0.7 mg/dL or 7 mg/L)
- Complete blood count: Slight elevation in WBC count with a normal differential; slight anemia; thrombocytosis
- Positive anticitrullinated protein antibodies (ACPA)

Other Diagnostic Tests

- *Synovial fluid analysis:* Straw colored, slightly cloudy, WBC 5–25 × 10^3/mm^3 (10^9/L), no bacterial growth if cultured
- *Joint x-rays:* To establish baseline and evaluate joint damage
- *MRI:* May detect erosions earlier in the course of disease than x-rays but is not required for diagnosis

Assessing Disease Activity

- Common tools to assess disease activity include Patient Activity Scale, Clinical Disease Activity Index, Simplified Disease Activity Index, and Disease Activity in 28 joints (DAS-28).[14] Components involved in calculating a DAS-28 score are the number of swollen and tender joints, ESR or CRP, and a subjective measure of the patient's general health. A DAS-28 score of 3.2 or less indicates low disease activity, between 3.2 and 5.1 is considered moderate activity, and 5.1 or more is considered to be high activity. Remission as defined by DAS-28 is a score of less than 2.6.[14] An online DAS-28 calculator is available at www.4s-dawn.com/DAS28/.

3. *Oligoarticular (about 40% of cases)*: More likely to affect girls than boys (5:1). Uveitis is more likely to be present. Arthritis is present in four or fewer joints. The age of onset is younger than 8 years.

TREATMENT

Desired Outcomes

KEY CONCEPT The goals of treatment in RA are to: (a) reduce or eliminate pain, (b) reduce disease activity to the lowest possible level, ideally remission, as soon as possible, (c) protect articular structures and function, (d) control systemic complications, and (e) improve/maintain quality of life. The goals for JIA are the same, with the added goals of maintaining normal growth, development, and activity level.[15] It is a common misconception that patients with JIA grow out of the disease. Many children with JIA become adults with JIA. Knowing this, it is essential that early, aggressive treatment is initiated to achieve the goals of therapy.

General Approach to Treatment

The clinician must evaluate patient-specific factors and select appropriate treatment to maximize the care of each patient. Joint damage accumulates over time; therefore, early diagnosis and early aggressive treatment are necessary to reduce disease progression and prevent joint damage. Aggressive treatment is defined as one or more disease-modifying antirheumatic drugs (DMARDs) at effective doses. Delaying treatment will result in more destructive disease that is very difficult to delay or reverse to preserve joint function.

KEY CONCEPT It is imperative that one or more DMARDs be initiated in all patients as soon as possible to reduce disease activity. DMARDs are the mainstay of RA treatment because modifying the disease process can prevent or reduce joint damage. The umbrella term DMARD includes conventional synthetic (csDMARD), biologic (bDMARD), and targeted synthetic (tsDMARD). The drugs in these classes modify the underlying disease process rather than merely providing symptomatic relief. In addition to safety and efficacy data, the initial DMARD choice depends on disease severity, patient characteristics (ie, comorbidities, likelihood of adherence), cost, and clinician experience with the medication.[4,14] Methotrexate is the initial treatment of choice for moderate to high disease activity.[15]

Depending on disease severity, combination therapy may be initiated at the time of diagnosis or after an adequate trial of

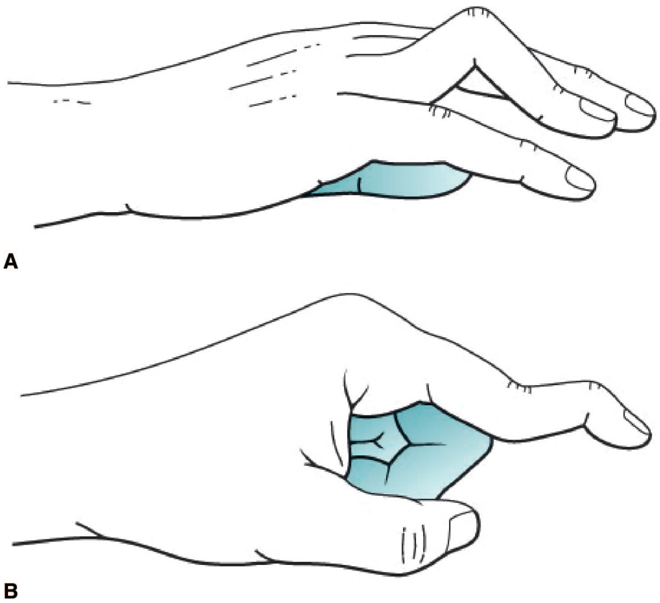

FIGURE 58–1. Boutonnière **(A)** and swan-neck **(B)** deformities. (Reproduced with permission from Toy EC, Patlan Jr JT, Warner MT. Case Files: Internal Medicine, 5th ed; 2017. http://accessmedicine.mhmedical.com/ViewLarge.aspx?figid=140919481.)

DMARD monotherapy. If a patient has evidence of rapid disease progression (eg, worsening radiographic erosions), a more aggressive treatment plan may be warranted with more frequent follow-up to achieve the goal of remission or low disease activity.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids also have specific roles in the treatment of RA, as discussed below. Agents such as azathioprine, cyclosporine, minocycline, gold salts, and anakinra are used rarely today.[14]

Patient Encounter Part 1

A 64-year-old woman presents to her primary care physician for routine follow-up. She was diagnosed with RA 15 years ago and presents today with concerns of increased morning stiffness (average 90 minutes daily) and symmetrical tenderness/swelling in her hands. She wishes to improve function as soon as possible because she has plans to retire soon and would like to continue her active lifestyle. She follows a low carb diet and consciously strives to maintain a healthy weight. She walks 3 miles every evening with her friends. She does not smoke and consumes alcohol socially. She has been taking medications for RA since diagnosis and sets regular reminders to make sure she does not miss a dose.

What additional information do you need to assess disease activity?

What variables in this scenario may inhibit optimal patient care?

Which features suggest that the patient is experiencing symptoms of RA rather than OA?

What additional information do you need before creating a care plan for this patient?

Figures 58–2 and 58–3 outline the course of treatment for adult RA according to the ACR 2015 and 2021 Recommendations.[14,15] The recommendations are based on the disease activity level and duration of disease activity (early vs established). Figure 58–2 applies to patients with early RA (defined as < 6 months). csDMARD monotherapy includes methotrexate (preferred), hydroxychloroquine, leflunomide, or sulfasalazine. Examples of combination csDMARD therapy include methotrexate/sulfasalazine, methotrexate/hydroxychloroquine, or methotrexate/sulfasalazine/hydroxychloroquine.

Figure 58–3 outlines the course of treatment for patients with established RA (disease duration 6 months or longer). Combination bDMARDs or tsDMARDs should be avoided because of the increased risk of infection due to excessive immunosuppression. There is no evidence that the benefits of any combination of bDMARD or tsDMARD therapy outweigh the potential risks, especially the increased risk of infections.

Nonpharmacologic Therapy

All patients should receive education about the nonpharmacologic and pharmacologic measures to help manage RA and JIA. Empowered patients take an active role in care by participating in therapy-related decisions. Certain forms of nonpharmacologic therapy benefit all levels of severity, whereas others (ie, surgery) are reserved for severe cases only.

Occupational and physical therapy may help patients preserve joint function, extend joint range of motion, and strengthen joints and muscles through strengthening exercises. Patients with joint deformities may benefit from the use of mobility or assistive devices that help to minimize disability and allow continued activities of daily living. When appropriate, patients should also be counseled about stress management. In situations where the disease has progressed to a severe form with extensive joint erosions, surgery to replace or reconstruct the joint may be necessary.

Pharmacologic Therapy

▶ *Bridge Therapy/Symptomatic Relief*

The current standard of care for RA treatment is to initiate disease-modifying therapy immediately. While this step is critical to control the underlying disease activity, it may take weeks to months for the patient to experience relief. It is acceptable to initiate “bridge therapy” or short-term use of certain medications to provide symptomatic relief until the disease-modifying drug reaches its therapeutic effect. The most common classes used for bridge therapy are NSAIDs and glucocorticoids.

NSAIDs These agents provide analgesic and anti-inflammatory benefits for joint pain and swelling. However, they do not prevent joint damage or change the underlying disease. Selecting an NSAID depends on multiple patient-specific factors, including cardiovascular risk, potential for GI-related adverse events, adherence to medication regimens, and insurance coverage or lack thereof. NSAID therapy is conditionally recommended as adjunct therapy in children with JIA. NSAIDs are not recommended for monotherapy.[4] However, they are strongly recommended over no treatment if enthesitis is present. Clinicians must carefully evaluate the potential risks of NSAID therapy against the potential benefits. See Chapter 59 (Osteoarthritis) for additional discussion of NSAID therapy.

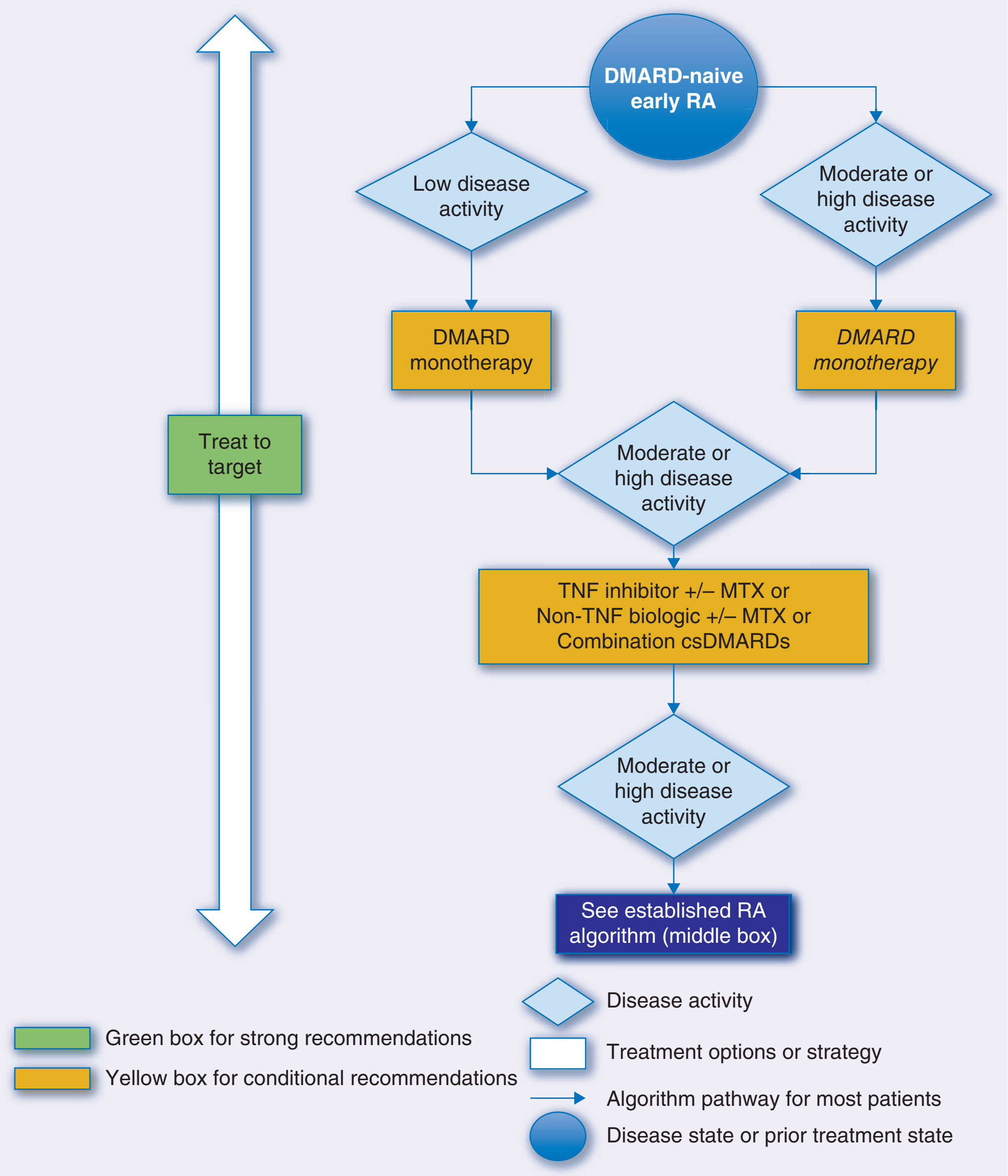
DMARD-naive early RA
Low disease activity
Moderate or high disease activity
DMARD monotherapy
DMARD monotherapy
Treat to target
Moderate or high disease activity
TNF inhibitor +/– MTX or Non-TNF biologic +/– MTX or Combination csDMARDs
Moderate or high disease activity
See established RA algorithm (middle box)
Green box for strong recommendations
Yellow box for conditional recommendations
Disease activity
Treatment options or strategy
Algorithm pathway for most patients
Disease state or prior treatment state

FIGURE 58–2. American College of Rheumatology (ACR) recommendations for the treatment of the treatment of early RA (disease duration < 6 months). (Reproduced with permission from Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res. 2016;68:1–25. With modifications based on the 2021 ACR guideline.[15])

(csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; RA, rheumatoid arthritis; TNF, tumor necrosis factor).

Glucocorticoids In contrast to NSAIDs, low-dose glucocorticoid treatment (equivalent to prednisone 10 mg/day or less) effectively reduces inflammation through inhibition of cytokines and inflammatory mediators and prevents disease progression. However, due to the adverse effect profile, the goal of glucocorticoid use is to keep doses low and use the drugs as infrequently as possible. For the purposes of bridge therapy, if necessary, the recommended duration is 3 months or less.[15] Patients taking more than 2.5 mg/day of prednisone or equivalent are at increased risk for clinically significant adverse reactions, especially bone loss leading to osteoporosis. Other glucocorticoid-related adverse reactions include Cushing syndrome, peptic ulcer disease, hypertension, weight gain, infection, mood changes, cataracts, dyslipidemia, and hyperglycemia.[18] Intra-articular administration of glucocorticoids may be considered in RA for rapid control of inflammation if a limited number of joints are affected. Intra-articular glucocorticoid injections are conditionally recommended as bridge treatment of JIA for 3 months or less if moderate to high disease activity is present.[4]

▶ *Conventional Synthetic (cs) DMARDs*

Methotrexate KEY CONCEPT Methotrexate is the csDMARD of choice in RA because of its documented efficacy and safety profile when monitored appropriately. Methotrexate exerts its anti-inflammatory effect through inhibition of dihydrofolate reductase, which causes inhibition of purines and thymidylic acid, and by inhibiting production of certain cytokines. Unless the patient has contraindications to methotrexate or takes other medications that should be

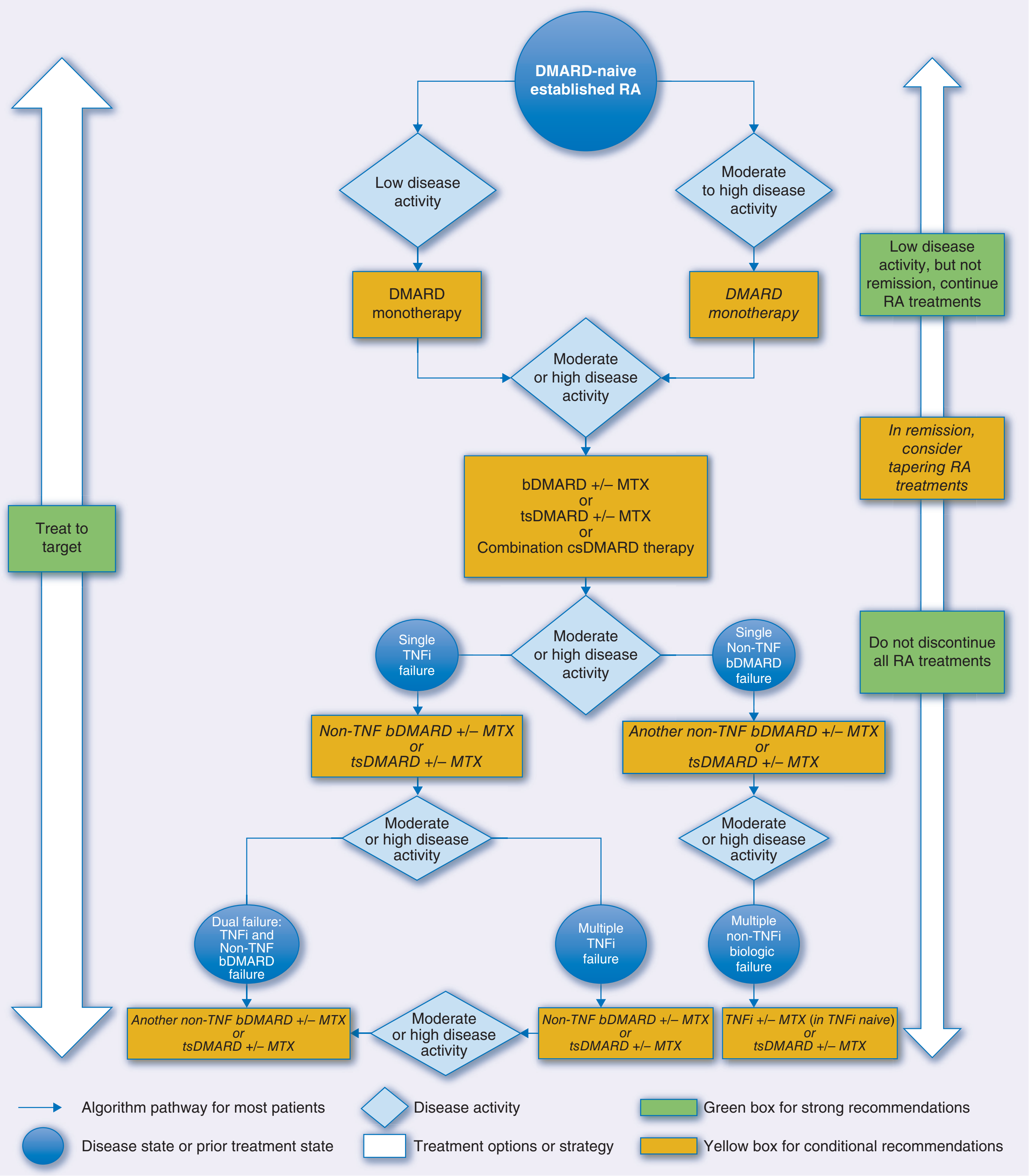
DMARD-naive established RA
Low disease activity
Moderate to high disease activity
DMARD monotherapy
DMARD monotherapy
Moderate or high disease activity
bDMARD +/– MTX or tsDMARD +/– MTX or Combination csDMARD therapy
Single TNFi failure
Moderate or high disease activity
Single Non-TNF bDMARD failure
Non-TNF bDMARD +/– MTX or tsDMARD +/– MTX
Another non-TNF bDMARD +/– MTX or tsDMARD +/– MTX
Moderate or high disease activity
Moderate or high disease activity
Dual failure: TNFi and Non-TNF bDMARD failure
Multiple TNFi failure
Multiple non-TNFi biologic failure
Another non-TNF bDMARD +/– MTX or tsDMARD +/– MTX
Moderate or high disease activity
Non-TNF bDMARD +/– MTX or tsDMARD +/– MTX
TNFi +/– MTX (in TNFi naive) or tsDMARD +/– MTX
Treat to target
Low disease activity, but not remission, continue RA treatments
In remission, consider tapering RA treatments
Do not discontinue all RA treatments
Algorithm pathway for most patients
Disease activity
Green box for strong recommendations
Disease state or prior treatment state
Treatment options or strategy
Yellow box for conditional recommendations

FIGURE 58–3. American College of Rheumatology (ACR) recommendations for the treatment of established RA (disease duration 6 months or longer). (Reproduced, with permission from Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res. 2016;68:1–25. With modifications based on the 2021 ACR guideline.[15])

(bDMARD, biologic DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; RA, rheumatoid arthritis; tsDMARD, targeted synthetic DMARD; TNFi, tumor necrosis factor inhibitor).

used with caution or avoided in combination with methotrexate, once-weekly doses should be initiated and increased steadily until the patient has symptomatic improvement or a maximum dose of 20 mg/week is reached. It is important to emphasize to patients and healthcare providers that the dosing is once weekly (not once daily) to avoid medication errors resulting in serious complications from profound myelosuppression (eg, infections, bleeding). If oral monotherapy does not produce complete resolution of symptoms, converting to subcutaneous administration may be considered prior to using methotrexate in combination with other csDMARDs or bDMARDs. If a patient experiences intolerable gastrointestinal effects, switching to subcutaneous methotrexate will reduce those effects. Concomitant folic acid is given routinely to reduce the risk of folate-depleting reactions induced by methotrexate therapy (eg, stomatitis, diarrhea, nausea, alopecia, myelosuppression, and elevated liver function tests).

Methotrexate is recommended as initial treatment for JIA in patients with more than four active joints, preferably subcutaneous over oral administration.[4] There are insufficient published data to assess the risk of serious toxicity in children receiving doses greater than 20 mg/m^2/week. Methotrexate therapy in children should be monitored the same way that is recommended in adults.

Hydroxychloroquine and Sulfasalazine The exact mechanism of action of these drugs is unknown, but both agents are fairly well tolerated. Because of their slow onset of action, each drug must be given at therapeutic doses for at least 6 months before it can be deemed a treatment failure. If a patient has low disease activity upon diagnosis, hydroxychloroquine is recommended.[15]

Hydroxychloroquine is not associated with renal, hepatic, or bone marrow suppression and therefore may be an acceptable treatment option for patients with contraindications to other DMARDs because of their toxicities.

Starting sulfasalazine at low doses and titrating slowly will minimize the nausea and abdominal discomfort caused by the drug. Patients with a sulfa or salicylate allergy should not receive sulfasalazine.

In patients with JIA, sulfasalazine is recommended only for patients with the enthesitis-related category with contraindications to TNF inhibitors or mild enthesitis. Enthesitis-related arthritis is a less common form of JIA that affects boys more than girls and is characterized by lower extremity joint involvement, including heel pain and enthesitis. Hydroxychloroquine is not recommended as monotherapy in JIA patients with active arthritis.[4]

Leflunomide This drug inhibits dihydroorotate dehydrogenase, an enzyme within mitochondria that supplies T lymphocytes with the necessary components to respond to cytokine stimulation. Thus, leflunomide inhibits the T-lymphocyte response to various stimuli and halts the cell cycle. Its efficacy is similar to that of moderate doses of methotrexate or sulfasalazine. Because of its extended half-life, leflunomide therapy begins with a loading dose followed by a maintenance dose. Leflunomide may be used in combination with methotrexate, but the added efficacy comes with a dramatic rise in the risk of hepatotoxicity. If therapy requires abrupt discontinuation (eg, due to toxicity or pregnancy), administering cholestyramine will accelerate leflunomide removal from the body.[19]

Leflunomide is recommended as an alternative to methotrexate in patients with JIA experiencing disease activity in five or more joints.[17] However, leflunomide does not have an FDA-approved indication for this use.

▶ *Biologic DMARDs and Associated Biosimilars*

bDMARDs are indicated in patients who have received an adequate trial of csDMARD monotherapy or combination therapy but have failed to achieve treatment goals. These agents may be added to csDMARD monotherapy (eg, methotrexate), or replace ineffective csDMARD therapy.

"Biosimilars" are highly similar to an FDA-approved biologic agent (called the reference product) and have been shown to have no clinically meaningful differences in efficacy or adverse effects from the reference product. They are not completely identical to the originator compound because of molecular complexity and production using recombinant DNA techniques in living organ systems. The FDA will approve a biosimilar product only if it has the same mechanism of action, route of administration, dosage form, and strength as the reference product. Also, a biosimilar can only be approved for indications that were previously approved for the reference product. Biosimilars have a nonproprietary name plus an FDA-designated suffix consisting of four lowercase letters that have no intended meaning. Biosimilars are not considered to be interchangeable with the reference product unless the manufacturer fulfills additional requirements for interchangeability.[20]

Patients with concomitant serious infections, lymphoproliferative disorders, hepatitis, history of malignancy, or heart failure should be evaluated thoroughly to determine if or which biologic DMARD is appropriate, preferred, or contraindicated in their treatment regimen. The 2021 treatment guidelines provide recommendations for those scenarios based on available evidence.[15]

Tumor Necrosis Factor (TNF) Inhibitors There are currently five reference TNF inhibitors approved for the treatment of RA: etanercept, adalimumab, infliximab, golimumab, and certolizumab.

Etanercept is a recombinant form of human T receptor. Etanercept provides a therapeutic effect by binding to soluble TNF and preventing its binding with TNF receptors. Etanercept is very effective as monotherapy or in combination with other csDMARDs. Etanercept has an FDA-approved indication for treatment of JIA.

Adalimumab is a recombinant human IgG1 monoclonal antibody specific for human TNF. Adalimumab binds to soluble and bound TNF-α. It can be administered in combination with methotrexate or other DMARDs. Adalimumab has an FDA-approved indication for JIA.

Infliximab is a chimeric IgG1 monoclonal antibody that binds to soluble and bound TNF-α. Methotrexate is given with it to suppress antibody production against the mouse-derived portion of the molecule. Qualified healthcare personnel must be present during the infliximab infusion to respond to infusion-related reactions, if they occur (rash, urticaria, flushing, headache, fever, chills, nausea, tachycardia, dyspnea). These reactions may be treated by: (a) temporarily discontinuing the infusion, (b) slowing the infusion rate, or (c) administering corticosteroids or antihistamines. Patients may be pretreated with corticosteroids or antihistamines if they continue to experience infusion reactions. Infliximab was shown in clinical trials to be effective for treatment of JIA, but it has not yet received FDA approval for this indication.

Golimumab is a human monoclonal antibody that binds to membrane-bound and soluble TNF. Golimumab can be administered in combination with methotrexate in patients with moderate to severe RA. One advantage of this agent over others in the class may be the once-monthly subcutaneous dosing or every-other-month IV dosing. Golimumab is not FDA approved for use in JIA.

Certolizumab is a humanized antibody Fab fragment conjugated to polyethylene glycol, which delays its metabolism and elimination. Certolizumab can be administered alone or in combination with methotrexate in patients with moderate to severe RA. Certolizumab is not FDA approved for use in JIA.[4]

IL-1 Inhibitors Anakinra is a recombinant form of human IL-1 receptor inhibitor. Anakinra inhibits the activity of IL-1 by binding to it and preventing cell signaling. It is indicated for adults with RA who have failed one or more csDMARDs. Anakinra is not recommended in the ACR treatment guidelines for patients with JIA or RA due to infrequent use and lack of new data. Anakinra is not FDA approved for treatment of JIA.[4]

Canakinumab is a human monoclonal antibody that binds to IL-1 and blocks binding with the IL-1 receptor, thereby neutralizing its activity. Canakinumab is not indicated for treatment of adult RA. Canakinumab is indicated for the treatment of systemic JIA in patients 2 years and older. The recommended dose is 4 mg/kg (maximum 300 mg) subcutaneously every 4 weeks.[22] Canakinumab is not recommended in the ACR treatment guidelines for patients with JIA or adult RA.

T Cell Costimulatory Inhibitor Abatacept interferes with T-cell signaling, ultimately blocking T-cell activation and leading to anergy, or lack of response to an antigen. Abatacept is indicated as monotherapy or in combination with csDMARDs following inadequate response to methotrexate or anti-TNF agents. Abatacept is FDA approved for the treatment of moderate to severe JIA; it is recommended as an option for patients who did not respond to an adequate trial of methotrexate.[4,22]

Anti-CD20 Antibody Rituximab is a genetically engineered chimeric anti-CD20 monoclonal antibody that causes B-lymphocyte depletion in bone marrow and synovial tissue. Rituximab is indicated for patients with moderate to severe RA and a history of inadequate response to one or more TNF inhibitor therapies. Patients with RF-positive RA tend to respond more favorably to rituximab than patients with RF-negative disease. Rituximab carries a black box warning of fatal infusion reactions, severe mucocutaneous reactions, hepatitis B reactivation, and progressive multifocal leukoencephalopathy. The benefits of rituximab must be tempered against the safety concerns reported with use of rituximab in the oncology setting. The role of rituximab in JIA is unclear, and the medication is not FDA approved for this purpose.[4]

Interleukin-6 Inhibitors Interleukin-6 (IL-6) production is increased in patients with RA. Presence of IL-6 shifts inflammation from acute to chronic.[23] In addition, IL-6 plays a significant role in the pathogenesis of anemia associated with RA. Tocilizumab, an anti–IL-6 receptor monoclonal antibody, inhibits the binding of IL-6 to the IL-6 receptor. Tocilizumab is FDA approved for treatment of moderate to severe RA and JIA. In JIA, it is recommended for patients with moderate to high disease activity with an inadequate response to a TNF inhibitor.[7]

Sarilumab is an IL-6 receptor inhibitor that binds to soluble and membrane-bound IL-6 receptors. It is indicated for treatment of moderate to severe RA following inadequate response or intolerance to one or more DMARDs. It is not FDA approved for JIA nor included in the JIA treatment guidelines.[4,23]

▶ *Targeted Synthetic (ts) DMARDs*

Janus-Kinase (JAK) Inhibitors A distinct advantage of JAK inhibitors over biologic DMARDs is that they are given orally because they are synthetic small molecules rather than large proteins produced by recombinant DNA techniques. A JAK inhibitor may be initiated if a patient does not have an adequate response to or is otherwise unable to receive csDMARDS or bDMARDs.[24] Although oral administration is advantageous, consideration of JAK inhibitor use must be assessed in the context of potential adverse reactions (eg, hematologic effects, malignancy, thrombosis risk).

Tofacitinib selectively inhibits JAK, with greatest affinity for JAK3.[24] Tofacitinib is indicated for treatment of moderate to severe RA as monotherapy or in combination with csDMARDs. Baricitinib inhibits JAK1 and JAK2. It is approved as monotherapy or in combination with methotrexate in moderate to severe RA. Upadacitinib is highly selective for JAK1. It is approved as monotherapy or in combination with methotrexate or other csDMARDs.[24-26]

▶ *Selecting Disease-Modifying Therapy*

The decision to select a particular agent generally is based on the prescriber's comfort level with monitoring medication safety and efficacy, severity of disease activity, presence of factors suggestive of poor prognosis, the frequency and route of administration, the patient's comfort level or manual dexterity to self-administer subcutaneous injections, the cost, and the availability of insurance coverage. Table 58–4 highlights dosing, safety, monitoring, and patient counseling information for DMARDs used in the treatment of RA. Together, Figures 58–2 and 58–3 and Table 58–4 can be used to build an individualized treatment plan. While monotherapy is preferred, combination therapy may be necessary to achieve the target of low disease activity or remission. When selecting a treatment plan, cost should also be considered. The expense of biologic DMARDs can limit their use in patients without adequate insurance or other means of covering the drug cost. Cost analyses indicate that the increased expenses associated with biologic DMARDs may be offset by the costs avoided for treatment of advanced RA. It is anticipated that introduction of biosimilars will reduce RA treatment costs because they are expected to be less costly than the reference products.

KEY CONCEPT The risk of infection in patients treated with bDMARDs and tsDMARDs must be considered when selecting and monitoring therapy.[14] Influencing the immune response to reduce symptoms of RA may influence the body's response to pathogens. Of particular concern is use of TNF inhibitors in patients with a history of tuberculosis exposure. TNF is important in the formation of granulomas that wall off tuberculosis infection. In theory, if TNF is inhibited, patients with latent tuberculosis may have a reactivated infection. Patients receiving any bDMARD or tsDMARD should be screened for tuberculosis and other infections (hepatitis B, hepatitis C). Antituberculosis therapy should be initiated in patients with active or latent tuberculosis.[14] Patients with active tuberculosis should receive the full course of antituberculosis treatment prior to initiating biologic DMARDs. If there is latent infection, biologic DMARD therapy may be initiated after at least 1 month of antituberculosis treatment. Biologic DMARDs should not be initiated and should be discontinued temporarily during an acute, serious infection. Biologic DMARD therapy can be continued during

Table 58–4

FDA-Approved DMARDs for Treatment of RA[1,2,21-26]

Drug	Dose[a]	Time to Effect (weeks)	ADRs	Dosing in Hepatic Impairment	Dosing in Renal Impairment	Monitoring	Counseling Points
Conventional Synthetic DMARDs (csDMARDs)							
Methotrexate	Adults: 7.5–20 mg orally, SC or IM once weekly Polyarticular-course JIA: Recommended starting dose: 10 mg/m^2 oral, IM, or SC once weekly; usual max dose: 20 mg/m^2 once weekly	4–8	N, D, hepatotoxicity, alopecia, new-onset cough or SOB, MYL	Contraindicated	CrCl (mL/min)[b]: 61–80: 75% of dose 51–60: 70% of dose 10–50: 50% of dose Less than 10: Avoid use	CBC, creatinine, LFTs every 4–8 weeks; monitor for signs of infection	Use of folic acid concomitantly Avoid alcohol Use contraception if childbearing potential
Hydroxychloroquine	Adults: 200 mg orally twice daily or 400 mg once daily	8–24	N, D, HA, vision changes, skin pigmentation	Use with caution	No change	Specialized retinal eye examination at baseline and at 5 years	
Sulfasalazine	Adults: 1000 mg orally two to three times daily Polyarticular-course JIA: Initial: 10 mg/kg/day orally; increase weekly by 10 mg/kg/day; usual dose: 30–50 mg/kg/day orally in two divided doses; max 2 g/day	8–12	N, D, rash, yellow-orange discoloration of urine or skin, photosensitivity, MYL	Avoid use	CrCl (mL/min)[b]: 10–30: Give twice daily Less than 10: Give once daily	CBC, LFTs, creatinine every 2–4 weeks for 3 months, then every 8–12 weeks	Sunscreen use
Leflunomide (Arava)	Adults: 100 mg orally daily for 3 days; then 20 mg daily	4–12	Hepatotoxicity, D, N, HTN, rash, HA, abdominal pain	Avoid use	Guidelines not available	CBC, LFTs, creatinine every 2–4 weeks for 3 months, then every 8–12 weeks Monitor for signs of infection	Avoid alcohol Use contraception if childbearing potential
Biologic DMARDs (bDMARDs) and Associated Biosimilars							
Tumor Necrosis Factor (TNF) Inhibitors							
Etanercept (Enbrel) Biosimilar: Etanercept-szzs (Erelzi) Etanercept-ykro (Eticovo)	Adults: 25 mg SC twice weekly or 50 mg SC once weekly Children ages 2–17: 0.8 mg/kg SC once weekly; max 50 mg/week	1–4	ISR	No change	No change	Monitor for infection	ISR—topical corticosteroids, antipruritics, analgesics, rotate injection sites Screen for tuberculosis, Hepatitis B
Infliximab (Remicade) Biosimilars: Infliximab-dyyb (Inflectra) Influximab-abda (Renflexis) Infliximab-axxq (Avsola) Infliximab-qbtx (Ixifi)	Adults: 3–10 mg/kg by IV infusion at 0, 2, and 6 weeks; then every 8 weeks	1–4	IR (rash, urticaria, flushing, HA, fever, chills, nausea, tachycardia, dyspnea)	No change	No change	Monitor for infection	Screen for tuberculosis, Hepatitis B

Adalimumab (Humira) Biosimilar: Adalimumab-atto (Amjevita) Adalimumab-adbm (Cyltezo) Adalimumab-afzb (Abrilada) Adalimumab-bwwd (Hadlima) Adalimumab-fkjp (Hulio) Adalimumab-adaz (Hyrimoz)	Adults: 40 mg SC every other week Children older than 4 years and weighing 15–29 kg: 20 mg SC every other week Children weighing 30 kg or more: 40 mg SC every other week	1–4	ISR	No change	No change	Monitor for infection	Screen for tuberculosis, Hepatitis B
Golimumab (Simponi)	Adults: 50 mg SC once monthly 2 mg/kg IV infusion at weeks 0, 4, then every 8 weeks	1–4	ISR, IR	No change	No change	Monitor for infection	Screen for tuberculosis, Hepatitis B
Certolizumab (Cimzia)	Adults: 400 mg SC initially, at 2 weeks, 4 weeks, then 200 mg every other week	1–4	ISR	No change	No change	Monitor for infection	Screen for tuberculosis, Hepatitis B
T Cell Costimulatory Inhibitor							
Abatacept (Orencia)	Adult IV infusion: < 60 kg, 500 mg; 60–100 kg, 750 mg; > 100 kg, 1000 mg IV on days 1, 15 and every 28 days thereafter SC Injection: Weight-based loading dose, then 125 mg SC within 1 day, 125 mg SC once weekly; or 125 mg once weekly in patients unable to receive IV. JIA (> 6 years of age): < 75 kg: 10 mg/kg; 75–100 kg: 750 mg; > 100 kg: 1000 mg IV infusion on days 1, 15, 28, and every 28 days thereafter	2	HA, infection, IR, ISR	No change	No change	Monitor for infection	Screen for tuberculosis, Hepatitis B
Anti-CD20 Monoclonal Antibody							
Rituximab (Rituxan) Biosimilars: Rituximab-pvvr (Ruxience) Rituximab-abbs (Truxima) Rituximab-arrx (Riabni)	Adults: Two 1000-mg IV infusions separated by 2 weeks; timing of the third dose is based on patient symptoms (no earlier than 16 weeks)	4	IR	No change	No change	Monitor for infection	Screen for tuberculosis, Hepatitis B
IL-6 Inhibitors							
Tocilizumab (Actemra)	Adults: 4–8 mg/kg IV infusion every 4 weeks SC: if > 100 kg, 162 every week; if < 100 kg, 162 every other week JIA (2 years and older): < 30 kg: 12 mg/kg IV infusion every 2 weeks; > 30 kg: 8 mg/kg every 2 weeks		Elevated LFTs, total cholesterol, triglycerides, and high-density lipoprotein; nasopharyngitis, infection	No data available	No data available	Monitor for infection; LFTs	Screen for tuberculosis, Hepatitis B

(*Continued*)

Table 58–4

FDA-Approved DMARDs for Treatment of RA[1,2,21-26] (*Continued*)

Drug	Dose[a]	Time to Effect (weeks)	ADRs	Dosing in Hepatic Impairment	Dosing in Renal Impairment	Monitoring	Counseling Points
IL-6 Inhibitors (continued)							
Sarilumab (Kevzara)	Adults: 200 mg SC every 2 weeks		ISR, elevated LFTs, neutropenia	Not recommended in patients with hepatic impairment	CrCl < 30 mL/min[b]: no data available	Monitor for infection, LFTs, lipids	Screen for tuberculosis, Hepatitis B
Targeted Synthetic DMARDs (tsDMARDs)							
Janus-Kinase Inhibitors							
Tofacitinib (Xeljanz) Tofacitinib extended-release (Xeljanz-XR)	Adults: 5 mg orally twice daily Adults: 11 mg orally once daily		Infection, headache, HTN, elevated LFTs, D, worsening lipid profile, thrombosis	Mild impairment: no adjustment Moderate: 5 mg once daily Severe: Use not recommended	Mild: no adjustment; Moderate/severe: 5 mg once daily	CBC, Hgb, lipids, LFTs, monitor for infection	Screen for tuberculosis, Hepatitis B
Baricitinib (Olumiant)	Adults: 2 mg once daily		Infection, elevated LFTs, increased LDL cholesterol, thrombosis	Not recommended in patients with severe hepatic impairment	Mild: no adjustment Moderate: 1 mg daily Severe: not recommended	CBC, LFTs, lipids, monitor for infection	Screen for tuberculosis, Hepatitis B
Upadacitinib (Rinvoq)	Adults: 15 mg once daily		Infection, elevated LFTs, thrombosis	Mild/moderate: no adjustment Severe: use not recommended	No adjustment necessary	CBC, LFTs, lipids, monitor for infection	Screen for tuberculosis, Hepatitis B

[a] Geriatric patients should receive the usual adult dose unless renal or hepatic impairment is present. Pediatric doses are provided for drugs that have FDA-approved indications for juvenile idiopathic arthritis (JIA).

[b] To convert to SI units of mL/s, multiply by 0.0167.

CBC, complete blood count; D, diarrhea; HA, headache; Hgb, hemoglobin; HTN, hypertension; IR, infusion reactions; ISR, injection site reactions; LFTs, liver function tests; MYL, myelosuppression (watch for fever, symptoms of infection, easy bruisability, and bleeding); N, nausea; SC, subcutaneous injection; SOB, shortness of breath.

nonserious infections.[27] Concomitant use of two bDMARDs and tsDMARDs in any combination is contraindicated due to increased infection risk.

▸ *Vaccinations*

In theory, initiation of DMARD therapy suppresses the immune system and reduces the body's ability to mount a response to a pathogen or a vaccine. Studies are underway to determine how much the immune system is affected as data are emerging that vaccines may be safer than originally thought during DMARD-induced immunosuppression. Specifically, administration of killed vaccines (pneumococcal, influenza, hepatitis B), recombinant vaccines (human papillomavirus, recombinant zoster vaccine [Shingrix]), and live attenuated vaccines should be considered prior to and reevaluated during treatment with DMARDs. Live vaccines should be avoided in patients taking bDMARDs and tsDMARDs. Herpes zoster status should be determined prior to initiation of bDMARDs and tsDMARDs and the vaccine administered, if appropriate. The CDC Advisory Committee on Immunization Practices (ACIP) recommends Shingrix for prevention of herpes zoster and related complications in immunocompetent adults aged 50 years or more. At the time of this writing, the CDC ACIP does not recommend use of the newer recombinant zoster vaccine (Shingrix) in immunocompromised persons and those on moderate to high doses of immunosuppressive therapy because these patients were excluded from the efficacy studies.[27] Additional vaccine information is available on the Centers for Disease Control and Prevention website (www.cdc.gov). Vaccination rates in RA are low, therefore every effort should be made during the initial workup to determine immunization status and update if necessary.[28-30]

▸ *Fertility, Pregnancy, and Fetal Development*

Women of childbearing potential should be counseled early and often about the impact of antirheumatic drugs on fertility, pregnancy, fetal development, and lactation. Some women may experience a reduction in disease symptoms during pregnancy; however, many agents used to treat RA are known teratogens. In addition, some women may present with signs and symptoms of RA for the first time during the postpartum period. Women desiring motherhood must consult with their physicians to discuss contraception and carefully plan for a pregnancy to reduce risks to the developing fetus and the patient.[19]

Methotrexate use is associated with spontaneous abortion, fetal myelosuppression, limb defects, and CNS abnormalities; therefore, pregnancy must be avoided. Methotrexate should be discontinued 3 months prior to attempting conception.[19] Patients of childbearing potential receiving methotrexate should be counseled on the importance of effective contraception (ie, oral contraceptives, condoms plus spermicidal foam). If pregnancy occurs, the patient should notify their healthcare providers immediately. Leflunomide is teratogenic in animal studies, and discontinuation prior to conception is recommended.[19]

TNF inhibitors are considered safe during pregnancy. Certolizumab may be the preferred TNF inhibitor during pregnancy because the transfer of medication across the placenta is very low. Abatacept and tocilizumab may be continued while the patient is trying to conceive and should be discontinued when pregnancy is confirmed. Use of rituximab in pregnancy will risk the fetus having reduced B cells upon delivery, but use is recommended if the mother has severe or life-threatening disease. Insufficient data exist regarding use of JAK inhibitors during pregnancy.[19]

Patient Encounter Part 2: Medical History, Physical Examination, and Laboratory Tests

PMH: Rheumatoid arthritis (15 years)

FH: Mother died age 88 from cardiovascular disease, also had RA; father died age 89 from pancreatic cancer

Allergies: NKDA

Meds: Methotrexate 20 mg orally once weekly; folic acid 1 mg orally daily; prednisone 10 mg orally every morning; leflunomide 20 mg orally daily

Previous Meds: Hydroxychloroquine (ineffective), sulfasalazine (ineffective)

ROS: (+) Fatigue, (–) N/V/D, HA, SOB, chest pain, cough

PE:

VS: BP 138/76 mm Hg, P 64 beats/min, RR 16 breaths/min, T 38.0°C (100.4°F); Ht 5′4″ (163 cm), Wt 56 kg (124 lb)

Skin: Warm, dry

HEENT: NC/AT, PERRLA, TMs intact

CV: RRR, normal S_1 and S_2, no m/r/g

Chest: CTA

Abd: Soft, NT/ND

Neuro: A&O × 3; CN II to XII intact

Ext: Bilateral tender and swollen PIPs and MCPs

Labs: ESR 64 mm/hour, RF (+), ACPA (high +), AST 85 IU/L (1.42 μkat/L) , ALT 92 IU/L (1.53 μkat/L)

Synovial fluid analysis: Yellow, cloudy, decreased viscosity

Hand x-rays: Soft-tissue swelling, joint space narrowing, evidence of erosions

Disease Activity Score 28 (DAS-28): 5.2

DXA Scan: T score –2.5

How would you categorize this patient's disease activity—low, moderate, or high? Why? How does this affect your treatment plan?

What nonpharmacologic and pharmacologic alternatives are appropriate for this patient?

Treatment plans must also consider the potential effects on breastfeeding babies. Low-dose corticosteroids, certain NSAIDs, hydroxychloroquine, sulfasalazine, and certain biologic DMARDs (eg, certolizumab, etanercept) may be considered

Patient Encounter Part 3: Creating a Care Plan

Based on the information available, create a care plan for this patient's RA. The plan should include the following:

(a) A statement of the drug-related needs and/or problems

(b) A patient-specific detailed care plan (including specific medications and associated doses)

(c) Monitoring parameters to assess safety and efficacy

(d) Key patient education topics

Patient Encounter Part 4: Patient Counseling

While meeting with the patient, she tells you that she is deathly afraid of needles. She is most comfortable with her current medication regimen and is frustrated that she has swelling and tenderness in her hands.

How does this information change your care plan?

during pregnancy. Healthcare providers and patients are encouraged to visit MotherToBaby (https://mothertobaby.org) for educational information regarding medication use in pregnancy and ongoing studies designed to learn more about medication exposure during pregnancy.

Male patients with RA must receive counseling about the effects of certain medications on their fertility. It is difficult to establish causality between use of a medication by a male and the effect on fertility or fetal development; therefore, a conservative approach must be taken. **KEY CONCEPT** Women of childbearing

Patient Care Process

Collect Information:

- Perform a medication history to determine current prescription, nonprescription, and dietary supplements. Inquire about previous medications for RA and reasons why they were discontinued. Ask about allergies (and the associated reaction) and immunizations.
- Determine whether physical examination findings and patient-reported symptoms are consistent with RA. Evaluate the duration of symptoms and impact on daily living.
- Review the medical history. Determine if comorbidities are present.

Assess the Information:

- Determine if any of the patient's medications are causing the signs or symptoms.
- Review laboratory test results to establish baseline renal and hepatic function and blood cell status. Review other findings specific to RA (RF, ACPA, etc).
- Determine disease severity.
- If the patient is already receiving pharmacotherapy for RA, assess efficacy, safety, and patient adherence.
- Review immunization history and determine if vaccinations are necessary prior to initiating new medications.

Develop a Care Plan:

- If newly diagnosed with RA, make sure the patient receives DMARD therapy immediately to minimize disease progression and joint destruction.
- Consider bridge therapy with an NSAID or glucocorticoid to provide symptomatic relief until the DMARD reaches its time to effect (Table 58–4).
- Review current medications to proactively identify potential drug interactions with the addition of one more DMARDs.
- Select DMARD therapy that is likely to be safe and effective (see Figures 58–2 and 58–3).
- Ensure that drug doses are optimal (see Table 58–4).
- Incorporate measures to control the increased risk of present comorbidities.
- *Cardiovascular:* Keep doses of NSAIDs and glucocorticoids low; consider initiating folic acid, low-dose aspirin, hypertensive and/or lipid therapy; encourage tobacco cessation, physical activity, and a healthy diet.[8,9] Screen and aggressively treat elevated blood pressure and lipids.
- *Infection:* Inform the patient to wash hands routinely, limit contact with individuals who are ill, and report signs and symptoms of infection immediately (eg, fever, weight loss, and night sweats).
- *Malignancy:* Have the patient report new signs and symptoms (eg, fever, chills, anorexia, and night sweats) immediately.
- *Osteoporosis:* Encourage the patient to ingest adequate amounts of calcium and vitamin D; consider initiating medications for prevention/treatment of osteoporosis (eg, a bisphosphonate) if the patient is taking glucocorticoids chronically or has evidence of low bone mineral density. Review glucocorticoid-induced osteoporosis guidelines.[17]

Implement the Care Plan:

- Educate the patient on pharmacologic and nonpharmacologic measures, including medication administration.
- Screen for tuberculosis if initiation of a bDMARD or tsDMARD is under consideration.
- Stress the importance of adherence with medications and laboratory monitoring.
- Determine whether the patient has prescription coverage. If not, determine if the patient is eligible for prescription assistance programs.

Follow-up: Monitor and Evaluate:

- Assess the patient's response to initiation of DMARD therapy after allowing adequate time for the medication to achieve its therapeutic effect.
- Determine whether any adverse reactions to medications are present.
- Reevaluate need for bridge therapy and discontinue if possible.
- Monitor laboratory parameters to ensure patient safety and reduce the risk of adverse reactions.
- Longitudinally evaluate the patient's clinical response to therapy and the impact on quality of life and mobility. If disease is controlled, consider tapering therapy to the lowest effective dose.[31]
- Assess patient understanding of RA and their medications. Provide additional education where appropriate.

potential and their partners must be counseled to: (a) use proper birth control while undergoing treatment for RA, and (b) involve healthcare providers in discussions regarding family planning to carefully consider all risks and treatment options.[19]

OUTCOME EVALUATION

- Rheumatologists rely on standardized criteria to assess treatment interventions through measurement of disease activity. The ACR uses criteria for improvement based on percentage improvement in tender and swollen joint count, and the presence of at least three or more of the following measures: (a) pain, (b) patient global assessment, (c) physician global assessment, (d) self-assessed physical disability, and (e) acute-phase reactants.[32] ACR20, ACR50, and ACR70 are common efficacy endpoints in clinical trials. The number corresponds with the percentage improvement. As drug development continues to evolve, the acceptable criteria for 20% improvement may be too low.
- Physical disability from RA can be measured through the Stanford Health Assessment Questionnaire (HAQ).[33,34] This patient self-assessment tool was developed to evaluate patient outcomes in five dimensions of chronic conditions: (a) disability, (b) discomfort, (c) drug adverse effects, (d) dollar costs, and (e) death. Clinicians and clinical studies in rheumatology use the HAQ to assess longitudinal changes that influence the patient's quality of life.[33,34]
- Before starting treatment for RA, assess the subjective and objective evidence of disease. For joint findings, this includes the number of tender and swollen joints, pain, limitations on use, duration of morning stiffness, and presence of joint erosions. Systemic findings may include fatigue and the presence of extraarticular manifestations. Obtain laboratory measurements of CRP and ESR. The impact of the disease on quality of life and functional status is also important.
- At follow-up visits, compare the patient's status to baseline or previous visits using standardized criteria for improvement of disease activity (ie, DAS-28) and the influence on quality of life.
- **KEY CONCEPT** In addition to designing an individualized therapeutic regimen to control the progression of RA, the clinician must evaluate the presence of comorbidities and implement measures to control the increased risk.

Abbreviations Introduced in This Chapter

ACPA	Anticitrullinated protein antibodies
ACR	American College of Rheumatology
CRP	C-reactive protein
DAS	Disease Activity Score
DMARD	Disease-modifying antirheumatic drug
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
HAQ	Health Assessment Questionnaire
HLA	Human leukocyte antigen
IL	Interleukin
JIA	Juvenile idiopathic arthritis
MCP	Metacarpophalangeal joint
MTP	Metatarsophalangeal joint
NSAID	Nonsteroidal anti-inflammatory drug
PIP	Proximal interphalangeal joint
RA	Rheumatoid arthritis
TNF	Tumor necrosis factor

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59

Osteoarthritis

Christopher R. Piszczatoski, Steven M. Smith, and John Gums

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the pathophysiologic mechanisms involved in the development of osteoarthritis (OA).
2. Identify risk factors associated with OA.
3. Recognize the clinical presentation of OA.
4. Determine the goals of therapy for individual patients with OA.
5. Formulate a rational nonpharmacologic plan for patients with OA.
6. Recommend a pharmacologic plan for treating OA, taking into consideration patient-specific factors.
7. Develop monitoring parameters to assess effectiveness and adverse effects of pharmacotherapy for OA.
8. Modify an unsuccessful treatment strategy for OA.
9. Deliver effective patient counseling, including lifestyle modifications and drug therapy, to facilitate effective and safe management of OA.

INTRODUCTION

KEY CONCEPT Osteoarthritis (OA) is the most common form of arthritis and is strongly related to age. Sometimes called degenerative joint disease, OA primarily affects the weight-bearing joints (eg, hips, knees, spine), but non–weight-bearing joints, especially hands, may also be involved. OA causes tremendous morbidity and financial burden because of its high prevalence and effect on joints critical for daily functioning.[1] OA is the leading cause of chronic mobility disability and the most common reason for total-hip and total-knee replacement.[2]

EPIDEMIOLOGY AND ETIOLOGY

Approximately 32.5 million Americans have signs and symptoms of OA.[3] OA is more common in women and older persons, affecting an estimated 18% of women and 10% of men over age 60 years. The knee is the most commonly affected joint, followed by the hand and hip.[4] Hip OA occurs more frequently in men. However, women tend to have more generalized disease and joint inflammation. The prevalence of OA in Black individuals is similar to Whites, but African Americans often experience more severe and disabling disease.

PATHOPHYSIOLOGY

OA is characterized by damage to diarthrodial joints and joint structures (Figure 59–1). The pathophysiology is multifactorial and typified by progressive destruction of joint cartilage, erratic new bone formation, thickening of subchondral bone and the joint capsule, bony remodeling, development of osteophytes, variable degrees of mild synovitis, and other changes.[5]

The earliest stages of OA are characterized by increasing water content and softening of cartilage in weight-bearing joints. As the disease progresses, proteoglycan content of cartilage declines, and eventually, cartilage becomes hypocellular. Procatabolic and proinflammatory changes precede cartilage degradation and are thought to play important roles in OA development and progression.[6]

Subchondral bone undergoes metabolic changes, including increased bone turnover, that appear to be precursors to tissue destruction. The normally contiguous bony surface becomes fissured. Persistent use of the joint eventually results in loss of cartilage, permitting bone-to-bone contact that ultimately promotes thickening and eburnation of exposed bone. Microfractures may appear in subchondral bone, and osteonecrosis may develop beneath the surface, especially in advanced disease.

New bone is formed haphazardly, creating osteophytes that extend into the joint capsule and ligament attachments and may encroach on joint space. Progressive loss of joint cartilage, subchondral damage, joint space narrowing, and changes in underlying bone and soft tissue may culminate in deformed, painful joints.

Classification

OA is classified as primary (idiopathic) or secondary. *Primary OA* is the predominant form, occurring in the absence of a known precipitating event. Primary OA may be localized, generalized, or erosive. Localized OA is distinguished from generalized disease by the number of sites involved. Erosive disease—typically in hand or foot joints—is characterized by erosive bone destruction and in some cases bony proliferations. Secondary OA results from congenital or developmental disorders or inflammatory, metabolic, or endocrine diseases.

Risk Factors

OA develops when systemic factors and biomechanical vulnerabilities combine. Systemic factors include increased age, female sex, genetic predisposition, and nutritional status. Age is the

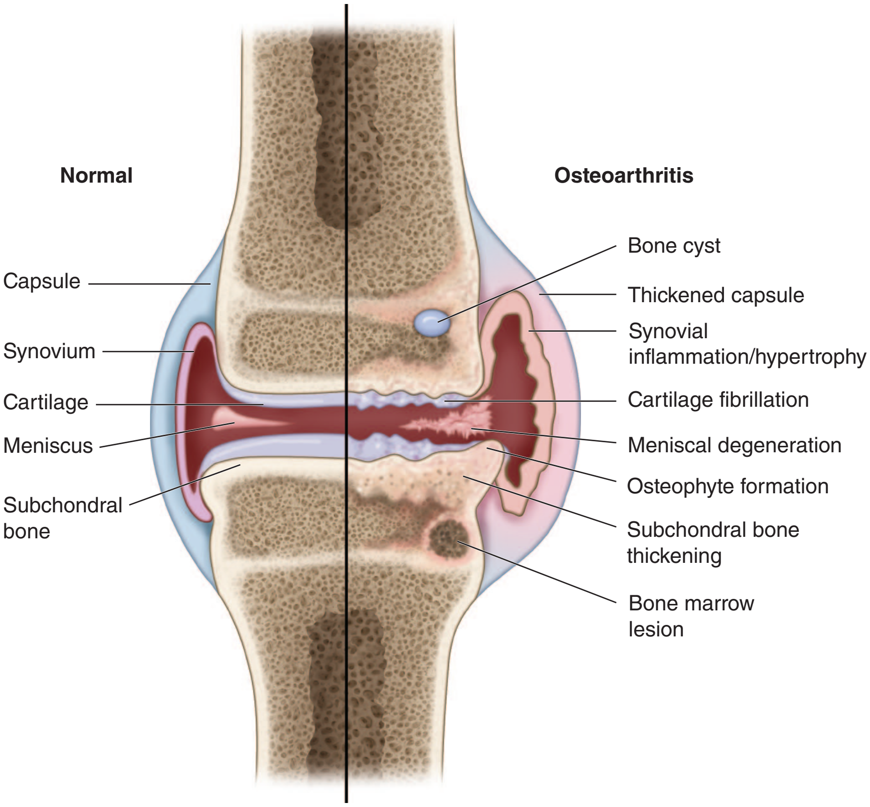
Normal
Osteoarthritis
Capsule
Synovium
Cartilage
Meniscus
Subchondral bone
Bone cyst
Thickened capsule
Synovial inflammation/hypertrophy
Cartilage fibrillation
Meniscal degeneration
Osteophyte formation
Subchondral bone thickening
Bone marrow lesion

FIGURE 59–1. Characteristics of osteoarthritis in the diarthrodial joint. (From DiPiro JT, Yee GC, Posey M, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York: McGraw-Hill; 2020: Fig. 90–2; with permission.)

strongest predictor of OA, although advanced age alone is insufficient to cause OA.

Joints exposed to biomechanical factors are at increased risk. Occupational and recreational activities involving repetitive motion or injury can provoke OA, although most daily activities do not produce enough joint trauma to cause OA. However, daily activities may lead to OA if a joint is susceptible because of previous injury, joint deformity, muscle weakness, or systemic factors. Heavy physical activity is a stronger predictor of OA than light-to-moderate activities, especially for older individuals, in whom

Clinical Presentation of OA

General

- Patients usually are more than 50 years old.
- Presentation may range from asymptomatic to severe joint pain and stiffness with functional limitations.
- Joint involvement has an asymmetric local distribution without systemic manifestations.
- Unlike some other arthritic conditions (eg, rheumatoid arthritis, gout), inflammation is usually absent or mild and localized.

Symptoms

- KEY CONCEPT The most common symptoms are joint pain, reduced range of motion, and brief joint stiffness after inactivity.
- The cardinal symptoms are use-related joint pain, typically described as deep and aching in character, and stiffness. In advanced cases, pain may occur continuously and at rest.
- Joint stiffness ("gelling") abates with motion and recurs with rest.
- Joint stiffness generally lasts fewer than 30 minutes after extended periods of inactivity, limits the range of joint motion, impairs daily activities, and may be related to weather.
- Weight-bearing joints may be unstable.

Signs

- One or more joints may be involved, usually in an asymmetric pattern.
- The following sites are most often involved in primary OA:
  - Distal interphalangeal finger joints (Heberden nodes)
  - Proximal interphalangeal finger joints (Bouchard nodes)
  - First carpometacarpal joint
  - Knees, hips, and cervicolumbar spine
  - Metatarsophalangeal joint of the great toe
- Joint examination may reveal local tenderness, bony prominence, soft tissue swelling, **crepitus**, muscle atrophy, limited motion with passive/active movement, and effusion.

joint structures are less capable of coping with highly stressful activities.[7] Obesity increases load-bearing stress on hip and knee joints. OA risk increases by 10% for each kilogram above ideal body weight.[8]

CLINICAL PRESENTATION AND DIAGNOSIS

OA is diagnosed clinically from symptoms and physical examination of the joint(s), sometimes supported by radiographic evidence (see Clinical Presentation of OA). Peripheral joint OA can be diagnosed by the presence of persistent usage-related joint pain in one or more joints, with morning stiffness lasting no more than 30 minutes, in patients at least 45 years of age.[9] Some patients develop bony enlargements of the fingers, called **Bouchard nodes** or **Heberden nodes**, in the absence of inflammation. Radiographic changes are often absent in early OA. As OA progresses, joint space narrowing, subchondral bone sclerosis, and osteophytes may develop. Laboratory tests are not helpful for diagnosing OA but may rule out related diseases. The erythrocyte sedimentation rate (ESR) and the hematologic and chemistry panels are usually unremarkable in OA. Synovial fluid aspirated from an affected joint should be sterile, without crystals, and with a white blood cell (WBC) count less than $1.5 \times 10^3/\text{mm}^3$ ($1.5 \times 10^9/\text{L}$). Gross joint deformity and joint effusions may occur in late severe OA.

TREATMENT

Desired Outcomes

KEY CONCEPT Goals of therapy include: (a) educating the patient and caregivers, (b) relieving pain, (c) maintaining or restoring mobility, (d) minimizing functional impairment and associated adverse outcomes (eg, falls), (e) preserving joint integrity, and (f) improving quality of life.

General Approach to Treatment

Treatment is individualized considering medical history, physical examination, radiographic findings, distribution and severity of joint involvement, and response to previous treatment. Comorbid diseases, concomitant medications, and allergies are integrated into a holistic treatment approach.

As shown in Figure 59–2, nonpharmacologic treatment is integral to achieving optimal outcomes and is the first step in OA management. Pharmacologic therapy is an adjunctive measure to relieve pain; available medications do not substantially modify the disease course. Surgical intervention generally is reserved for patients with advanced disease complicated by unremitting pain or severely compromised function.

Patient Encounter Part 1

A 72-year-old obese man presents to his primary care physician with right knee pain that has significantly worsened over the past several years. He describes the pain as deep and aching, with stiffness when he wakes up and that abates after moving around. He has used acetaminophen infrequently in the past, but states that the pain is now so significant and consistent that he is seeking recommendations. He is retired and states that the knee pain has interfered with his weekly golf game. This activity is the only exercise he gets and is his primary form of socializing, so he wants to regain as much function as possible.

What information is suggestive of osteoarthritis (OA)?

What risk factors for OA does this patient have?

What other information will you need to differentiate OA from rheumatoid arthritis?

What potential comorbidities should be considered in this patient?

What other information will be required before formulating a treatment plan?

Nonpharmacologic Therapy

KEY CONCEPT Nonpharmacologic therapy is the cornerstone of treatment: education, exercise, weight loss, and cognitive behavioral intervention are integral components.

Educational programs are designed to improve health behaviors and health status, thereby slowing OA progression. The goal is to increase patient knowledge and self-confidence in adjusting daily activities in the face of evolving symptoms. Effective programs produce positive behavioral changes, decrease pain and disability, and improve functioning and psychological outcomes (eg, depression, self-efficacy, life satisfaction). Patients can be referred to the Arthritis Foundation (www.arthritis.org) for educational materials and information on support groups.

Lifestyle modification should be encouraged for all patients at risk for, or with established OA. Low-impact exercise is advisable for most patients, especially with knee or hip OA. Aerobic exercise and strength-training programs improve functional capacity in older adults. Balance and stretching exercises, such as Tai Chi or yoga, can also be recommended. In general, exercises should target affected and vulnerable joints. Isokinetic and isotonic exercises performed at least three to four times weekly improve physical functioning and decrease disability, pain, and analgesic use. Clinicians should consider the patient's physical capabilities when implementing any exercise program. Referral to a physical or occupational therapist may be helpful, particularly in patients with functional disabilities. Physical therapy is tailored to the patient and may include assessment of muscle strength, joint stability, and mobility; use of heat (especially prior to increased activity); structured exercise regimens; and assistive devices such as canes, crutches, and walkers. Occupational therapists advise on optimal joint protection and function, energy conservation, and use of splints and other assistive devices.

The association between body weight and OA onset and progression make weight loss a pivotal goal in overweight and obese patients. Weight loss significantly reduces pain and improves function in patients with knee OA.[10] Women who reduce body weight by 5 kg (11 lb) can halve their risk of developing OA.[11] Weight loss should be pursued through diet modification and increased physical activity (see Chapter 102, Overweight and Obesity).

Knee braces may delay the progression of knee OA. Cane use and tibiofemoral or patellofemoral knee braces can be recommended for patients with OA causing significant issues with ambulation or joint stability.[11] Kinesiology taping, the application of an adhesive elastic that provides joint stability without hindering range of motion, may also be considered. Hand orthoses are strongly recommended for patients with carpometacarpal (CMC) OA. Modified shoes or wedged insoles are not recommended.[12]

Application of heat or cold to involved joints may improve range of motion, reduces pain, and decreases muscle spasms. Applications of heat include warm baths or warm water soaks. Heating pads should be used cautiously, especially in older

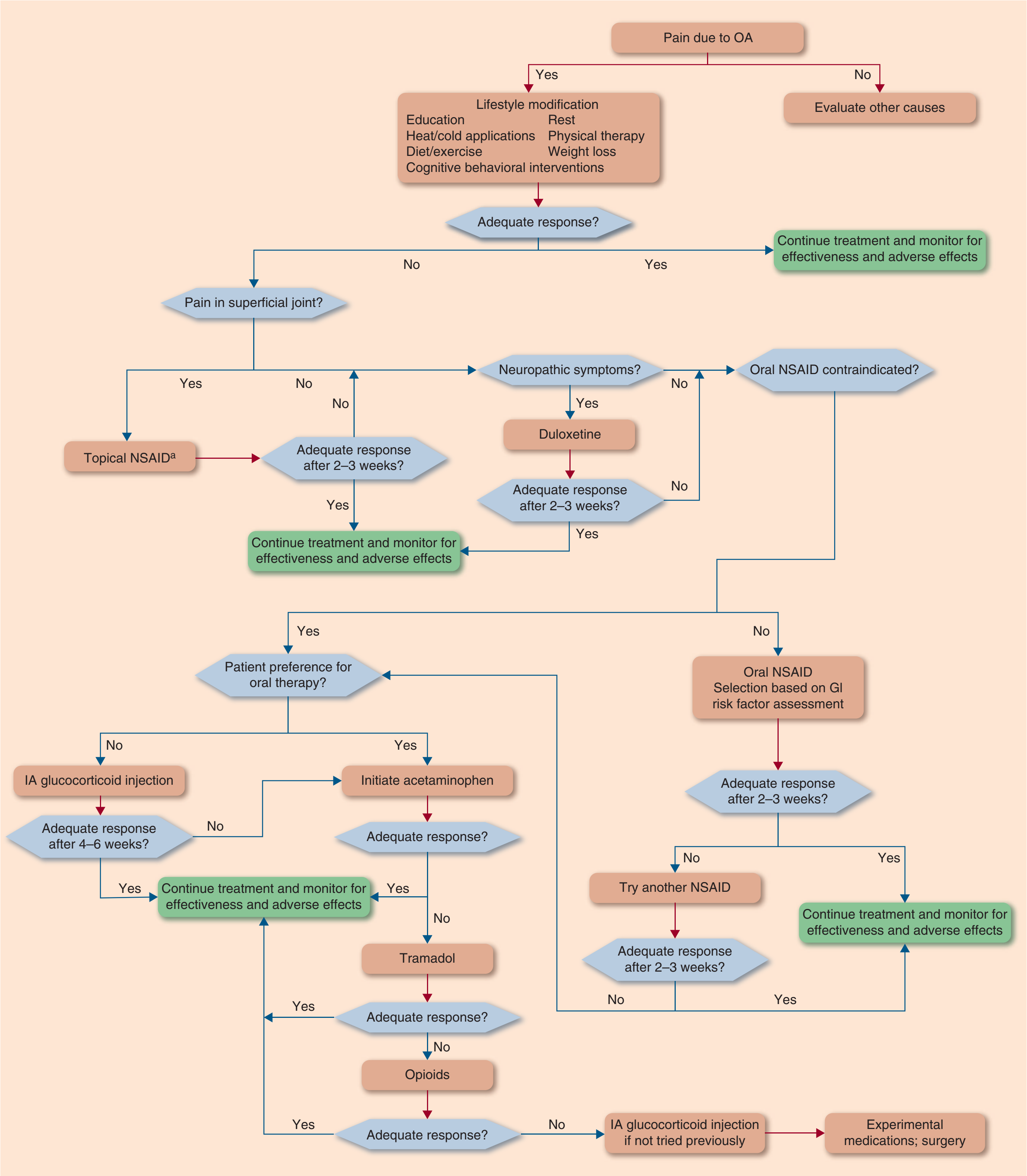
Pain due to OA
Yes
No
Lifestyle modification
Education
Rest
Heat/cold applications
Physical therapy
Diet/exercise
Weight loss
Cognitive behavioral interventions
Evaluate other causes
Adequate response?
No
Yes
Continue treatment and monitor for effectiveness and adverse effects
Pain in superficial joint?
Yes
No
Neuropathic symptoms?
No
Oral NSAID contraindicated?
No
Yes
Topical NSAID[a]
Adequate response after 2–3 weeks?
Duloxetine
Adequate response after 2–3 weeks?
No
Yes
Yes
Continue treatment and monitor for effectiveness and adverse effects
Yes
No
Patient preference for oral therapy?
Oral NSAID Selection based on GI risk factor assessment
No
Yes
IA glucocorticoid injection
Initiate acetaminophen
Adequate response after 2–3 weeks?
Adequate response after 4–6 weeks?
No
Adequate response?
No
Yes
Yes
Yes
Continue treatment and monitor for effectiveness and adverse effects
Try another NSAID
Continue treatment and monitor for effectiveness and adverse effects
No
Tramadol
Adequate response after 2–3 weeks?
No
Yes
Yes
Adequate response?
No
Opioids
Yes
Adequate response?
No
IA glucocorticoid injection if not tried previously
Experimental medications; surgery

FIGURE 59–2. Treatment of osteoarthritis.

(OA, osteoarthritis; CV, cardiovascular; IA, intra-articular; NSAID, nonsteroidal anti-inflammatory drug.)

[a]Topical NSAIDs can be considered before oral NSAIDs for superficial joints due to their favorable side effect profile.

persons, and patients must be warned of the potential for burns if used inappropriately.

Acupuncture, radiofrequency ablation, and paraffin (an alternative method of heat therapy) may offer some benefit, but robust evidence is lacking. Massage therapy may offer indirect benefits in symptom management. Current evidence does not support use of iontophoresis, pulse vibration therapy, and transcutaneous electrical stimulation (TENS).

Pharmacologic Therapy

Various topical, oral, and intra-articular (IA) therapies exist for managing OA, with nonsteroidal anti-inflammatory drugs (NSAIDs) representing the first line of treatment (Table 59–1).

▸ *Nonsteroidal Anti-Inflammatory Drugs*

Prostaglandins play an important role in the function of several organ systems. These compounds are synthesized via the interaction of two isoforms of the cyclooxygenase enzyme (COX-1 and COX-2) with their substrate, arachidonic acid.

The COX-1 enzyme is expressed constitutively in various body tissues (eg, gastric mucosa, kidney, platelets). Prostaglandins produced by the actions of the COX-1 enzyme in the gastrointestinal (GI) tract preserve GI mucosal integrity by increasing mucous and bicarbonate secretion, maintaining mucosal blood flow, and decreasing gastric acid secretion. Prostaglandins associated with COX-1 also promote normal platelet activity and function. In the kidney, COX-1–mediated prostaglandins dilate the afferent arteriole, thereby maintaining intraglomerular pressure and glomerular filtration rate when renal blood flow is reduced.

In contrast, the COX-2 enzyme is normally undetectable in most tissues, but its expression can be induced rapidly in the presence of inflammation and local tissue injury. This change leads to the synthesis of prostaglandins involved in pain and inflammation. Consequently, blocking the COX-2 enzyme is thought to result in analgesic and anti-inflammatory effects. All NSAIDs inhibit both the COX-1 and COX-2 enzyme isoforms, but nonselective NSAIDs (eg, ibuprofen, naproxen) are not particularly selective for one isoform, whereas COX-2 inhibitors (eg, celecoxib, and to a lesser extent, diclofenac) preferentially inhibit COX-2.

KEY CONCEPT NSAIDs are the first-line therapy, regardless of affected joint location.[12] NSAIDs reduce pain and improve functioning in patients with OA, although individual responses vary widely. The route of administration (ie, oral or topical) should be based on affected joint(s), patient preference, ability to administer, and an assessment of risk for adverse effects of systemic NSAIDs.

Topical NSAID administration minimizes systemic exposure while providing pain relief comparable to oral NSAIDs. Consensus guidelines strongly recommend topical NSAIDs in patients with knee OA. They may also be preferable in hand OA, although evidence regarding efficacy in this setting is less robust, and concerns have been raised regarding inadvertent drug removal during daily activities (eg, handwashing). Deeper joints, especially the hip, should not be treated with topical NSAIDs owing to insufficient drug penetration. Currently, the only commercially available topical NSAID in the United States is diclofenac, which is marketed in a variety of preparations (ie, solution, gel, topical patch) available both over-the-counter (gel formulation only) and by prescription. These products decrease pain and improve joint function, with similar efficacy across dosage forms.[13,14] Systemic absorption of topical diclofenac is significantly less than that of oral diclofenac. Thus, with proper administration, GI, cardiovascular, and renal adverse effects are rare and similar in incidence to placebo.[13,14] The most common adverse effects are application site dermatitis, pruritus, and phototoxicity.

For patients with OA affecting deeper joints (ie, hip, shoulder, spine), or who have not achieved adequate response to topical NSAIDs, an oral NSAID should be considered. **KEY CONCEPT** At equipotent doses, the analgesic and anti-inflammatory activities of all oral NSAIDs, including COX-2–selective inhibitors, are similar. The selection of a specific oral NSAID should be based on patient preference, previous response, tolerability, side-effect profile, dosing frequency, cost, and underlying GI risk. Pain relief occurs rapidly (within hours), but anti-inflammatory response occurs after 2 to 3 weeks of continuous therapy. This latter period is the minimal duration that should be considered an adequate oral NSAID trial. If an insufficient response is achieved with one oral NSAID, another oral NSAID should be tried.

KEY CONCEPT All systemic NSAIDs are associated with adverse GI, renal, hepatic, cardiovascular, central nervous system (CNS), and hypertensive effects, particularly in older individuals. Inhibition of the COX-1 enzyme is thought to be responsible primarily for the adverse effects on the gastric mucosa, kidney, and platelets. Direct irritant effects also may contribute to adverse GI events. Minor GI complaints, including nausea, dyspepsia, anorexia, abdominal pain, flatulence, and diarrhea, are reported by 10% to 60% of patients treated with oral nonselective NSAIDs. Asymptomatic gastric and duodenal mucosal ulceration can be detected in 15% to 45% of patients. Perforation, gastric outlet obstruction, and GI bleeding are the most severe complications and occur in 1.5% to 4% of patients annually.[15]

KEY CONCEPT COX-2 inhibitors are preferred for patients at high risk for GI complications.[16,17] Several risk factors predict a greater likelihood of GI complications in oral NSAID-treated patients (see Chapter 19, Peptic Ulcer Disease). Identifying at-risk patients based on symptoms alone is impractical because the presence of symptoms and actual gastroduodenal damage are poorly correlated. For patients at particularly high GI risk (eg, previous history of NSAID-induced GI bleed), a selective COX-2 inhibitor combined with a proton pump inhibitor reduces risk for GI hemorrhage more than a COX-2 inhibitor alone, which in turn has lower GI bleed risk than a nonselective NSAID combined with a proton pump inhibitor.[18-21] A COX-2 inhibitor alone, or a nonselective NSAID plus proton pump inhibitor, can be used in patients at moderate risk of GI complications.[16] See Chapter 18 (Gastroesophageal Reflux Disease) for more information on proton pump inhibitors.

COX-2 inhibitors have been associated with a greater risk of myocardial infarction than nonselective NSAIDs, which led to removal of rofecoxib and valdecoxib from the market.[22] However, direct comparison of naproxen, ibuprofen, and celecoxib suggests similar cardiovascular risk between these agents.[23,24] Nevertheless, all NSAIDs, except low-dose aspirin, increase cardiovascular risk.[25] To limit this risk, NSAIDs should be used at the lowest effective dose for the shortest duration, consistent with individual patient treatment goals. All oral NSAIDs can increase blood pressure, and patients with hypertension should be monitored within the first 2 to 4 weeks of initiation and periodically thereafter.[26]

All NSAIDs can cause adverse renal effects. Patients who are particularly susceptible include older persons and patients with chronic renal insufficiency, left ventricular dysfunction, and those taking diuretics or drugs that interfere with the renin–angiotensin system. These effects include decreased glomerular filtration, hyperkalemia, and sodium and water retention. Therefore, both nonselective NSAIDs and selective COX-2 inhibitors

Table 59–1

Dosing Parameters of Select Agents Used to Treat OA

Medication	Dosage and Frequency
Oral NSAIDs by Chemical Class	
Carboxylic acid (salicylates)	
Aspirin	325–650 mg every 4–6 hours; max 3600 mg/day
Salsalate	500–1000 mg two to three times daily; max 3000 mg/day
Acetic acid	
Etodolac	300–600 mg twice daily; max 1200 mg/day 400–1000 mg once daily (extended-release)
Diclofenac	50 mg two to three times daily 75 mg twice daily (delayed-release tablets) 100 mg once daily (extended-release tablets) 35 mg three times daily (submicron particle capsules) Max 150 mg/day from any formulation
Indomethacin	25 mg two to three times daily 75 mg one to two times daily (sustained-release) Max 200 mg/day from any formulation
Nabumetone	500–1000 mg one to two times daily; max 2000 mg/day
Propionic acid	
Ibuprofen	400–800 mg three to four times daily; max 3200 mg/day
Naproxen	250–500 mg two times daily 750–1000 mg once daily (controlled-release) 275–550 mg two times daily (naproxen sodium) Max 1650 mg/day from any formulation
Enolic acid	
Meloxicam	7.5–15 mg once daily; max 15 mg/day
Piroxicam[c]	20 mg once daily; max 20 mg/day
Coxibs	
Celecoxib[c]	100 mg twice daily or 200 mg once daily; max 200 mg/day
Para-aminophenol Derivative	
Acetaminophen	325 mg every 4–6 hours or 1000 mg every 6–8 hours; max 4000 mg/day (from all sources)
Serotonin-Norepinephrine Reuptake Inhibitors	
Duloxetine	30–60 mg once daily; max 60 mg/day
Opioids	
Tramadol	50–100 mg every 4–6 hours; max 400 mg/day (300 mg in elderly) CrCl < 30 mL/min (0.50 mL/s): 50–100 mg every 12 hours; max 200 mg/day
Oxycodone	5–15 mg every 4–6 hours (initial dose for opioid naïve); dose depends on degree of opioid tolerance and patient response
Topical Analgesics	
Capsaicin 0.025% or 0.075% cream	Apply to affected joint every 6–8 hours
Diclofenac sodium 1% gel	Upper extremity joints: 2 g four times daily; max 8 g[b] per upper extremity joint per day Lower extremity joints: 4 g four times daily; max 16 g[b] per joint per day
Diclofenac sodium 1.5% solution	40 drops per affected knee, four times per day; max 160 drops per day per knee
Diclofenac sodium 2% solution	40 mg (2 pump actuations) on each painful knee, two times a day; max 80 mg per day per knee
Intra-Articular Glucocorticoid Injection	
Triamcinolone acetonide	2.5–15 mg for single injection; doses can be adjusted to 20–40 mg; administered not more often than every 3 months
Triamcinolone acetonide extended-release	32 mg for a single knee injection
Methylprednisolone acetate	Small joints 4–10 mg; medium joints 10–40 mg; large joints 20–80 mg; administered no more often than every 3 months
Intra-articular Hyaluronic Acid Injection	
Hyaluronic acid	16–30 mg injected into the affected knee every week for a total of 3–5 weeks, depending on the product (see text)
Dietary Supplements	
Glucosamine sulfate	500 mg three times daily or 1500 mg once daily
Chondroitin	400–800 mg up to three times daily with glucosamine

[a] Serum salicylate levels should be monitored for doses greater than 3 g/day.

[b] Total daily dose of diclofenac 1% gel should not exceed 32 g for all affected joints.

[c] Substrate for CYP2C9, consider a 50% reduction in the initial dose in known or suspected poor metabolizers.

CrCl, creatinine clearance.

should be used with caution in patients with hypertension, heart failure, or chronic renal insufficiency. NSAIDs rarely cause tubulointerstitial nephropathy and renal papillary necrosis.

NSAIDs should be avoided if possible during pregnancy due to potential risks to the fetus. However, all NSAIDs should be strictly avoided starting at 30 weeks' gestation to prevent premature closure of the ductus arteriosus in the fetus.

Nonselective NSAIDs and selective COX-2 inhibitors are prone to drug interactions due to high protein binding, detrimental renal effects, and antiplatelet activity. Interactions are encountered frequently with aspirin, warfarin, oral hypoglycemics, antihypertensives, and lithium. When potential interactions are present, vigilant monitoring is warranted for therapeutic efficacy (eg, NSAIDs blunt the antihypertensive efficacy of diuretics) and adverse effects (eg, NSAIDs increase the risk of bleeding in anticoagulated patients).

▶ *Acetaminophen*

Acetaminophen is a centrally acting analgesic that inhibits prostaglandin production in the brain and spinal cord that has historically been recommended as a first-line treatment option for OA. Recent evidence indicates that acetaminophen monotherapy is ineffective or only modestly better than placebo for long-term OA treatment in most individuals.[27] **KEY CONCEPT** Nevertheless, acetaminophen is an inexpensive analgesic appropriate for short-term/episodic use in those who cannot tolerate or have contraindications to NSAID use.[12]

Acetaminophen should be administered initially on an as-needed basis in divided doses up to 4 g daily. Single doses should not exceed 1 g. Some patients may require scheduled dosing to achieve adequate pain relief. Periodic assessment of pain control should be performed to maintain the lowest effective dose. A sufficient trial is defined as up to 4 g daily in divided doses for 4 to 6 weeks.

Despite being among the safest analgesics, acetaminophen can cause significant adverse effects, including hepatic and renal toxicity.[28] Acetaminophen overdose, both intentional and unintentional, is the leading cause of acute liver injury in the United States.[29] Total daily doses greater than 4 g are associated with increased risk of hepatotoxicity. Daily doses of 4 g have been associated with significant liver enzyme elevations, but such elevations do not necessarily portend hepatotoxicity.[30] Concomitant use of alcohol may increase risk of hepatic injury; a maximum acetaminophen dose of 2.5 g daily is recommended for patients who consume more than 2 to 3 alcoholic beverages daily. Acetaminophen does not appear to exacerbate stable, chronic liver disease, but liver function should be monitored regularly in this population.[28] Careful inventory should be taken of all concomitant prescription and over-the-counter (OTC) products to minimize the risk of inadvertent acetaminophen overdose.

▶ *Duloxetine*

Duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI), is a centrally acting adjunctive option for patients achieving suboptimal response to oral NSAIDs. Duloxetine can be used as monotherapy or in combination with other agents.[12] Studies of duloxetine have primarily been in knee OA and revealed moderate benefits on pain, function, and quality of life.[31] Such effects may be reasonably extrapolated to hand and hip OA. Benefits typically are observed only after several weeks of therapy with moderate doses (ie, 60 mg/day); larger doses do not provide additional benefit. Duloxetine may be preferred as an adjunct in patients experiencing concurrent neuropathic and musculoskeletal pain. The most common adverse events are nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis.[32] Other centrally acting agents with similar mechanisms of action (eg, selective serotonin reuptake inhibitors [SSRI], SNRIs, tricyclic antidepressants [TCA], gabapentin, and pregabalin) have no current role in OA treatment. Concomitant use with other serotinergic agents should be pursued cautiously due to an increased risk of serotonin syndrome. For more duloxetine information, see Chapters 39 (Major Depressive Disorder) and 40 (Bipolar Disorder).

▶ *Tramadol*

Tramadol is an oral, centrally acting synthetic opioid analgesic that also weakly inhibits serotonin and norepinephrine reuptake. Evidence suggests that it imparts a modest benefit in the long-term management of noncancer pain.[33] However, tramadol appears to have minimal effect for OA pain specifically.[34] It is therefore only recommended in patients who have failed or have contraindications to other oral and IA options.[12] Tramadol should be recommended over other opioid agents if an opioid is being considered.

Common adverse events include dizziness, vertigo, nausea, vomiting, constipation, and lethargy. These effects are more pronounced for several days after initiation or a dose increase, and often lead to treatment discontinuation.[34] Seizures have been reported rarely; the risk is dose-related and appears to increase with concomitant use of antidepressants, such as tricyclics or SSRIs. Tramadol should be avoided in patients receiving other serotenergic agents due to the potential for serotonin syndrome.

▶ *Other Opioid Analgesics*

Opioid analgesics other than tramadol are reserved for patients experiencing severe pain for which alternative options are inadequate or contraindicated (eg, renal failure, heart failure, anticoagulation). Opioids may offer symptomatic improvement in patients with OA who are unresponsive to nonpharmacologic therapy and nonopioid analgesics. However, opioids also greatly increase the risk for addiction and other serious adverse effects that limit their use in most patients. Current guidelines strongly recommend against initiating opioids before exhausting other options.[12,17] Evidence has shown only modest improvements in OA pain with oxycodone, oxymorphone, morphine, hydromorphone, codeine, buprenorphine, and transdermal fentanyl, but with significant risk of serious side effects.[35]

Opioids should be initiated with short-acting agents at low doses and titrated to the lowest effective dose for the shortest possible duration to minimize adverse events. When feasible, opioids should be combined with acetaminophen or oral NSAIDs to reduce the opioid requirement. However, adverse effects from opioids are common even with the lowest effective doses.[35] Common or serious adverse effects include nausea, constipation, sedation, and respiratory depression. Use of combination opioid-acetaminophen products should be accompanied by clear instructions to limit additional use of OTC acetaminophen to avoid unintentional overdose.

Clinicians should establish realistic pain and function goals for all patients before starting opioid therapy. The US Centers for Disease Control and Prevention recommends taking a detailed history, providing information regarding treatment expectations, and developing a management plan with goals and safeguards, including how opioid therapy will be discontinued if benefits do not outweigh risks (see Chapter 35, Pain

Management). Additional recommendations to mitigate the risk of opioid therapy misuse include frequent follow-up, urine drug testing initially and at least yearly thereafter to assess use of prescribed medications or other illicit substances, and use of prescription drug monitoring programs to identify filling of opioid prescriptions from other providers. Patient response to opioid therapy should be assessed within 1 to 4 weeks of initiation or dose increase and every 3 months thereafter. Clinicians should use both nonopioid analgesics and nondrug therapies, as appropriate, to lower opioid doses or taper to opioid discontinuation.

▸ *Intra-Articular Therapy*

IA therapy is an alternative to oral and topical agents for joint pain treatment, typically used after failure of first-line oral or topical NSAID therapy. Two therapies, glucocorticoids and hyaluronic acid, are approved for IA injection. IA glucocorticoid injection is remarkably effective for reducing pain in the short term (weeks). Glucocorticoids are strongly recommended over hyaluronic acid in consensus guidelines, especially for knee or hip OA.[12] Hylauronic acid may offer some benefit, however many of the studies supporting its use are of low quality.[36] Both treatments are used to improve symptoms but do not reverse disease progression.

Glucocorticoids Glucocorticoids with reduced solubility, such as methylprednisolone and triamcinolone, are usually preferred. The affected joint can be aspirated and subsequently injected with the chosen agent. The aspirate should be examined for the presence of crystal formation and infection. Pain relief begins within days after the injection but may wane beyond 3 weeks for most agents. Triamcinolone acetonide extended-release may provide pain relief for up to 12 weeks. Glucocorticoid injections should be administered as infrequently as possible to avoid joint damage. Specifically, a single joint should generally not be treated more than every 3 months to reduce the risk of glucocorticoid-induced cartilage and joint damage. Because the recommended dosing interval exceeds the typical duration of benefit for most agents, IA glucocorticoids are usually ineffective as monotherapy for chronic OA treatment.

The crystalline nature of glucocorticoid suspensions can provoke a postinjection flare that mimics the flare of arthritis and inflammation that accompanies infection. Cold compresses and analgesics are recommended to treat symptoms in affected patients. There is concern that use of IA glucocorticoid therapy can lead to loss of hyaline cartilage and acceleration of OA progression.[37,38]

Hyaluronic Acid The mechanism of action of hyaluronic acid is not fully understood. Healthy cartilage and synovial fluid are replete with hyaluronic acid, a viscous substance believed to facilitate lubrication and shock absorbency under varying load-bearing conditions. Patients with OA demonstrate an absolute and functional decline in hyaluronic acid; thus, exogenous administration is referred to as viscosupplementation.

Pain and joint function following IA hyaluronic acid injections have been evaluated frequently in clinical trials, most of which were of low quality. Treatment courses are typically expensive and may not confer benefit over the placebo effect. Several hyaluronic acid formulations are available in the United States for knee OA:

- Durolane: 60 mg (3 mL) for a single injection
- Euflexxa: 20 mg (2 mL) injected every week for a total of 3 weeks
- Gelsyn-3: 16.8 mg (2 mL) injected every week for a total of 3 weeks
- Gel-One: 30 mg (3 mL) for a single injection
- GenVisc 850: 25 mg (2.5 mL) injected every week for a total of five injections
- Hyalgan: 20 mg (2 mL) injected every week for a total of five injections
- Monovisc: 88 mg (4 mL) for a single injection
- Orthovisc: 30 mg (2 mL) injected every week for a total of 3 to 4 weeks
- Supartz FX: 10 mg (1 mL) injected every week for a total of five injections
- Synvisc: 16 mg (2 mL) injected every week for a total of 3 weeks
- Synvisc-One: 48 mg (6 mL) for a single injection
- TriVisc: 25 mg (2.5 mL) injected every week for a total of 3 weeks

Injections are generally well tolerated, although patients may report injection site reactions. A local anesthetic such as lidocaine may be injected simultaneously to provide more rapid onset of pain relief. Patients should be counseled to minimize activity and stress on the joint for several days after each injection. As an injectable agent, there is a small risk of infection. Additionally, injections are more expensive than oral options, which may limit their use.

▸ *Over-the-Counter Agents*

Glucosamine and Chondroitin Glucosamine is believed to function as a "chondroprotective" agent, stimulating the cartilage matrix and protecting against oxidative chemical damage. Consensus guidelines do not support the use of glucosamine due to inconsistent efficacy and large placebo effects in most trials. Despite this, glucosamine is one of the most commonly used dietary supplements. Chondroitin, often administered with glucosamine, is thought to inhibit degradative enzymes and serve as a substrate for proteoglycan production.[12] Chondroitin is not recommended in knee and hip OA, but limited evidence from a single trial suggest it may be suitable for hand OA.[12] If used, these agents should be adjuncts to evidence-based nonpharmacologic and pharmacologic therapies and discontinued after 3 to 6 months if no benefit is achieved.

Patients with shellfish allergies should be warned of the potential for severe anaphylactic reactions with the use of glucosamine products (derived from crab, lobster, or shrimp shells). Because the allergic reaction is caused by shellfish proteins rather than the animal shell, most products pose little risk.[39] However, patients should be aware that products may be contaminated with shellfish proteins given that these agents are loosely regulated in the United States as dietary supplements, product standards are inconsistent, and the constituents are not validated by any regulatory agency. Additionally, glucosamine may alter cellular glucose uptake, thus elevating blood glucose levels in patients with diabetes.[40] Because the clinical significance of this is unclear, blood glucose levels in diabetic patients should be monitored closely after glucosamine initiation or dosage adjustments.

Other Topical Agents Limited data support use of salicylate-containing rubefacients (eg, methyl salicylate, trolamine salicylate) or other counterirritants (eg, menthol, camphor, methyl nicotinate) in OA.[41] See Chapter 61 (Musculoskeletal Injuries) for more information on these products.

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Obesity (BMI 37 kg/m^2), HTN, T2DM × 15 years, asthma, COPD, hyperlipidemia

PSH: Carpal tunnel surgery 5 years ago

FH: Father had OA of the hip and knee; mother died of breast cancer at 76

SH: Retired businessman; drinks 6 to 12 beers per week; smokes cigars while golfing; denies illicit drug use

Allergies: NKDA; shellfish allergy (hives)

Meds: Lisinopril 40 mg once daily; atorvastatin 40 mg once daily; fluticasone 250 mcg/salmeterol 50 mcg 2 inhalations twice daily; albuterol 1 to 2 puffs as needed for wheezing/shortness of breath; metformin 1000 mg twice daily; empagliflozin 10 mg once daily

ROS: (+) SOB on exertion, right knee pain 7/10 in the mornings, 5/10 while golfing

PE:

VS: BP 130/76 mm Hg, pulse 64 beats/min, RR 11 breaths/min, T 98.6°F (37.0°C).

Skin: Warm, dry, cracked skin on feet bilaterally.

HEENT: NC/AT, PERRLA, TMs intact.

CV: RRR, normal S_1 and S_2, no m/r/g.

Chest: CTA

Abd: Soft, NT/ND.

Neuro: A&O × 3; CN II to XII intact.

Ext: No edema, swelling, or tenderness of the soft tissue surrounding right knee. Noticeable decreased range of motion of the right knee. No other joint involvement.

Labs: ESR 11 mm/hour; basic metabolic panel within normal limits.

Knee x-rays: Right knee shows joint space narrowing, minor osteophyte formation, and subchondral bone sclerosis.

What clinical parameters are consistent with a diagnosis of OA?

What are the treatment goals for this patient?

What nondrug options are available to treat this patient?

What pharmacologic options are available to treat this patient?

What factors are important to consider when selecting medications for this patient?

Capsaicin relieves pain by depleting substance P from spinal sensory neurons, thereby decreasing pain transmission. Capsaicin is not effective for acute pain; it may take up to 2 weeks of daily administration to relieve pain. As with other topical products, capsaicin is best suited for treating superficial joints (eg, hand OA). The lower concentration (0.025%) is better tolerated, but most patients experience a localized burning sensation. The discomfort usually does not result in discontinuation and often abates within the first week with regular use. Contact with eyes or mucous membranes should be avoided and patients should be counseled to wash their hands after application.

Surgery

Surgery generally is reserved for patients who fail medical therapy and have progressive limitations in activities of daily living. In joint replacement surgery (arthroplasty), the damaged joint surfaces are replaced with metal or plastic prostheses. Hip and knee joints are most commonly replaced, but arthroplasty may also be performed on shoulders, elbows, fingers, and ankles. Total knee arthroplasty combined with physical and medical therapy improves knee OA symptoms more than physical and medical therapy alone.[42] Most patients achieve significant pain relief and functional restoration after arthroplasty, and it is a reasonable option in carefully selected patients.

Surgical debridement may be performed arthroscopically. With this procedure, a tiny video camera is inserted into the affected joint through a small incision, and the surgeon removes torn cartilage or other debris from the joint. The long-term benefits of arthroscopic surgery for OA are unclear, and it may be no better than optimized physical and medical therapy.[43]

OUTCOME EVALUATION

- At baseline, quantify pain using a visual analog scale, assess range of motion of affected joints, and identify activities of daily living that are impaired.
- In patients treated with acetaminophen or oral NSAIDs, assess pain control after 2 to 3 weeks. Full anti-inflammatory effects of NSAIDs may take longer to occur.
- Incorporate other measures to track disease progress. Use radiography to assess severity of joint destruction, determine 50-ft (~15-m) walking time and grip strength, and administer the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Stanford Health Assessment Questionnaire, where appropriate, to assess activities of daily living.
- If pain control is adequate, continue the current therapy at the lowest effective dose. If pain is improving but still inadequate, titrate to maximum therapeutic dose or consider adjunctive agents. If the patient has no improvement after 2 weeks, assess medication adherence and consider switching therapy.
- Ask patients if they are experiencing side effects or other problems with their medications and respond with more specific questions.
- Educate patients to not exceed maximum daily doses of medications.

Patient Encounter Part 3: Creating a Care Plan

Based on the available information, create a care plan for this patient's OA. The plan should include:

(a) A statement of the drug-related needs and/or problems

(b) An individualized, detailed therapeutic plan

(c) A plan for follow-up monitoring to document the patient's response and identify adverse reactions

Pharmacist's Patient Care Process

Collect Information:

- Obtain a thorough history of previous device and drug use, including prescription drugs, OTC drugs, and dietary supplements.
- Ask the patient about known allergies to medications and other substances, including type and severity of reaction.
- Determine lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect overall patient care.
- Consider obtaining laboratory tests depending on degree of clinical suspicion for inflammatory etiology (eg, ESR, C-reactive protein [CRP], rheumatoid factor [RF], antinuclear antibodies [ANA]).

Assess the Information:

- Determine whether the patient's symptoms are consistent with OA. Review the medical history to determine whether other rheumatic diseases may be involved.
- Assess symptoms to determine whether pain warrants additional attention. Does the pain affect quality of life or interfere with activities of daily living?
- Assess radiographs for diagnosis and disease severity (joint-space narrowing, subchondral bone sclerosis, osteophyte formation, joint deformity, joint effusion).

Develop a Care Plan:

- At baseline, quantify pain using a visual analog scale, assess range of motion of affected joints, and identify activities of daily living that are impaired.
- Evaluate the effectiveness of current or previous pharmacotherapy, including dose, frequency, and duration to determine whether an adequate trial was given.
- Establish realistic treatment goals with the patient, including acceptable levels of pain and function.
- Formulate a plan for lifestyle modifications and alteration/addition of pharmacotherapy that considers risks, benefits, and patient preference, given the patient's medical history, concomitant medications, and previous response to OA therapies.

Implement the Care Plan:

- Discuss with the patient any modifications to nondrug or pharmacological treatment plans and how to implement the new care plan.
- Address patient concerns related to OA and its treatment, with special focus on the expected benefits and potential adverse effects of medications.
- Emphasize the value of adherence to medication regimens and lifestyle modifications.
- Facilitate adherence by implementing medication regimens and lifestyle plans that are simple and consistent with the patient's lifestyle.

Follow-up: Monitor and Evaluate:

- Schedule follow-up within 1 to 2 weeks to assess the effectiveness of therapy and associated adverse effects; the specific time frame depends on patient factors and the treatment regimen chosen.
- If laboratory tests (eg, renal function for NSAIDs) are appropriate for monitoring drug therapy, provide the patient with an order for the laboratory test(s) and instructions to complete them before the follow-up appointment.
- If the patient has hypertension and is taking an oral NSAID, monitor blood pressure at each follow-up visit within 2 to 4 weeks of initiating therapy and then every 1 to 2 months.
- Document whether the patient has had improvements in pain, quality of life measures, mobility and functioning, ability to perform activities of daily living, and well-being.
- If pain control is adequate, continue the current therapy at the lowest effective dose. If pain is improving but still inadequate, titrate as needed to the maximum therapeutic dose or consider adjunctive agents. If the patient has no improvement after 2 weeks, assess medication adherence and consider switching therapy.
- Ascertain new OTC medication use; for patients prescribed acetaminophen or oral NSAIDs, pay particular attention to OTC sources of these drugs.
- Evaluate for the presence of adverse drug reactions, drug hypersensitivity, and potential drug interactions.

- Consider baseline liver function tests in patients being prescribed acetaminophen who are at high risk for hepatotoxicity.
- Assess acetaminophen exposure from all sources, including OTC products.
- In patients with hypertension, who are taking oral NSAIDs, monitor blood pressure at baseline, every 2 to 4 weeks for 1 to 2 months, and then periodically thereafter.
- For patients prescribed NSAIDs, monitor for weight gain, edema, and skin rash, and inquire about CNS adverse effects such as headaches and drowsiness at baseline and at least every 6 to 12 months.
- Evaluate serum creatinine, complete blood count, and serum transaminases at baseline and at every 6 to 12 months in patients treated with oral NSAIDs or acetaminophen.
- Perform stool guaiac in patients taking oral NSAIDs when clinically indicated.
- Monitor for drug interactions, including with alcohol, at every visit.

Abbreviations Introduced in This Chapter

ANA	Antinuclear antibodies
BMI	Body mass index
CMC	Carpometacarpal
CNS	Central nervous system
COX	Cyclooxygenase
CRP	C-reactive protein
CYP	Cytochrome P450

ESR	Erythrocyte sedimentation rate
GI	Gastrointestinal
IA	Intra-articular
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
OTC	Over-the-counter
RF	Rheumatoid factor
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

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Gout and Hyperuricemia

Maria Miller Thurston and Jenny Lin

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the pathophysiologic mechanisms underlying gout and hyperuricemia.
2. Recognize major risk factors for developing gout in a given person.
3. Assess the signs and symptoms of an acute gout attack.
4. List the treatment goals for a patient with gout.
5. Develop a pharmacotherapeutic plan for a patient with acute gouty arthritis that includes individualized drug selection and monitoring for efficacy and safety.
6. Identify patients for whom prophylactic urate-lowering therapy for gout and hyperuricemia is warranted.
7. Formulate appropriate educational information for a patient on lifestyle modifications to help prevent gouty arthritis attacks.
8. Select an appropriate drug to reduce serum uric acid (SUA) levels in patients with gout, and outline a plan for monitoring efficacy and toxicity.

INTRODUCTION

KEY CONCEPT Gout is an inflammatory condition of the arthritis-type that results from deposition of uric acid crystals in joint spaces or surrounding tissues, leading to an inflammatory reaction that causes intense pain, erythema, and joint swelling. It is associated with hyperuricemia, defined as a serum uric acid (SUA) level of 6.8 mg/dL (404 μmol/L) or greater, but not all patients with hyperuricemia demonstrate symptoms.[1] Four organizations publish guidelines that provide recommendations for the diagnosis and/or management of gout.[2–8] There is much similarity in the recommendations, and this chapter focuses primarily on the American College of Rheumatology (ACR) guideline for the management of gout.[5] However, the American College of Physicians (ACP) guideline includes some distinct and controversial differences.[7,8]

EPIDEMIOLOGY AND ETIOLOGY

The National Health and Nutrition Examination Survey (NHANES) 2019 estimates that gout affected about 9.2 million adults (3.9%) in 2015–2016, with gout occurring two to six times more frequently in men than women.[9,10] The incidence increases due to unhealthy dietary habits, lack of exercise, and obesity.[10] There is also a significant economic cost and humanistic burden associated with gout that increases with worsening disease severity.[11]

Dietary risk factors for developing gout include ingestion of purines, fructose, and alcohol. Patients experiencing frequent attacks and those with poorly controlled advanced disease should be educated to avoid sweetbreads (organ meats such as thymus and pancreas), liver, and kidney meat; high-fructose corn syrup; and alcohol use.[5] Other risk factors include male sex and obesity.[12] Trauma and surgery may also trigger acute gout attacks by increasing SUA.[13] Uric acid excretion is reduced in patients with chronic kidney disease (CKD), putting them at risk for hyperuricemia. Gout involves multiple organ systems and is associated with cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), CKD, and metabolic syndrome. There is an association between high SUA and endothelial dysfunction, which can promote atherosclerosis.[14] Prospective data indicate that gout is an independent risk factor for coronary heart disease,[15] and the cardiovascular impact of urate-lowering therapy continues to be investigated.[16–18]

KEY CONCEPT Some drugs can cause hyperuricemia and precipitate gout, such as thiazide and loop diuretics, niacin, pyrazinamide, calcineurin inhibitors, and aspirin. In most cases, these drugs block uric acid secretion in the kidney. The effect of aspirin on uric acid is dose-dependent. Aspirin in high analgesic doses (600–2400 mg/day) blocks uric acid reabsorption by the kidneys, increasing uric acid excretion. Aspirin doses below 600 mg/day inhibit uric acid excretion and can elevate SUA levels.[4] However, patients with hyperuricemia or gout and cardiovascular risk factors should continue low-dose aspirin (eg, 81–325 mg/day) for myocardial infarction or stroke prevention, if indicated, because the cardiovascular benefit outweighs the minimal effect on serum urate.[5]

PATHOPHYSIOLOGY

Gout is caused by an abnormality in uric acid metabolism. Uric acid is a waste product of purine breakdown contained in the DNA of degraded body cells and dietary protein. It is water-soluble and excreted primarily by the kidneys, although some is broken down by colonic bacteria and excreted via the gastrointestinal (GI) tract. The SUA level is determined by hepatic production of urate minus urate excretion by the kidneys and GI tract.[13]

Uric acid solubility is dependent on concentration and temperature. At SUA concentrations greater than 6.8 mg/dL (404 µmol/L), monosodium urate (MSU) precipitates, forming crystals. Collections of these crystals (called microtophi) can form in joint spaces in distal extremities as well as soft tissues such as tendons and ligaments. Larger tophi may take 10 years or longer to develop.

Free urate crystals can activate neutrophils and macrophages, which release proinflammatory mediators, including tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), and IL-8. This signals chemotactic movement of neutrophils into the joint space that phagocytize MSU crystals. These neutrophils are then lysed, releasing proteolytic enzymes that trigger the clinical manifestations of an acute gout attack, such as pain and swelling. Inflammatory mechanisms in gout, especially in untreated disease, can lead to cartilage and joint destruction.

The reference range for SUA is 3.6 to 6.8 mg/dL (214–404 µmol/L), and the risk of gout increases as the SUA concentration increases. However, only about 20% of patients with asymptomatic hyperuricemia and SUA greater than 9 mg/dL (535 µmol/L) develop gout within 5 years.[5] Increased SUA concentration involves either the underexcretion (90% of patients) or overproduction of uric acid.[1] The cause is unknown, but there may be genetic influences on uric acid regulation.[10] Observational studies also imply that multifactorial variables, such as sex, age, and ethnicity, affect the underexcretion and overproduction of SUA.[19] In patients with persistently acidic urine and hyperuricemia, uric acid nephrolithiasis can occur. In severe cases, uric acid stones can cause nephropathy and renal failure. KEY CONCEPT Long-term consequences of gout and hyperuricemia include joint destruction, tophi, nephrolithiasis, and nephropathy.

CLINICAL PRESENTATION AND DIAGNOSIS

Refer to the accompanying box for the clinical presentation of acute gout.

Diagnosis

A presumptive diagnosis is often based on presenting symptoms, such as development of severe pain within the past 24 hours, erythema, and swelling in a joint.[1] Gout may be confirmed later with laboratory and other diagnostic tests. Not all patients with signs and symptoms of an acute gout attack have hyperuricemia. The SUA level may be normal or even decreased during an acute attack. An acute gout attack usually occurs in the lower extremities, especially the first metatarsophalangeal joint, which is known as podagra.[1] Acute gout is accompanied by markers of inflammation such as an elevated white blood cell (WBC) count, increased erythrocyte sedimentation rate, tenderness, swelling, and loss of function in the affected area.[10]

Chronic tophaceous gout is diagnosed when the crystals accumulate and form tophi, which may lead to destruction and deformity of the joints. Although difficult to perform, aspiration of affected joint fluid or a tophus is essential for a definitive diagnosis.[7] Needle-shaped negatively birefringent MSU crystals in the aspirate confirm the diagnosis, allowing for the differentiation of tophi from other nodules (Figure 60–1).[10] Joint fluid may also have an elevated WBC count with neutrophils predominating.[2]

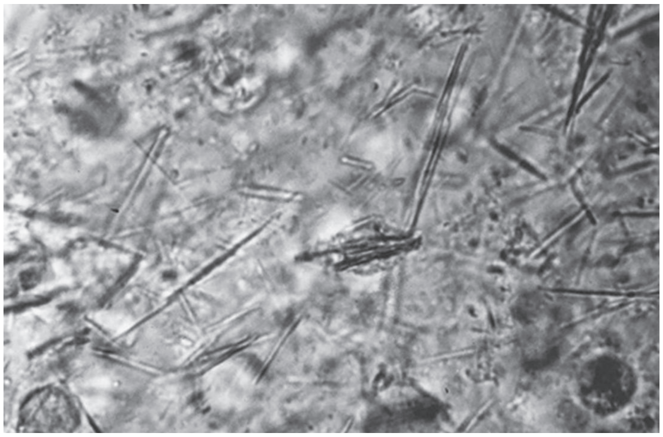

FIGURE 60–1. Synovial fluid containing extracellular and intracellular needle-like, negative birefringent monosodium urate crystals. (Reprinted with permission from: Schumacher HR, Chen LX. Chapter 365. Gout and Other Crystal-Associated Arthropathies. In: Jameson JL, Kasper DL, Longo DL et al., eds, Harrison's Principles of Internal Medicine, 20th ed. New York: McGraw-Hill; c2018 [cited 2020 May 20]. Available from: https://accesspharmacy.com.

Radiographs of affected joints may have characteristic cystic changes, punched-out lytic lesions with overhanging bony edges, and soft-tissue calcified masses. These signs may also appear in other arthropathies and are generally not apparent with the first acute gout attack.[20] Therefore, radiographs are often reserved for patients with long-standing disease.

A 24-hour urine collection can determine whether the patient is an overproducer or an underexcretor of uric acid. Individuals who excrete more than 800 mg (4.8 mmol) of uric acid are overproducers. Patients with hyperuricemia who excrete less than 600 mg/day (3.6 mmol/day) are classified as underexcretors. However, this approach is not often used because the urine collection is inconvenient for patients and clinicians, and it does not identify patients who may be both overproducers and underexcretors.

Clinical Presentation of Acute Gout

General

- Acute inflammatory monoarthritis.
- Patients are usually in acute distress.

Symptoms

- There is severe pain and swelling in the affected joint(s).
- Symptoms reach maximal intensity within 6 to 12 hours.
- The attack is usually monoarticular; the most common site is the metatarsophalangeal joint.
- In older patients, gouty attacks may be atypical with insidious and polyarticular onset, often involving hand or wrist joints.

Signs

- Affected joint(s) are warm, erythematous, and swollen.
- Mild fever may be present.
- Tophi (usually on hands, wrists, elbows, or knees) may be present in chronic, severe disease.

Patient Encounter Part 1

A 53-year-old African American woman presents to the rheumatology clinic with complaints of excruciating pain in her left elbow that has progressed quickly since onset yesterday evening. She is a poor historian but reports no recent injuries. She states that these symptoms have occurred three times within the past year. Furthermore, she reports using herbal supplements since pain medications seem to make her break out. On examination, she can barely move her left elbow due to pain, and it is red, swollen, tender, and warm to the touch. She also has radiographic evidence of multiple small, firm nodules under the skin on her left hand. She currently works as a caregiver, and she is concerned that she will not be able to work with this recurring pain.

What information is suggestive of acute gouty arthritis?

What additional information is necessary to differentiate gout from other joint abnormalities?

What additional information do you need before creating a treatment plan for this patient?

What are aspects to consider when providing care for a patient who has socioeconomic difficulties?

What is a potential when considering concomitant therapy risk for a patient who readily self-treats with herbals?

TREATMENT OF GOUT

KEY CONCEPT Treatment of gout involves: (a) acute relief of a gouty arthritis attack with topical application of ice and drug therapy commonly including NSAIDs, colchicine, glucocorticoids, or a combination thereof, and (b) in some patients, long-term prophylactic treatment with urate-lowering therapy (ULT) to prevent subsequent attacks.

Desired Outcomes

Treatment goals for gout are to: (a) achieve rapid and effective pain relief during an acute flare, (b) maintain joint function, (c) prevent disease complications, (d) avoid treatment-related adverse effects, (e) provide cost-effective therapy, and (f) improve quality of life.[3] Infrequent gouty arthritis is a self-limited disease, and treatment usually focuses on symptomatic relief.

TREATMENT OF ACUTE GOUT FLARE

Nonpharmacologic Therapy

Nondrug modalities play an adjunctive role and usually are not effective when used alone. Immobilization of the affected extremity speeds resolution of the attack. Applying ice packs to the joint is most effective in decreasing pain and swelling.[5]

Pharmacologic Therapy

KEY CONCEPT Nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and glucocorticoids are considered first-line monotherapy for acute flares, with the option of combination therapy for severe flares unresponsive to monotherapy.[5,13] Selection depends on the number of joints affected, presence/absence of infection, clinician/patient preference, prior response, and patient factors such as comorbidities and renal function (Figure 60–2). Each drug class has a unique safety and efficacy profile in gout that should be considered carefully before choosing a specific agent (Table 60–1). Generally, the earlier in the course of the arthritic attack these agents are employed (ie, within 24 hours), the better the outcome.[5] Therefore, the ACR guideline encourages an early approach with a "medication-in-pocket" strategy for patients to identify the early signs of an acute gout flare and treat with medication on-hand, since crystal formation is reversible and lowering the SUA quickly can limit solubility.[6,13] Corticotropin (adrenocorticotropic hormone, ACTH) and IL-1 inhibitors are alternatives in select cases.[5] Over a quarter of patients with an acute gout flare are prescribed opioids in emergency departments; however, opioid analgesics have little to no role in acute gout, which results from overwhelming inflammation.[21]

▶ *Nonsteroidal Anti-Inflammatory Drugs*

NSAIDs, which reduce the pain and inflammation associated with an acute attack, have largely supplanted colchicine as the treatment of choice (see Chapter 59, Osteoarthritis, for more detailed information on NSAIDs). These agents are most effective when given within the first 24 hours of the onset of pain. Most studies have shown similar results among agents, and no one NSAID is preferred over another. Doses should be prescribed at the higher end of the therapeutic range, for the shortest duration of time, typically until 24 hours after symptoms subside.[5,13] Lower doses can prolong duration of therapy and lead to further pain and discomfort.[13] Clinicians may consider tapering the dose if a patient has multiple comorbidities, including hepatic or renal failure.

Only naproxen, indomethacin, and sulindac are Food and Drug Administration (FDA) approved for treatment of acute gout. Although indomethacin has been used traditionally, its relative cyclooxygenase-1 (COX-1) selectivity increases its gastropathy risk. Studies comparing indomethacin to other NSAIDs consistently show similar efficacy with greater incidence of side effects with indomethacin; thus, other generic NSAIDs may be preferred. The patient's overall clinical status, including comorbidities and medications, should be evaluated prior to NSAID initiation because adverse effects include gastropathy (primarily peptic ulcers), renal dysfunction, and fluid retention.[5] In general, NSAIDs should be avoided in patients at risk for peptic ulcers; those taking anticoagulants; and those with renal insufficiency, uncontrolled hypertension, or heart failure. Gastroprotective agents such as proton pump inhibitors may protect against ulcer development in patients receiving NSAIDs for acute gout.

Cyclooxygenase-2 (COX-2)–selective inhibitors produce results comparable to traditional NSAIDs, with celecoxib being the only available product in the US market currently.[22] However, the need for large COX-2 inhibitor doses during an acute gouty attack (ie, celecoxib 800 mg daily), cardiovascular safety concerns, and high cost make the risk–benefit ratio unclear for this disorder.

▶ *Colchicine*

Colchicine has a long history of successful use for initial gout flares and was the treatment of choice for many years.[13] It is used less commonly today because of its low therapeutic index and increased cost compared to other acute treatments, despite generic availability. Colchicine is thought to exert its anti-inflammatory effects by interfering with the function of mitotic spindles in neutrophils by binding of tubulin dimers; this inhibits its phagocytic activity.[23] Colchicine is not considered to be an analgesic.

About two-thirds of patients with acute gout respond favorably if colchicine is given within the first 24 hours of symptom onset.[24]

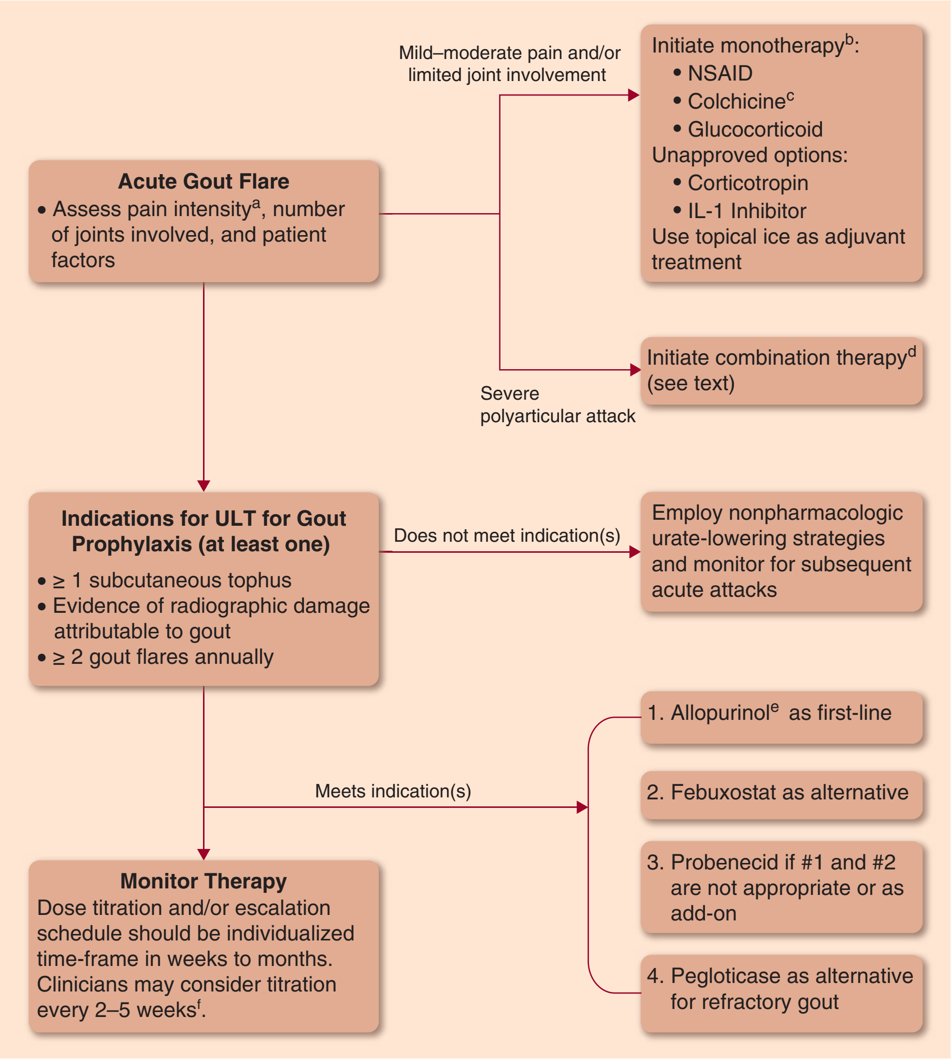
Acute Gout Flare
• Assess pain intensity[a], number of joints involved, and patient factors
Mild–moderate pain and/or limited joint involvement
Initiate monotherapy[b]:
• NSAID
• Colchicine[c]
• Glucocorticoid
Unapproved options:
• Corticotropin
• IL-1 Inhibitor
Use topical ice as adjuvant treatment
Severe polyarticular attack
Initiate combination therapy[d] (see text)
Indications for ULT for Gout Prophylaxis (at least one)
• ≥ 1 subcutaneous tophus
• Evidence of radiographic damage attributable to gout
• ≥ 2 gout flares annually
Does not meet indication(s)
Employ nonpharmacologic urate-lowering strategies and monitor for subsequent acute attacks
Meets indication(s)
1. Allopurinol[e] as first-line
2. Febuxostat as alternative
3. Probenecid if #1 and #2 are not appropriate or as add-on
4. Pegloticase as alternative for refractory gout
Monitor Therapy
Dose titration and/or escalation schedule should be individualized time-frame in weeks to months. Clinicians may consider titration every 2–5 weeks[f].

FIGURE 60–2. Treatment algorithm for hyperuricemia in gout. (NSAID, nonsteroidal anti-inflammatory drug; SUA, serum uric acid.)

[a] Self-reported pain score using a visual analog scale of 6 or less may be considered mild/moderate pain and 7 or more may be considered severe pain.

[b] May consider switch to alternate monotherapy, add-on combination therapy, or off-label therapy for inadequate response (eg, < 20% improvement in pain score within 24 hours or < 50% at 24 hours or longer).

[c] Colchicine may be most beneficial if started within 36 hours of symptom onset.

[d] Intra-articular glucocorticoids may be used in combination when only one or two large joints are affected.

[e] Initiate concomitant anti-inflammatory prophylaxis and continue for indicated duration.

[f] May add on uricosuric therapy if unable to achieve target SUA on maximally dosed xanthine oxidase inhibitor therapy; switch to pegloticase for refractory cases.

Presently, colchicine is only indicated if given within 36 hours of attack onset.[5] GI effects (eg, nausea, vomiting, diarrhea, and abdominal pain) are most common and should warrant a dose reduction or interruption.[10] This is because GI effects are considered a forerunner of more serious systemic toxicity, including myopathy and bone marrow suppression (usually neutropenia). However, systemic colchicine toxicity can occur without prior GI effects, especially with renal insufficiency. In the presence of severe renal impairment (creatinine clearance [CrCl] less than 30 mL/min [0.5 mL/s]), dosing should be repeated no more than once every 2 weeks. Dose reductions are required when coadministered with p-glycoprotein or strong CYP3A4 inhibitors (eg, clarithromycin, verapamil, ritonavir, cyclosporine, ranolazine).[23] Colchicine should be used with caution in patients with liver disease or taking statins. Because of these problems, colchicine may be reserved for patients who are at risk for NSAID-induced gastropathy or who have failed NSAID therapy.

The FDA-approved dosage regimen is 1.2 mg (two 0.6-mg tablets) at the onset of an acute flare, followed by 0.6 mg 1 hour later.[23] Dose adjustment is required for renal insufficiency. Colchicine should not be used for an acute attack if the patient is currently prescribed colchicine for prophylaxis and was previously treated with colchicine for an acute attack within the last 14 days. Intravenous colchicine (no longer commercially available) should never be used in gout management.

Table 60–1

Pharmacotherapy Regimens for Acute Gout Treatment

Drug	Usual Dosage Range
NSAIDs	
Etodolac	200–400 mg po every 6 to 8 hours as needed; max 1200 mg/day
Fenoprofen	200 mg po every 4 to 6 hours as needed
Ibuprofen	400–800 mg po three to four times daily
Indomethacin[a]	50 mg po three times daily initially until pain is tolerable, then quickly taper to discontinue
Ketoprofen	25–50 mg po every 4 to 6 hours as needed; max 300 mg/day
Naproxen[a]	750 mg po initially, then 250 mg po every 8 hours
Sulindac[a]	200 mg po two times daily for 7 days
Celecoxib	800 mg po followed by 400 mg po on day 1, then 400 mg po twice daily for 1 week
Colchicine[b]	1.2 mg po at the onset of attack, then 0.6 mg po 1 hour later; **or** 0.6 mg three times daily on first day of attack
Glucocorticoids	
Local glucocorticoids	
Triamcinolone acetonide	5–15 mg (large joint), 2.5–5 mg (small joint) for one dose by intra-articular injection
Methylprednisolone	40 mg (large joint), 30 mg (medium joint), 10 mg (small joint) for one dose by intra-articular injection
Systemic glucocorticoids	
Prednisone	0.5 mg/kg/day po for 5–10 days
Triamcinolone acetonide	40–80 mg by IM injection for one dose[c]
Methylprednisolone	40–60 mg by IM injection as single dose; may repeat once or twice in 48 hour intervals
Corticotropin[d]	25–40 units SC as initial dose; may repeat if clinically indicated
Interleukin-1 Inhibitors[d]	
Anakinra	100 mg SC once daily for 3 days
Canakinumab	150 mg SC for 1 dose

[a] This drug has FDA approval for the treatment of acute gout.

[b] Dose reduction recommended for renal impairment.

[c] Administration of IM triamcinolone should be followed by oral prednisone or prednisolone.

[d] Not FDA approved for this indication.

Drug regimens derived from various sources.

IM, intramuscular; NSAIDs, nonsteroidal anti-inflammatory drugs; po, by mouth; SC, subcutaneous.

▶ *Glucocorticoid*

It is important to determine the number of joints affected when considering a glucocorticoid for first-line therapy. Glucocorticoids are a useful option in patients with contraindications to NSAIDs or colchicine (primarily renal impairment) or polyarticular attacks, especially in older patients. Furthermore, glucocorticoids and NSAIDs have been shown to be equally effective in acute gout treatment.[25,26] Glucocorticoids can be administered orally, intravenously, intramuscularly, and intra-articularly.[5] Clinicians generally use oral prednisone or prednisolone at a dose of at least 0.5 mg/kg daily for 5 to 10 days, followed by abrupt discontinuation, or full-dose therapy for 2 to 5 days with a 7- to 10-day taper to discontinue. Oral methylprednisolone (ie, the 6-day dose pack consisting of a 21-tablet taper of 4 mg tablets, starting with 6 tablets on day 1 [divided into three separate doses] and ending with one tablet on day 6) and naproxen have been shown to be equivalent in treating acute gout attacks.[27]

When only one or two large joints are affected, an intra-articular glucocorticoid injection can provide rapid relief with a relatively low incidence of side effects, and it may be used in combination with either an NSAID, colchicine, or glucocorticoid. Joint fluid obtained by arthrocentesis should be examined for evidence of joint space infection and crystal identification. If uric acid crystals are present and there is no infection, intra-articular injection can proceed. An alternative regimen consisting of a single intramuscular injection of a long-acting glucocorticoid such as triamcinolone acetonide for patients who cannot tolerate oral intake is acceptable. Due to insufficient evidence, guidelines do not support subsequent use of anti-inflammatory agents when patients do not respond to the initial administration of parenteral glucocorticoids.[5] For severe flares that require hospitalization, an intravenous glucocorticoid can be used, such as methylprednisolone 40 mg administered intravenously twice daily with a stepwise reduction when the patient improves.[13]

Adverse effects from glucocorticoids include fluid retention, hyperglycemia, CNS stimulation, weight gain, GI upset, and increased risk of infection. Patients with diabetes should have blood glucose levels monitored carefully during the glucocorticoid therapy course, and caution should be exercised when treating patients with a history of peptic ulcer disease.

▶ *Corticotropin (Adrenocorticotropic Hormone)*

Exogenous administration of intramuscular adrenocorticotropic hormone (ACTH) stimulates production of cortisol and corticosterone by the adrenal cortex. Clinical studies have shown efficacy similar to other agents for acute gout; however, its use is limited by its cost.[13] Although not a first-line option (or FDA approved for this use), the ACR supports its use for patients unable to take medications orally.[5] The product is available in the United States only through specialty pharmacy distribution.

▶ *Interleukin-1 Inhibitors*

Several small clinical trials have demonstrated efficacy of IL-1 inhibitors in inhibiting inflammation associated with acute gout attacks. While their role is unclear and the available products (anakinra and canakinumab) are not FDA approved for this purpose, the ACR guidelines conditionally recommend IL-1 inhibitors for patients who cannot tolerate or have contraindications to the other anti-inflammatory therapies. Interleukin-1 inhibitors provide rapid relief in severe acute attacks or in patients with refractory gout.[5,13] Canakinumab and anakinra are both administered subcutaneously, with the most commonly reported side effect being injection site reaction.[13]

▶ *Combination Therapy*

In severe polyarticular attacks, particularly attacks involving multiple large joints, colchicine may be used in combination with an NSAID or oral glucocorticoid. Intra-articular glucocorticoid injections may be used in combination with any other first-line agent (NSAID, colchicine, oral glucocorticoid).[5]

URATE-LOWERING THERAPY FOR GOUT PROPHYLAXIS

Gout is an episodic disease, and the number of attacks varies widely among patients. Thus, the benefit of long-term acute attack prophylaxis must be weighed against the cost and potential toxicity of therapy that may not be necessary in all patients. Urate-lowering therapy (ULT) is not recommended when patients experience their first gout flare. **KEY CONCEPT** Additionally, ULT is not recommended for patients with asymptomatic hyperuricemia.[5] It is conditionally recommended for patients who have experienced more than one gout flare but have fewer than two attacks a year.[5] However, the benefits of long-term use (more than 12 months) in patients with single or infrequent gout attacks have not been evaluated. Therefore, the duration of ULT therapy is unclear.[8]

Nonpharmacologic Therapy

Historically, lifestyle modifications alone have been insufficient for lowering SUA levels, and low purine diets are not well tolerated. Patients should be educated on general nutrition principles and advised to engage in regular exercise to lose weight if obese, strictly limit or discontinue ethanol consumption, maintain hydration, and manage other comorbidities (eg, hypertension, diabetes). Evidence suggests that men who follow the Dietary Approaches to Stop Hypertension (DASH) diet have a reduced risk for gout compared to those who eat a Western diet.[28] Furthermore, recent studies in both men and women demonstrated that the DASH diet had a greater SUA reduction in those with SUA ≥ 6 mg/dL (357 μmol/L) within the first 30 days.[29] While the ACR guideline encourages patients to consume low/nonfat dairy products and vegetables, it also cites a lack of specific evidence (similar to the ACP guidelines) that judge the available evidence insufficient to recommend specific dietary changes.[5,8] Complementary therapies are considered to be inappropriate for gout due to insufficient evidence of benefit, such as cherry juice/extract, flaxseed, and celery root.[5,30] Drugs that may cause or aggravate hyperuricemia should be discontinued if clinically appropriate, such as hydrochlorothiazide. Cardioprotective medications such as low-dose aspirin and statins should be continued in patients who require primary or secondary prevention.[5] Clinical experience indicates that few patients adhere to lifestyle modifications long-term, and pharmacologic therapy usually is needed to treat hyperuricemia adequately.

Pharmacologic Therapy

KEY CONCEPT Patients with frequent gout flares (2 or more per year), radiographic evidence attributable to gout, or at least one subcutaneous tophus are candidates for *prophylactic* therapy with allopurinol, febuxostat, probenecid, and/or pegloticase to lower SUA levels (see Figure 60–2).[5] However, ULT may be considered in patients who have experienced more than one flare in their lifetime but have infrequent flares (fewer than 2 per year) and if they also have one of the following: moderate to severe CKD (Stage ≥ 3), SUA levels greater than 9 mg/dL (535 μmol/L), or urolithiasis.[5] Prophylactic therapy commonly involves either decreasing uric acid production or increasing excretion (Table 60–2). For patients with asymptomatic hyperuricemia, initiation of ULT is not recommended.[5] The goal of therapy is to decrease SUA levels significantly, leaving less uric acid available for conversion to MSU crystals.[3] **KEY CONCEPT** ULT may be started during an acute attack if anti-inflammatory treatment has been initiated. Similarly, ULT should be continued during acute flares.

Table 60–2

Pharmacotherapy Regimens for Urate Lowering

Drug	Usual Dosage Range
Xanthine Oxidase Inhibitors	
Allopurinol[a]	100 mg po initially, then titrate to achieve SUA level < 6 mg/dL (357 μmol/L); maximum 800 mg po daily
Febuxostat	40 mg po once daily initially, then increase to 80 mg po once daily if SUA does not decline to 6 mg/dL (357 μmol/L) or lower after 2 weeks of treatment
Uricosurics	
Probenecid	250 mg po two times daily for 1 week, then 500 mg po twice daily; may increase by 500 mg every 4 weeks to achieve SUA level < 6 mg/dL (357 μmol/L); maximum 2 g po daily
Other	
Pegloticase	8 mg given as an IV infusion over at least 2 hours once every 2 weeks, optimal duration unknown

[a]Initial dose reduction recommended for renal impairment.

Drug regimens derived from various sources.

po, by mouth; SUA, serum uric acid.

Because allopurinol (which reduces uric acid production) is effective in both overproducers and underexcretors and is generally well tolerated, many clinicians treat patients empirically with it. Both allopurinol and febuxostat are xanthine oxidase inhibitors (XOIs) and are first-line and second-line ULT agents, respectively.[5] Probenecid, a **uricosuric** agent, is an alternative option. Combination therapy with an XOI and probenecid may be used if single-agent XOI therapy is insufficient. Pegloticase, a recombinant urate oxidase, is reserved for refractory cases.[5]

▸ *Allopurinol*

Allopurinol is considered first-line therapy for most patients in the United States due to its affordability and efficacy. In addition, it is not associated with renal function decline in patients with CKD.[31] The drug and its primary active metabolite, oxypurinol, reduce SUA concentrations by inhibiting the enzyme xanthine oxidase, thereby blocking the two-phase oxidation of hypoxanthine and xanthine to uric acid.

Allopurinol is well absorbed, with a short half-life of 2 to 3 hours. The half-life of oxypurinol approaches 24 hours, allowing allopurinol to be dosed once daily. Oxypurinol is primarily renally cleared and can accumulate in patients with reduced kidney function. Although there is no evidence that allopurinol is renal protective, it continues to be recommended for patients with moderate to severe CKD.[5,32]

Allopurinol may be started during an acute gout attack only if anti-inflammatory treatment is also initiated, because sudden shifts in SUA levels from mobilization of tissue urate stores may precipitate or exacerbate gouty arthritis. Thus, most clinicians provide anti-inflammatory prophylaxis during initiation of ULT with colchicine (0.6 mg once or twice daily or 0.3 mg daily if severe renal impairment) or a low-dose NSAID (eg, naproxen 250 mg twice daily) with acid-suppressing therapy (eg, omeprazole 20 mg once daily). If a patient is being treated with colchicine for an acute attack, the prophylactic colchicine dose may be administered 12 hours after the last treatment dose. This approach, with colchicine having a stronger evidence grade, is supported by the ACR guideline. The guideline recommends that all acute gout patients receive prophylaxis when ULT is started with continuation of therapy for 3 to 6 months after no clinical evidence of gout activity and the target SUA has been achieved.[5] Patients receiving colchicine for prophylaxis should be screened for drug–drug interactions (via the cytochrome p-450 system) that may increase the risk of colchicine adverse effects. Low-dose prednisone or prednisolone (< 10 mg/day) is an alternative for patients unable to take colchicine or NSAIDs. The IL-1 inhibitors have also been investigated off-label as potential alternatives.

The initial dose of allopurinol is based on the patient's renal function. If renal function is normal, an initial dose no greater than 100 mg daily is recommended. The initial dose should be reduced to 50 mg daily in patients with CKD.[5] However, the dose can be adjusted upward every 2 to 5 weeks as needed and tolerated to the SUA target, even in patients with renal insufficiency provided that they are monitored and educated appropriately.[5,33]

SUA levels must be monitored in an individualized time-frame in weeks to months during titration. Clinicians generally check SUA every 2 to 5 weeks during initiation then every 6 months after the target SUA is achieved. ACR recommends targeting an SUA level < 6 mg/dL (357 μmol/L).[5] It is not recommended to have an SUA level < 3 mg/dL (178 μmol/L) long term.[6] The allopurinol dose should be titrated upward (to a maximum of 800 mg/day) or downward as these levels dictate.[5] However, the ACP guideline does not support the ACR's proactive "treat-to-target" approach due to a lack of adequate supporting evidence; rather, the ACP recommends "treating-to-avoid-symptoms."[8] Nevertheless, most clinicians likely follow the ACR recommendations and strategies at this time. The typical allopurinol dose prescribed is 300 mg/day in patients with normal renal function, but this dose often fails to achieve the target SUA level.[5]

Allopurinol is typically well tolerated; nausea and diarrhea occur uncommonly. A generalized, maculopapular rash occurs in about 2% of patients. Although usually mild, this can progress to severe skin reactions such as Stevens-Johnson syndrome. The most serious side effect is allopurinol hypersensitivity syndrome (AHS), which occurs in about 1 in 1000 patients and may involve severe desquamating skin lesions, high fever (usually greater than 39.0°C [102.2°F]), hepatic dysfunction, leukocytosis with predominant eosinophilia, and renal failure.[34] The risk appears to be highest in the first few months of therapy, and although rare, this severe reaction has a 20% to 25% mortality rate.[5,35,36] Prior to initiating allopurinol, pharmacogenomic screening via human leukocyte antigen (HLA)-B*5801 testing is recommended for patients at an elevated risk for AHS (eg, patients of Southeast Asian descent [Han Chinese, Korean, and Thai], and African Americans).[5] Additional risk factors for AHS include renal impairment and concurrent thiazide use.[34] If results are positive, the patient should be provided with an alternative to allopurinol. Patients with a history of AHS should never again receive allopurinol (including desensitization) or oxypurinol (available outside the United States). Patients with a mild skin rash who require allopurinol can be desensitized to it using published protocols or be switched to febuxostat.[37] Febuxostat is more expensive than allopurinol, so testing for HLA-B*5801 can be more cost-effective than substituting febuxostat for allopurinol.[34]

There are several important drug–drug interactions with allopurinol. The effects of both theophylline and warfarin may be potentiated by allopurinol. Azathioprine and 6-mercaptopurine are purines whose metabolism is inhibited by concomitant allopurinol therapy; the dose of these drugs must be reduced by 75% with allopurinol cotherapy. Patients taking allopurinol who receive ampicillin are at increased risk of skin rashes.

▶ *Febuxostat*

Febuxostat is a nonpurine XOI structurally distinct from allopurinol that is FDA approved for chronic hyperuricemia associated with gout. The initial dose is 40 mg orally once daily. The dose may be increased to 80 mg orally once daily if the SUA does not decrease to 6 mg/dL (357 μmol/L) or less after 2 weeks of treatment. No dosage adjustment is necessary in patients with mild or moderate renal impairment (CrCl 30–89 mL/min [0.5–1.48 mL/s]); however, febuxostat is not recommended in severe renal insufficiency (CrCl < 30 mL/min [0.5 mL/s]).[38] Because of its potency and rapid reduction of SUA levels, anti-inflammatory prophylaxis with low-dose colchicine or an NSAID is also recommended during initiation and titration of therapy and for at least 6 months as previously discussed for allopurinol.

Adverse effects of febuxostat include nausea, arthralgias, rash, transient elevation of hepatic transaminases, and cardiovascular events. Periodic liver function tests are recommended (eg, at baseline, 2 and 4 months after starting therapy, and then periodically thereafter). Due to differences in chemical structure, febuxostat would not be expected to cross-react in patients with a history of AHS.

In patients with history of CVD, febuxostat was found to be noninferior to allopurinol in preventing cardiovascular events. However, febuxostat was associated with a higher rate of cardiovascular mortality than allopurinol.[39,40] Therefore, after considering risks vs benefits febuxostat may be an appropriate alternative for patients who do not tolerate allopurinol and those who cannot achieve SUA levels of 6 mg/dL (357 μmol/L) or less despite maximal allopurinol therapy.[1] Allopurinol remains first-line therapy due to greater dosing flexibility and a longer period of clinical experience with its use.

▶ *Probenecid*

Probenecid is a uricosuric agent that blocks the tubular reabsorption of uric acid and increases its excretion.[10] Because of its mechanism of action, probenecid is not recommended for urate overproducers and is contraindicated in patients with a history of urolithiasis or urate nephropathy. Probenecid loses its effectiveness as renal function declines and should be avoided in those with CKD (Stage ≥ 3) and when the CrCl is 50 mL/min (0.83 mL/s) or less.[41] Probenecid is an alternate first-line agent if XOI therapy is either not tolerated or contraindicated. It may also be added to XOI therapy that has been titrated to the maximum dose without attainment of the target SUA level.[5]

Although generally well tolerated, probenecid can cause GI side effects (nausea), as well as fever, rash, and rarely, hepatic toxicity.[41] Patients should maintain adequate hydration and urine output to decrease the risk of uric acid stone formation. Some experts advocate alkalinizing the urine to decrease this risk, but no specific recommendations are provided by the ACR.

▶ *Escalating Urate-Lowering Therapy*

Switching to another XOI or adding a uricosuric agent is recommended if the SUA level remains above 6 mg/dL (357 μmol/L), in patients who continue to have more than 2 gout flares annually, or in those with persistent subcutaneous tophi.[5] Other medications with mild uricosuric effects may be appropriate adjunctive therapy in some patients. Losartan increases both uric acid excretion and urine pH and is conditionally recommended in hypertensive patients with gout. For select dyslipidemic patients with gout, statins remain the preferred agents for lipid-lowering therapy. Switching to another lipid-lowering agent such as fenofibrate is

Patient Encounter Part 2

PMH: Stage 2 CKD, hypertension, dyslipidemia, seasonal allergies, prediabetes mellitus (type 2).

FH: Father has history of myocardial infarctions. Mother has heart disease. No siblings.

SH: Employed as caregiver. Reports drinking 2 cans of beer on weekends. Denies use of tobacco products. Diet consists of packaged and microwaveable food.

Allergies: No known drug allergies.

Meds: Hydrochlorothiazide 25 mg once daily, fenofibrate 67 mg once daily, aspirin 325 mg TID PRN pain, loratadine 10 mg once daily, turmeric supplement 2 capsules once daily.

ROS: Aside from pain in her wrist, she reports occasional shortness of breath. No fatigue, N/V/D, chest pain, or cough.

PE:

VS: 150/87, P 85, RR 17, T 37.3°C (99.1°F), Ht 63 inches (160 cm), Wt 79.3 kg.

Skin: Warm, dry with excessive warmth surrounding left elbow.

HEENT: NC/AT, PERRLA, TMs intact.

CV: RRR, normal S1 and S2, no m/r/g.

Chest: CTA.

Abd: Slightly overweight, but soft, NT/ND. Normal bowel sounds in all quadrants.

Ext: Left elbow is warm to the touch and extremely painful (9/10 on the pain scale). Signs of tophi on left hand. No swelling of other joints.

Neuro: A&O × 3, CN II to XII intact.

Labs: Serum creatinine 1.3 mg/dL (115 µmol/L), SUA 15.6 mg/dL (928 µmol/L), WBC $14 \times 10^3/\mu L$ ($14 \times 10^9/L$), AST 20 IU/L (0.33 µkat/L), ALT 51 U/L (0.85 µkat/L), LDL 137 mg/dL (3.54 mmol/L), HDL 46 mg/dL (1.19 mmol/L), TG 167 mg/dL (1.89 mmol/L).

Other: Joint aspirate from wrist tap: > 50 WBC/HPF, containing negatively birefringent monosodium urate crystals. Wrist and hand radiographs negative for break or trauma, but indicate cystic changes and calcified masses.

What risk factors promote gout and hyperuricemia in this patient?

Given this additional information, what is your assessment of the patient's condition?

Identify your gout treatment goals for this patient.

What nonpharmacologic and pharmacologic alternatives are available for this patient's acute gout flare?

What testing is recommended for the patient prior to initiating urate-lowering therapy for gout prophylaxis?

What is the recommended first-line agent for urate-lowering therapy for gout prophylaxis in this patient?

not recommended despite its urate-lowering effects because risks, such as side effects, outweigh the potential benefits.[5] Either losartan or fenofibrate may be combined with an XOI in patients who fail to achieve the target SUA level on maximized therapy.[5]

▶ *Lesinurad*

Lesinurad is a uric acid transporter 1 (URAT1) inhibitor that increases renal excretion of SUA and is approved for coadministration with a XOI (allopurinol or febuxostat) in patients who fail to meet their SUA target on a XOI alone.[42] Lesinurad was withdrawn from the market in 2019 due to business reasons and not because of any safety, efficacy, or quality issues.[43]

▶ *Pegloticase*

Gout does not occur in most nonprimate mammals because these species produce the enzyme uricase, which catalyzes oxidation of uric acid into the more soluble compound allantoin, which is readily excreted. Humans lack this enzyme, which allows uric acid to accumulate, leading to gout in some individuals.

Patient Encounter Part 3

The patient states that she was recently furloughed and her husband was laid off, so finances have been tight. She has medical insurance but worries about a potentially high copayment for the medications needed for gout.

Based on all of the information provided, create a care plan for this patient's gout. The plan should include: (a) a statement of the drug-related needs and/or problems, (b) a patient-specific detailed therapeutic plan, and (c) monitoring parameters to assess efficacy and safety.

Pegloticase is a recombinant form of uricase (also known as urate oxidase) conjugated to multiple strands of polyethylene glycol (PEG).[13] It is FDA approved for treatment of chronic gout refractory to other therapies. The approved dose of 8 mg by IV infusion over at least 2 hours every 2 weeks rapidly (within 6 hours) decreased SUA in subjects in published trials.[44] However, pegloticase should be limited to patients with severe gout with tophi or nephropathy who cannot tolerate oral ULT or who have not responded to other agents. Before initiation, ULT should be discontinued. Use of pegloticase is limited because of significant adverse effects, including gout flares, infusion reactions, anaphylaxis (in up to 5% of patients), need for pretreatment with antihistamines and glucocorticoids, the inconvenience of IV therapy, and its high cost.[13] Pegloticase is contraindicated in patients with G6PD deficiency due to the risk of hemolysis and methemoglobinemia; therefore, patients should be screened prior to initiation of therapy. Resistance to pegloticase have been reported in patients who develop anti-PEG antibodies, which increases the risk of adverse events.[13]

OUTCOME EVALUATION

Acute Gout Flare

- Monitor the patient for pain relief and decreased swelling of the affected joint(s). Both parameters improve significantly within 48 hours of starting therapy.
- Assess the patient's complaints and objective information for adverse effects:

  - NSAIDs: Be alert for new-onset epigastric pain, dark or tarry stools, blood in vomitus, dizziness or lightheadedness, development of edema, decreased urine output, or shortness of breath.
  - Colchicine: Monitor for nausea or vomiting, diarrhea, easy bruising, cold or flu-like symptoms, lightheadedness, muscle weakness, or pain. Advise the patient to inform you of any new medications started or stopped while taking colchicine.
  - Glucocorticoids: Assess for mental status changes, fluid retention, increased blood glucose, muscle weakness, or development of new infections.
- Intra-articular glucocorticoid injections: Monitor for increased swelling or pain at the injection site.

Urate-Lowering Therapy for Gout Prophylaxis

- Monitor the SUA level in an individualized time-frame in weeks to months (eg, every 2–5 weeks) during ULT initiation and titration. Adjust the dose of ULT to achieve a target SUA level of less than 6 mg/dL (357 μmol/L) or less for those with severe disease. Then continue measurements periodically thereafter and evaluate need for additional therapy.
- Concomitantly initiate anti-inflammatory prophylaxis and continue for 3 to 6 months after achieving target SUA level with no gout signs/symptoms.
- Assess for new gouty arthritis attacks or development of tophi.
- Evaluate patients for adverse medication effects:
  - Allopurinol: Assess for development of rash, nausea, or new fever. These symptoms usually appear within the first 3 months of therapy but can occur anytime.
  - Febuxostat: Monitor for presence of nausea, arthralgias, rash, transient elevation of hepatic transaminases, and cardiovascular events.

Patient Care Process

Collect Information:

- Perform allergy assessment and medication history for prescription, nonprescription, and dietary supplement use.
- Review medical history for contributing lifestyle factors (ie, alcohol use) and comorbidities including CKD that may exacerbate hyperuricemia or help guide therapy.
- Review physical assessment findings and patient symptoms to determine time of attack onset, joint(s) affected, pain level, and observe signs (joint warmth, swelling, redness).
- Identify patient preferences, beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Identify risk factors and comorbidities associated with gout.
- Determine whether patient is taking products such as diuretic therapy that may contribute to hyperuricemia.
- Determine if a medication is needed to lower SUA to the target level.
- Determine whether patient is experiencing signs/symptoms of an acute gout flare or long-term complications of hyperuricemia.
- If patient is currently receiving pharmacotherapy, assess efficacy (ie, frequency/severity of attacks), safety/adverse reactions, adherence, and potential drug interactions.
- Evaluate SUA level to confirm presence of hyperuricemia and document the level.
- If a gout diagnosis has not been confirmed previously, assess feasibility of aspirating the affected joint to identify uric acid crystals.

Develop a Care Plan: (Figure 60–2)

- Select a regimen for treatment of the acute attack, considering the patient's past response (if any) and comorbidities.
- Ensure patient has met criteria for ULT if already prescribed.
- Select appropriate lifestyle modifications and therapy based on comorbidities and potential safety/efficacy.
- Determine need for continuous ULT (Table 60–2). Use patient factors such as comorbidities to select an agent.
- Choose adjunctive therapy with low-dose colchicine or NSAID during initiation or titration of ULT to prevent rebound flare.
- Initiate ULT during acute attack only in conjunction with effective anti-inflammatory therapy.

Implement the Care Plan:

- Initiate therapy to treat acute gout attack within 24 hours (Table 60–1).
- Educate patient on hyperuricemia/gout, drug therapy, importance of adherence, and lifestyle modifications that may improve symptoms (eg, weight loss, alcohol avoidance).
- Address patient concerns about hyperuricemia/gout and its management.
- Determine if patient has prescription insurance and whether recommended agents (eg, colchicine) are included on formulary.
- Assess the need to continue medications that affect the SUA level.

Follow-up: Monitor and Evaluate:

- Monitor periodically in an individualized time-frame to assess effectiveness (eg, every 2–5 weeks), safety, and titrate ULT or add alternate agent to achieve target SUA; monitor SUA concentration during ULT titration and periodically thereafter.
- Review physical examination, lab tests, and results of other diagnostic tests to assess changes in clinical status.
- Once gout symptoms are controlled, monitor patient and SUA periodically (consider every 6 months); reinforce adherence with regimen to prevent future gout attacks and long-term complications (ie, development of tophi or nephrolithiasis).

- Probenecid: Assess for fever, nausea, or skin rash. Reevaluate therapy if a significant decrease in urine output occurs.
- Pegloticase: Monitor SUA levels before each 2-week IV infusion. Also evaluate patients on pegloticase for development of gouty flares and infusion reactions, which may include anaphylaxis. The manufacturer recommends giving an antihistamine and perhaps low-dose methylprednisolone before the infusion to minimize reactions.

Abbreviations Introduced in This Chapter

ACP	American College of Physicians
ACR	American College of Rheumatology
ACTH	Adrenocorticotropic hormone
AHS	Allopurinol hypersensitivity syndrome
COX	Cyclooxygenase
CKD	Chronic kidney disease
DASH	Dietary Approaches to Stop Hypertension
FDA	Food and Drug Administration
GI	Gastrointestinal
G6PD	Glucose-6-phosphate dehydrogenase
HLA	Human leukocyte antigen
IL-1	Interleukin-1
MSU	Monosodium urate
NSAID	Nonsteroidal anti-inflammatory drug
SUA	Serum uric acid
TLS	Tumor lysis syndrome
URAT1	Uric Acid Transporter 1
ULT	Urate-lowering therapy
WBC	White blood cell
XOI	Xanthine oxidase inhibitor

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Musculoskeletal Injuries

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the pathophysiologic principles of tissue injury and inflammation.
2. Identify the desired therapeutic outcomes for a patient with musculoskeletal injury or pain.
3. Identify the factors that guide selection of an analgesic or counterirritant for a particular patient.
4. Recommend appropriate nonpharmacologic and pharmacologic therapy for a patient with musculoskeletal injury or low back pain.
5. Design a patient education plan, including nonpharmacologic therapy and preventative strategies.
6. Develop a monitoring plan to assess treatment of a patient with a musculoskeletal injury.

INTRODUCTION

The musculoskeletal system consists of muscles, bones, joints, and associated structures (eg, ligaments, tendons, cartilage, bursas). Injuries related to the musculoskeletal system are classified by etiology. Acute soft-tissue injuries include strains and sprains of muscles and ligaments.[1] Repeated movements in sports, exercise, work, or activities of daily living can lead to repetitive strain injury, where cumulative damage occurs to the muscles, ligaments, or tendons.[2,3] Although tendonitis and bursitis can arise from acute injury, more commonly these conditions occur because of chronic microtrauma and stress.[4,5] This chapter addresses injuries to the skeletal muscle and joint components with a focus on self-care treatment and limited discussion of non–self-care options. Other forms of chronic musculoskeletal pain, such as pain from rheumatoid arthritis (see Chapter 58) or osteoarthritis (see Chapter 59), are discussed elsewhere in this textbook.

EPIDEMIOLOGY AND ETIOLOGY

Musculoskeletal injuries are commonly self-treated, so true estimates of the incidence of both acute and chronic injury are difficult to obtain. In the United States, a 3-year average from 2012 to 2014 demonstrated 145 million physician office visits per year and 423 million prescriptions attributed to musculoskeletal injury.[6] These injuries may arise from activities in the workplace or from sports, and the most common etiology may differ throughout the lifespan.

Workplace musculoskeletal injuries may be caused by trauma, acute overexertion, or repetition and overuse.[6] *Overuse injury* describes musculoskeletal injuries arising from repetitive motion.[2,3] Other common terms include repetitive strain injury or cumulative trauma disorders. The most common sites of workplace injury include the upper extremities (eg, hand, shoulder, and wrist), back, and lower extremities (eg, ankle, knee). Workplace injuries are a leading cause of lost workdays, resulting in a substantial economic burden from lost productivity and lost wages.

Sprains and strains comprise the majority of sports-related injuries.[6] In adults, the ankle is the most common site of injury, whereas in children the forearm, wrist, and hand are the most common injury sites.[7] Tendon injuries are common in the foot and ankle, whereas bursitis tends to occur in the hip, shoulder, elbow and knee.[4,5]

In older adults, musculoskeletal injuries may not be related to work but to daily life. Half of all musculoskeletal injuries occur in the home with falls being the most common cause for those aged 65 and older.[6] In children and adolescents, fractures are more common than muscle and tendon injuries. Half of pediatric sports-related injuries are attributed to overuse rather than acute injury.[8]

PATHOPHYSIOLOGY

Skeletal muscle consists of varying types of fibers and are attached to bones by connective tissues called tendons. Ligaments are connective tissues that connect bone to bone. Tendons and ligaments are composed of collagenous fibers with varying degrees of flexibility, facilitating skeletal movements at joints.

Muscle Strains and Sprains

A sprain is an overstretching of supporting ligaments that results in a partial or complete tear of the ligament.[1] Although a strain also arises from an overstretching of the muscle–tendon unit, it is marked by damage to the muscle fibers or tendon without tearing of the ligament. The key difference is that a sprain involves damage to ligaments, whereas a strain involves damage primarily to muscle.

Overloading the muscle and connective tissue results in complete or partial tears of the soft tissue.[9] Microtears are typically associated with overuse while complete tears (macrotears) may occur after acute trauma and be accompanied by changes in function. This is more likely to occur in mechanical overload such as when the muscle is activated in an *eccentric contraction*, defined as a contraction in which the muscle is being lengthened.[5] Examples of this type of contraction include putting down a large, heavy object or lowering oneself from a chin-up bar. These tears lead to rupture of blood vessels at the site of the injury, resulting in hemorrhage, which causes further tissue damage and extends the injury.[9] Next, leukocytes and other mediators arrive at the site of the injured tissue. During this inflammatory stage, macrophages remove necrotic fibers. Activated neutrophils then release growth factors that activate myocytes for regeneration. Finally, capillaries grow into the area, and muscle fibers regenerate during the repair and remodeling phases of healing.

Bursitis and Tendinopathy

Bursitis is an inflammation of the bursa often caused by overuse of the joint. The bursa, a fluid-filled sac near the joint where the tendons and muscles pass over the bone, serves to reduce friction within the joint space with motion.[4,10] Inflammation at the bursa causes stiffness and pain. Bursitis can be chronic when overuse leads to cumulative microtrauma, or it can arise from acute causes such as injury or infection.

Tendonitis (or *tendinitis*) refers to inflammation precipitated by small tears in the tendon.[5] Tendonitis often results from acute injury; however, repetitive overuse of a tendon can cause cellular changes in the tissues. Many patients diagnosed with chronic tendonitis may not have inflammation but instead have **tendinosis**, a condition marked by degenerative changes in the collagenous tendon tissue. As a result of the cellular changes, the tendon progressively loses elasticity and its ability to handle stress or weight.

Low Back Pain

Low back pain is pain of musculoskeletal origin that extends from the lowest rib to the gluteus and may result in referred somatic pain into the thigh to just above the knee.[11] Conditions such as spinal deformities (eg, **scoliosis** and **spondylolysis**, neurological dysfunctions, extraspinal conditions (eg, genitourinary or vascular), tumors, infections, metabolic disease, fracture, or pregnancy may result in low back pain. The discussion in this chapter will include low back pain from soft tissue injury (ie, without any aforementioned causative condition) where pain is somatic and non-neuropathic.

Inflammation and Peripheral Pain Sensation

Inflammation is a common pathway in soft-tissue injury. Inflammatory processes lead to two outcomes: swelling and pain. They are considered to be a necessary part of the remodeling process because inflammatory cells remove damaged tissue.[9,12] However, inflammation also contributes to continued pain and swelling that limits range of motion.

The initial injury exposes membrane phospholipids to phospholipase A_2, leading to the formation of arachidonic acid.[12] Next, arachidonic acid is transformed by cyclooxygenase (COX) to thromboxanes and prostaglandins (PGs), including prostaglandin E_2 (PGE_2). PGE_2 is the most potent inflammatory mediator; it increases vascular permeability, leading to redness, warmth, and swelling of the affected area. The increased permeability also increases proteolysis, or the breakdown of proteins in the tissue.

Neutrophils, lymphocytes, and monocytes are attracted to the area, and monocytes are converted to macrophages, which then stimulate additional PG production.[12] Phagocytic cells release cytokines, including interleukins, interferon, and tumor necrosis factor, which play a role in inflammation.

In addition to increasing vascular permeability, PGs also induce pain by sensitizing pain receptors to other substances such as bradykinin. Bradykinin, PGs, leukotrienes, and other inflammatory mediators lower the pain threshold through peripheral pain sensitization.[12] These substances make nerve endings more excitable, and the nerve fibers are more reactive to serotonin, heat, and mechanical stimuli. The increased sensitization in the damaged tissue causes tenderness, soreness, **hyperalgesia**, and production of additional PGs. In a cyclic fashion, the PGs then sensitize the nerves to bradykinin action.

Without interruption, the neurochemicals ultimately lead to a firing of the unmyelinated or thinly myelinated afferent neurons. This sends messages along the pain pathway in the periphery and communicates the pain message to the central nervous system (CNS). Interruption of this cycle may occur via the effects of anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs (NSAIDs).

Nerve receptors, or **nociceptors**, release substance P and other peptides when they are activated.[13] Substance P mediates the production and release of inflammatory mediators and acts as a potent vasodilator. This receptor activation also increases the sensitivity of nociceptors to painful stimuli. Capsaicin relieves pain by stimulating the release of substance P from sensory nerve fibers, ultimately depleting stores of substance P.[14]

CLINICAL PRESENTATION AND DIAGNOSIS

See next page for information on the clinical presentation and diagnosis of musculoskeletal injuries.

TREATMENT

Desired Outcomes

KEY CONCEPT The primary goals of treating musculoskeletal injuries are to: (a) relieve pain, (b) maintain functionality, and (c) prevent or minimize overuse injury. This is accomplished by decreasing the severity and duration of pain, shortening the recovery period, preventing the acute injury from becoming an overuse injury, and minimizing the potential for adverse events from nonpharmacologic and pharmacologic therapies. If these goals are achieved, functional limitations are decreased. Further goals include a return to usual activity, prevention of future injury, and allowing for full emotional recovery. Ideally, a patient should be able to continue to perform activities of daily living and maintain normal functions. Children should be able to maintain usual play activities and sports schedules.

General Approach to Treatment

Treatment of musculoskeletal injury involves three phases: (a) nonpharmacologic therapy of an acute injury (eg, using the rest, ice, compression, and elevation [RICE] principle); (b) pain relief using oral or topical agents; and (c) lifestyle and behavioral modifications for rehabilitation and to prevent recurrent injury, overuse injury, or disability (**Figure 61–1**).

The approach to treatment for low back pain with nonpharmacologic and pharmacologic therapies is stratified by duration of pain. In acute low back pain, nonpharmacologic therapy (eg, superficial heat) is preferred, whereas for chronic low back pain pharmacologic therapy may be warranted after failure of nonpharmacologic measures.[11,17]

Acute pain typically improves within 1 to 5 days of therapy. Further evaluation may be warranted if the acute injury symptoms persist longer than 7 to 10 days with treatment.[9,18,19] Some warning signs of more serious conditions that may warrant immediate emergency care include joint deformity, dislocation, immobility, or instability.[1] Some red flags specifically for low back pain include fracture, infection, urinary or bowel incontinence, or foot drop (inability to dorsiflex or lift the front part of the foot).[16]

Clinical Presentation and Diagnosis of Musculoskeletal Injuries[1,3-5,10,15,16]

General

- Clinical presentation varies based on etiology of the disorder.
- Repetitive strain or overuse injuries may have a gradual onset.
- Disorders due to acute injury may be associated with other signs of injury, such as abrasion.

Signs and Symptoms of Acute Soft-Tissue Injury (Strains, Sprains)

- Discomfort ranging from tenderness to pain may occur at rest or with motion.
- Swelling and inflammation of the affected area.
- Bruising.
- Loss of motion.
- Mechanical instability.

Signs and Symptoms of Repetitive Strain or Overuse Injury

- Pain and stiffness that occur either at rest or with motion.
- Localized tenderness on palpation.
- Mild swelling of the affected area.
- Decreased range of motion.
- Muscle atrophy.

Low Back Pain

- Low back pain is often chronic, but some cases may present acutely.
- Pain is often nonspecific and may be accompanied by stiffness upon waking.
- Lifting, twisting, or bending may worsen pain.
- In some cases, pain may radiate to the hip or thigh.

Other Diagnostic Tests and Assessments

- *Radiograph (x-ray)*: Evaluates bony structures to rule out fracture, malalignment, or joint erosion as the primary cause of pain.
- *MRI*: Soft-tissue imaging to evaluate for tendon or ligament tears.
- *Ultrasound*: Superficial soft-tissue imaging evaluates for tears in tendons or ligaments. Ultrasound can be used to detect fluid in the bursa or to rule out other causes of pain. Ultrasound does not penetrate bone, so it is of limited usefulness for assessing tendons or ligaments deep within joints.
- *Electromyogram*: Evaluates electrical activity in muscles and may be used when low back pain is accompanied by leg pain or sciatica to rule out other causes of the pain.
- *Pain scale*: Patient self-rates on a pain scale. For example, a numeric pain scale with zero (no pain) to 10 (worst possible pain) or a visual analog scale. It is used to assess pain both at rest and with movement and determined at baseline and to assess response to therapy.

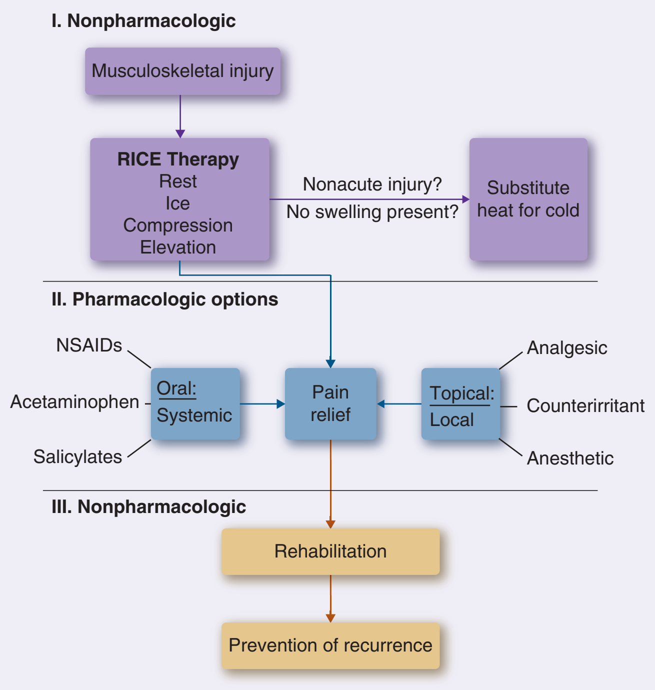
I. Nonpharmacologic
Musculoskeletal injury
RICE Therapy
Rest
Ice
Compression
Elevation
Nonacute injury?
No swelling present?
Substitute heat for cold
II. Pharmacologic options
NSAIDs
Acetaminophen
Salicylates
Oral:
Systemic
Pain relief
Topical:
Local
Analgesic
Counterirritant
Anesthetic
III. Nonpharmacologic
Rehabilitation
Prevention of recurrence

FIGURE 61–1. Treatment plan for musculoskeletal injury. (See Table 61–2 for treatment of low back pain.)

In children and adolescents, treatment practices are similar to the approach in adults with a focus on nonpharmacologic therapy and oral analgesics. Children younger than 2 years, older adults, and pregnant women also may need special care.[14,18,20]

Nonpharmacologic Therapy: RICE

KEY CONCEPT The cornerstone of nonpharmacologic therapy for acute injury in the first 24 to 72 hours is known by the acronym RICE: rest, ice, compression, and elevation.[9,10,19,21] These four

Patient Encounter 1, Part 1

A 38-year-old man presents with right knee pain. He was playing volleyball with his friends 3 days ago and twisted his knee when he fell. The pain occurs at rest and is worsened with pressure or weight on the knee and with rotation or movement. There is moderate swelling and bruising of the right knee. Abrasions across his knee and leg are noted.

What information is suggestive of a musculoskeletal injury?

What is your assessment of the patient's knee pain?

What additional information do you need to formulate a treatment plan?

Table 61–1

RICE Therapy[9,10,19,21-24]

Therapy	General Guidelines	Therapeutic Benefit
*R*est	Rest the affected area	Analgesia
	Use supports such as slings and crutches as necessary	Anti-inflammatory
	Use during the acute inflammatory phase, 1–5 days after injury	Prevent further injury
*I*ce	Cool the affected area by submersion in cool water (13°C [55°F]) or by application of crushed ice in a plastic bag covered with a thin cloth	Analgesia
	Cool the affected area for 10–20 minutes; for the first 72 hours	Anti-inflammatory
*C*ompression	Compress the affected area with an elastic bandage or support	Anti-inflammatory
	Begin wrapping the bandage at the point most distal to the injury (eg, at the toes for an ankle injury); bind firmly but not tightly	
	If the area distal to the injury (eg, fingers, toes) throbs or turns cold or blue, the bandage is too tight and should be loosened	Adjunctive analgesia
*E*levation	Elevate the area (especially the extremities) above heart level	Anti-inflammatory

methods initially minimize bleeding from broken blood vessels followed by anti-inflammatory and analgesic actions to allow for appropriate healing at the site of injury. See Table 61–1.

Rest eases pressure on the affected area, promotes pain control during the acute inflammatory phase (the first 1–5 days after injury), and prevents additional injury to the affected area.[9,19,24] During acute injury, the ability of muscles and tendons to stretch is limited. Movement in the injured tissue can cause further retraction of the ruptured muscle and increase the size of the gap in the muscle to be healed. For simple injuries, immobilization may be appropriate for 3 to 5 days depending on injury type and severity.[24] Low impact, isometric, and passive stretching or exercise modalities may be started 3 to 4 days after injury while minimizing pain.[9,24] Mobilization too early after injury predisposes a patient to further injury, but prolonged inactivity can lengthen recovery time and delay healing. Longer immobilization may be warranted for more severe injuries (eg, extensive muscle tears or fractures) and may require additional support devices (eg, crutches). In acute injury, braces, splints, and proper taping by a trained professional can immobilize joints and protect them, thereby reducing pain and swelling.[7,10]

The benefits of cryotherapy (modalities that lower tissue temperatures) following acute musculoskeletal injury are well documented.[9,20,22,24] Cold causes vasoconstriction, assisting in prevention of a large hematoma, edema, and providing analgesia by slowing nerve impulses. Immediately after injury, ice also helps to reduce metabolic rate and oxygen demand, thereby reducing tissue damage from hypoxia. Examples of cryotherapy methods include but are not limited to: (1) crushed ice (preferred over large ice pieces to provide more even cooling), (2) cold/ice packs, (3) ice massage, or (4) cold whirlpools. Depending on the method of cryotherapy, application may range from 10 to 20 minutes but should not exceed 20 minutes. For instance, if using crushed ice, patients should wrap the injured surface with a thin moist towel and then apply the crushed ice to the injured site for no longer than 10 minutes and then remove.[22] Applying ice directly to the affected area or for longer than recommended can cause tissue damage; any ice application should be stopped if the area becomes white or blue. When using an ice pack, a cold moist towel should be placed on the injury site, then the ice pack is applied for no more than 20 minutes. For small areas, direct ice massage for 7 to 10 minutes can cool the area and add relief. Alternatively, soaking the area for 7 to 15 minutes in a cool bath (13°C [55°F]) provides effective cooling, but this method must be used cautiously while monitoring for frostbite. Cryotherapy should be repeated for at least the first 72 hours after injury. If swelling is present, cryotherapy can be continued throughout the recovery process, but the duration may be shortened as pain and swelling are reduced.[9,19] There is little evidence for the effectiveness of cryotherapy in relieving low back pain, regardless of presentation.[11,17]

After the acute inflammatory phase when swelling or edema resolves, many patients find that heat decreases pain and eases muscle stiffness.[9,20,22] KEY CONCEPT Heat should not be applied during the acute injury phase (when edema is present) because it promotes swelling and inflammation. A heating pad, heat wrap, or warm bath can be used as long as no edema is present and no swelling develops after heat is applied. Application time should not exceed 20 minutes to minimize tissue injury. Patients should avoid sleeping with, sitting on, or lying on heating pads because this can result in burns. Low-level heat, such as that supplied by therapeutic heat wraps (eg, ThermaCare), may provide a safer means of heat application.

In the presence of low back pain, superficial heat application provides effective pain relief and reduces disability after 4 to 5 days of application.[11,17] For chronic low back pain, there is insufficient evidence to support the effectiveness of superficial heat for reduction of pain or disability (Table 61–2).

Table 61–2

Treatment for Low Back Pain[11,17]

Low Back Pain Type by Duration	Nonpharmacologic Therapy[a]	Pharmacologic Therapy
Acute (< 4 weeks) or Subacute (4–12 weeks)	Superficial heat application, spinal manipulation, massage, acupuncture, exercise	NSAIDs or muscle relaxants
Chronic (> 12 weeks)	Exercise, multidisciplinary rehabilitation, acupuncture, massage, psychological stress reduction, spinal manipulation	NSAIDs, duloxetine[b], opioids[b]

[a] Evidence supporting use ranges from low to moderate.

[b] Refer to Chapter 35 (Pain Management) for further drug review.

Compression and elevation are important steps in the initial treatment of an acute injury. Compression, achieved by wrapping the area with an elastic bandage, massage, or intermittent pneumatic pressure devices, also reduces the size of the developing hematoma and swelling.[9,23,24] Preventing hematoma formation is important because a large hematoma can limit mobility and range of motion. Alternating compression with cryotherapy provides more swelling reduction than use of either method alone.[23] Elevating the injured area is most critical within the first 24 to 48 hours, but elevation should continue as long as swelling is present. Elevation, ideally above the heart level, decreases blood flow and reduces fluid accumulation at the injured site.[9,21,23,24]

Pharmacologic Therapy

KEY CONCEPT There are two main approaches to pharmacologic intervention for pain relief: oral (systemic) and topical agents. In many cases, musculoskeletal injuries are self-treated with over-the-counter (OTC) oral or topical agents, but there are prescription medications available depending on injury type and severity. The choice between systemic or topical options is often guided by patient preference. The extent of musculoskeletal pain also guides treatment choice. **KEY CONCEPT** Localized pain may be treated effectively with local topical therapy, whereas generalized pain is best treated with systemic agents. Factors such as alcohol use, liver function, renal function, allergies, age, and comorbid conditions should be considered when choosing among therapeutic options.

▶ *Oral Analgesics*

Nonopioid analgesics, such as acetaminophen and NSAIDs (including aspirin), are used commonly for musculoskeletal injuries. These agents all provide analgesia, but aspirin and NSAIDs work peripherally by inhibiting the enzyme COX to decrease production of PGE_2, the principal mediator of acute inflammation.[13,19] Although the mechanism of action of acetaminophen is less clear, it appears that acetaminophen acts as a weak inhibitor of PG production via COX-2 inhibition and exerts only a mild anti-inflammatory effect.[14]

Acetaminophen **KEY CONCEPT** Acetaminophen is the drug of choice for mild-to-moderate regional musculoskeletal pain without inflammation.[13,14] However, acetaminophen does not provide adequate analgesia for patients with low back pain.[11,17] Comparative trials between acetaminophen and oral NSAIDs demonstrate equivalent analgesia in some situations, but NSAIDs may be preferred in others. If adequate analgesia is not achieved with acetaminophen, switching to an NSAID is a reasonable alternative. Acetaminophen offers the advantage of less gastrointestinal (GI) toxicity than NSAIDs. Although tolerability of acetaminophen is high at therapeutic doses, hepatotoxicity has been reported after overdose and at therapeutic doses, especially in combination with other factors such as liver disease or excessive alcohol consumption (greater than 15 drinks per week for men and eight drinks or more a week for women).[14,25] Due to concern over liver injury, OTC products are labeled with a maximum recommended dose of 3 g/day.[14] In addition, oral prescription combination products are limited by the US Food and Drug Administration (FDA) to 325 mg acetaminophen per dosage unit.[26] Acetaminophen can be administered using specific dosing regimens in infants, children, adolescents, and older adults.

NSAIDs Oral NSAIDs are used commonly for musculoskeletal pain because of their availability without a prescription and anti-inflammatory effects.[10,13,14] **KEY CONCEPT** NSAIDs are a preferred choice over acetaminophen in musculoskeletal injuries in which inflammation is the primary problem. As a result, NSAIDs are particularly beneficial for chronic overuse injury, in which inflammation is central to the pain and loss of motion.[19] Although NSAIDs may be helpful in relieving pain and inflammation in tendonitis, when inflammation is not present acetaminophen may relieve pain adequately. For patients with low back pain, NSAIDs are first-line pharmacotherapy given evidence demonstrating efficacy.[11,17] There has been some debate that early NSAID use in severe injuries, such as fractures or extensive muscle tears, may impede healing by reducing collagen formation, causing further chronic instability.[19,27] However, use of NSAIDs for less severe injury has shown beneficial effects in the recovery and healing process.[19]

The analgesic effects of NSAIDs are attributed to inhibition of the COX-2 enzyme, whereas the negative GI effects are due to inhibition of COX-1.[14] Patients taking oral anticoagulants, those with a history of peptic ulcer disease, or others at high risk for GI complications may be considered candidates for a selective COX-2 inhibitor (eg, celecoxib) or a combination of a nonselective NSAID with a gastroprotective agent such as a proton pump inhibitor (see Chapter 59). Combination of any NSAID, including COX-2 inhibitors, with alcohol can increase GI adverse effects.[14]

Both nonselective NSAIDs and COX-2 inhibitors are associated with nephrotoxicity.[14,19] NSAIDs should be avoided or used cautiously in the presence of renal dysfunction. See Chapter 59 (Osteoarthritis) for discussion of the relative risks of nonselective NSAIDs and COX-2 inhibitors, treatment options based on an individual patient's cardiovascular and GI risk profile, and maximum dosing recommendations. Refer to the drug package labeling for children and adolescents to ensure correct dosing and safe use. For example, ibuprofen is approved for use in infants 6 months and older, whereas naproxen is approved for individuals age 12 years and older.

Additionally, salicylates, like aspirin, are classified as NSAIDs. These drugs provide analgesic, anti-inflammatory, and antipyretic effects through similar mechanism of NSAIDs. **KEY CONCEPT** Aspirin is not more effective than acetaminophen, and it is not recommended for initial treatment of acute musculoskeletal pain because its adverse effects may be more common and severe.[14] Gastric irritation is more common with aspirin, and bleeding risk is increased because aspirin irreversibly inhibits platelet aggregation. Patients with aspirin-induced asthma should avoid aspirin and other salicylates. Due to the risk of Reye syndrome, aspirin should be avoided in persons younger than age 19.

Some salicylates are specifically marketed for musculoskeletal back pain, such as magnesium salicylate. However, use of salicylates is not supported given the limited evidence showing benefit in treating acute pain.[28] Magnesium salicylate should be used with caution in patients with renal impairment due to risk of hypermagnesemia and should be avoided in patients 19 years old and younger due to risk of Reye syndrome.[29]

▶ *Topical (External) Analgesics*

Topically (or externally) applied drugs exert a local analgesic, anesthetic, or antipruritic effect by either suppressing cutaneous sensory receptors or by stimulating these receptors in a counterirritant fashion, which may lessen acute localized muscle injury symptoms.[14] These medications are applied directly to the affected area to create high local concentrations of the drug and exert action locally in the nerves or tissues. Negligible systemic concentrations are achieved with intact skin, minimizing systemic adverse effects.[14] Occluding or wrapping the area after topical application increases the potential for systemic adverse effects.

Formulations include gel, cream, lotion, patch, liquid, liniment, or aerosol spray. Topical delivery should not be confused with transdermal delivery, in which drug absorption into the bloodstream produces a systemic effect. Musculoskeletal injuries often are treated with topical (not transdermal) medications.

After application, the topical medication penetrates the skin to the soft tissue and peripheral nerves.[14] Topical analgesics suppress the sensitization of pain receptors at the site, thereby reducing pain and burning. Examples include topical NSAIDs and local anesthetics. In contrast, *counterirritant* products are external analgesics that stimulate cutaneous sensory receptors, producing a burning, warming, or cooling sensation that masks the underlying pain. In effect, the irritation or inflammation caused by the counterirritant distracts from the underlying pain.

External analgesics are useful adjuvants to nonpharmacologic therapy and systemic analgesic therapy to provide additional relief. These agents are also an option in patients who cannot tolerate systemic analgesics. However, because these products are not in pill form and many are available without a prescription, they may be overused or misused. Clinicians should advise patients to read and follow directions on the labels of OTC products.

Topical NSAIDs In acute soft-tissue injury such as strains and sprains, efficacy of topical NSAIDs is superior to that of placebo and similar to that of oral NSAIDs.[30] Tissue concentrations of topical NSAIDs are high enough to produce anti-inflammatory effects, but systemic concentrations after application remain low.

Diclofenac is the only topical NSAID commercially available in the United States.[14] Topical diclofenac solution (Pennsaid) and gel (Voltaren) are only indicated for treatment of osteoarthritis, with gel (Voltaren Arthritis) now available OTC (see Chapter 59).[31-33] The diclofenac patch (Flector Patch) is indicated specifically for topical treatment of acute pain from minor sprains and strains in adults.[34] One patch is applied to the most painful area twice daily to intact skin only.[14,34] Patients should be instructed to wash hands before and after application, discard the patch after use, avoid wearing the patch while bathing or showering, and to tape the patch in place if it begins to peel off.

Theoretically, the risk of serious GI adverse events should be less than with oral NSAIDs, but long-term studies evaluating these events are lacking. Like oral NSAIDs, topical NSAIDs should be used with caution in patients with a history of GI bleeding or ulcer.[14] Use of topical NSAIDs with oral NSAIDs is not recommended given the potential for increased systemic adverse effects. See Chapter 59 (Osteoarthritis) for further review of NSAID-related adverse effects. A Cochrane review demonstrated that topical NSAIDs were beneficial to manage acute musculoskeletal pain, but further comparative studies to other topicals (eg, counterirritants) are needed.[30] Local cutaneous adverse reactions (eg, erythema, rash, pruritus, and irritation) are reported and may be due in part to the vehicle used.[14,31,32,34]

Local Anesthetics Nonprescription topical anesthetics such as lidocaine and benzocaine are available in many types of products. Local anesthetics decrease discharges in superficial somatic nerves and cause numbness on the skin surface but do not penetrate deeper structures such as muscle where the pain often lies.[35] Although these topical anesthetics are not effective in direct treatment of musculoskeletal pain, they are helpful when abrasion accompanies the injury. Frequently, anesthetics are formulated in combination with an antibiotic for OTC use; the anesthetic provides soothing relief to the abrasion site while the antibiotic promotes healing of abrasions and prevents soft-tissue infection.

Prescription topical anesthetic agents are not approved for the treatment of acute musculoskeletal pain.[14] Agents include topical lidocaine patch (Lidoderm) and heated lidocaine/tetracaine patch (Synera). The patches deliver lidocaine to local tissues to reduce neuronal impulse, induce an anesthetic effect, and reduce inflammation. The heated lidocaine/tetracaine patch provides a similar mechanism of action but is formulated with an added oxygen-activated heating component to enhance local anesthetic delivery. These agents may be considered for off-label treatment of musculoskeletal and low back pain when other first-line or approved therapies have not provided adequate pain relief.

Counterirritants These products are indicated for temporary relief of minor aches and pains related to muscles and joints.[18] These symptoms may be associated with arthritis, strains, or sprains. Many are available as combination products with ingredients from different counterirritant groups. Active ingredients in marketed products sometimes change; clinicians should be aware of the current ingredients before recommending a product. These products are applied multiple times a day (ranging from 3 to 4 applications daily) for up to 7 days; if pain relief is not achieved by that time, the patient should follow up with the provider to further evaluate the acute musculoskeletal pain.

Nonprescription counterirritants are categorized by the FDA into four groups (groups A through D) based on their primary actions (Table 61–3).[18] They produce a feeling of redness, cooling, warmth, or irritation that diverts sensation from the pain. Because these irritant effects are central to the beneficial actions, counterirritants should not be combined with topical analgesics or topical anesthetics. **KEY CONCEPT** Patient education on proper use of counterirritants is essential to therapeutic success (Table 61–4).[18]

Rubefacients (group A) are counterirritants that produce redness on application. Evidence from clinical trials and a systematic review showed rubefacients to be ineffective for relieving acute pain from strains, sprains, and sports injuries, and for chronic musculoskeletal pain.[28] However, topical rubefacients containing salicylates (eg, methyl salicylate) may be used if a patient does not tolerate or has contraindications to other therapy or prefers an alternative route of administration for acute pain. Topical formulation of salicylates can lead to systemic effects similar to aspirin or NSAID therapy.[14,36] When recommending topical salicylate products, the same factors for use of NSAIDs and aspirin should be considered.[36] Additionally, methyl salicylate, including oil of wintergreen, is a common source of pediatric poisonings.[36,37]

The group B counterirritants menthol and camphor exert a sensation of cooling through direct action on sensory nerve endings, followed by a sensation of warmth.[36,38] The agents cause a burning sensation by stimulating cutaneous nociceptors.[36] For topical analgesic use, menthol is available in creams, lotions, ointment, and patches. The patches can be trimmed to fit the affected area. Despite limits on the concentration of available products, camphor can be toxic to children even in small amounts, posing a seizure risk.[39]

The group C counterirritants methyl nicotinate and histamine dihydrochloride produce vasodilation.[18] Methyl nicotinate produces PG-mediated vasodilation.[40] NSAIDs and aspirin block the production of PGs and decrease methyl nicotinate–induced vasodilation. Application over a large area has been reported to cause systemic symptoms and syncope, possibly due to vasodilation and a decrease in blood pressure.[41] Patients should be educated to apply only scant amounts to the affected area.

The primary counterirritant in group D is capsaicin, a natural substance found in red chili peppers.[14,36] Capsaicin stimulates the release of substance P from local sensory nerve fibers, depleting substance P stores over time, and ultimately reduces transmission

Table 61–3

Nonprescription Counterirritant External Analgesics[18]

Group and Effect	Agents and Concentration	Example Products (If Applicable)	Comments
Group A Rubefacients: Produce redness	Allyl isothiocyanate 0.5%–5%		Mustard derivative; pungent odor; avoid inhalation
	Ammonia water 1%–2.5%		More concentrated solutions are highly caustic; avoid inhalation
	Methyl salicylate 10%–60%	BenGay Ultra Strength,[a] Flexall Plus,[a] Icy Hot Stick[a]	Caution in aspirin sensitivity May produce systemic concentrations May increase INR with warfarin Use in adults and children > 12 years old
Group B Produce cooling	Camphor 3%–11% Menthol 1.25%–16%	JointFlex BenGay Patch, Icy Hot Patch, Mineral Ice[c]	Medicinal odor Sensation of heat follows cooling Mild anesthetic effects at low concentrations Use in adults and children > 12 years old[d]
Group C Produce vasodilation	Methyl nicotinate 0.25%–1%	Arth Arrest[b]	May produce systemic vasodilation Use in adults and children > 2 years old
Group D Irritate without redness	Capsaicin 0.025%–0.25% Capsicum oleoresin 0.025%–0.25%	Capzasin-HP, Zostrix	Must use regularly Burning effect subsides with regular use Use in adults only (ages > 18 years old)

[a] Combination products that also contain menthol and/or camphor.

[b] Combination product that also contains capsaicin.

[c] May be used in adults and children age 2 years old and older.

[d] Based on product labeling; Federal Register recommends to avoid in children less than 2 years old.

INR, international normalized ratio.

of pain impulses to the CNS. As with other counterirritants, capsaicin and its derivatives (capsicum and capsicum oleoresin) exert a warming or burning sensation.[14,36] With repeated application, desensitization occurs, and the burning sensation subsides within the first 1 to 2 weeks. Pain relief is usually noted within 2 to 6 weeks.[14,36] After discontinuation, resensitization occurs gradually over 6 weeks.[36]

Because of the lag time between initiation and effect, capsaicin is not used for treatment of acute pain from injury. Topical capsaicin is used for chronic pain from musculoskeletal (ie, overuse injury) and neuropathic disorders. Capsaicin preparations have been studied for treatment of pain from diabetic neuropathy, osteoarthritis, postherpetic neuralgia, and other disorders.[14,36] It is often used as an adjuvant to systemic analgesics in these chronic pain conditions.

Table 61–4

Patient Education for Counterirritants[18]

Apply up to three to four times daily to affected area.
Only for external use on the skin; do not ingest.
Do not apply to broken or damaged skin or cover large areas.
Wash hands immediately after application.
Avoid contact with the eyes and mouth.
Do not use with heating pads or other methods of heat application, because burning or blistering can occur.
Do not wrap or bandage the area tightly after application.
Discontinue product if excessive skin irritation or rash occurs.
Consult a physician if:

- Symptoms worsen.
- Symptoms persist for more than 7 days[a] for acute pain.
- Symptoms resolve but then recur.

[a] Capsaicin is used for chronic pain, and efficacy is evaluated after 2 weeks.

Although systemic adverse effects to capsaicin are rare, local adverse effects are expected and common.[14,36] Patient education regarding consistent use of capsaicin products is essential to achieving desired outcomes. The product should be applied in a thin layer and rubbed into the skin thoroughly until little remains on the surface. KEY CONCEPT Patients using capsaicin should be advised to apply it regularly and consistently three to four times daily and that full effect may take 2 weeks or longer. Patients should be assured that the burning effects will diminish with repeated application. Adherence to therapy is essential because the burning sensation persists if applications are less frequent than recommended. Patients should avoid hot showers or baths immediately before or after application because the burning sensation is enhanced with heat. Wearing nitrile gloves during application and washing hands immediately after application can decrease the potential for unintended contact with eyes or mucous membranes. Dried product residue has been reported to cause respiratory effects on inhalation (eg, coughing), and caution should be used in patients with asthma or other respiratory illnesses.[14]

▶ *Oral Muscle Relaxants*

Oral muscle relaxants are a useful adjunct to therapy when pain is worsened by muscle spasm.[14] Antispasmodic agents are preferred over antispastic agents for musculoskeletal pain because antispasmodics exert their effect directly on skeletal muscle fibers, polysynaptic reflexes, and/or descending facilitatory systems; whereas antispastic agents mostly target upper motor neuron conditions. Examples of antispasmodic agents include carisoprodol, cyclobenzaprine, metaxalone, and methocarbamol. Muscle relaxants decrease spasm and stiffness associated with either acute or chronic musculoskeletal injuries. For low back pain, a systematic review demonstrated that muscle relaxants provide significant acute or subacute pain relief but are not effective in treating chronic low back pain.[17,42] These agents should be used with caution because they all may cause sedation, especially in combination with alcohol or opioid analgesics. Many produce anticholinergic effects, such as xerostomia and blurred vision, and have potential for abuse. Sudden discontinuation should be avoided because it may lead to withdrawal symptoms. Muscle relaxants should be used with caution in older adults (age 65 years and older), with use reserved for those with no other reasonable alternatives. Clinicians should monitor such adults more closely given the potential adverse effects. Patient-specific factors should be reviewed before recommending muscle relaxants.

▶ *Opioid Analgesics*

Opioid analgesics may be considered in acute pain management if nonopioid analgesics are already optimized and the patient is still experiencing moderate to severe pain.[13,19] Opioids may be used in combination with nonopioids such as acetaminophen or NSAIDs, but the dose should not exceed the recommended daily dose of the respective nonopioid agent(s). Opioids are not recommended as initial therapy for acute or subacute low back pain, given the low level of evidence of effectiveness in reducing pain. Patients presenting with chronic low back pain who are having inadequate response to NSAIDs or duloxetine may benefit from opioid medications.[17] Given the concern for abuse potential and adverse events with opioids, a full patient medical history is recommended before prescribing. See Chapter 35 (Pain Management) for more information on use of duloxetine and opioids.

Patient Encounter 1, Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH/PSH: Heartburn (food induced).

SH: Smokes 2 to 3 cigarettes per week socially; drinks 6 to 7 beers 4 times a week with friends.

Meds: Famotidine 10 mg one to two tablets once to twice daily as needed; acetaminophen 500 mg two tablets every 6 to 8 hours for knee pain since injury.

Allergies: Sulfa drugs (rash).

Intolerances: None.

Preferences: No preference to topical or oral medications at this time.

Diagnostic Tests: Radiographs of right knee show no evidence of fracture or underlying medical conditions.

Pain (numerical rating scale): 5 out of 10.

What are your treatment goals and desired outcomes?

What nonpharmacologic and pharmacologic treatment options are available? Are there treatment options that should be avoided? If so, which options and why?

▶ *Complementary and Alternative Medicine for Pain Relief*

Various complementary and alternative modalities are available for patients seeking additional or alternative treatments for pain relief or recovery from musculoskeletal injury. Integrative practices include manipulation therapy, acupuncture, massage therapy, yoga, electrical stimulating currents, low-power laser, hyperbaric oxygen therapy, platelet-rich plasma injections, and ultrasound therapy.[9,10,14,21,24]

Massage therapy, spinal manipulation, and acupuncture have shown potential benefit in relieving acute or subacute low back pain.[11,17] Acupuncture and cognitive behavioral therapy have demonstrated moderate benefit in reducing chronic low back pain.

Dietary supplements that have been shown to potentially reduce pain and/or inflammation include devil's claw, willow bark extract, aspen or goldenrod, cannabinoids, and turmeric.[14] Given the mechanisms of action and metabolism of these supplements, it is highly recommended to review potential adverse events, drug interactions, and a patient's current medical history before recommending any of these supplements.[43] Overall evidence of benefit may be limited or conflicting, and patients should be educated on the benefits and risks of these therapies before initiation as additional treatment.

Lifestyle and Behavioral Modifications

After treatment of an acute injury, repetitive strain injury, or low back pain with nonpharmacologic and pharmacologic therapy, the final phase of therapy is rehabilitation and prevention of future injury. For most injuries, prolonged immobilization can lengthen the recovery time by causing wasting of the healthy muscle fibers and increased scarring.[9,19,22,24] Rehabilitation starts with decreasing inflammation, then increasing range of motion and flexibility via stretching exercises. The patient should warm the muscle first with light activity or moderate heat. Warmth produces relaxation and increases elasticity. Next, the patient may start general strengthening exercises. The focus of the rehabilitation may not be the injured muscle itself but nearby muscles to assist with stability. End goals of rehabilitation are specific to each patient and may range from return to activities of daily living to a rigorous sports schedule. Similar to the acute injury phase, braces, splints, and proper taping by a trained professional can protect the joint and promote alignment.[7,10]

Patient Encounter 1, Part 3: Creating a Care Plan

Based on the information presented, create a care plan to treat this patient's knee injury. Your plan should include the following:

(a) The goals of therapy and desired outcomes

(b) A patient-specific therapeutic plan, including nonpharmacologic therapy

(c) A plan to monitor the outcome of therapy to determine whether goals of therapy have been met and adverse effects avoided

Patient Encounter 2

A 32-year-old woman presents with left wrist pain. Upon questioning, you find she is a triathlon athlete for the past 5 years. She reports gradual onset of wrist pain over the last few months while cycling. When she wakes in the morning, she has minimal pain after resting overnight, but the pain begins to intensify during the middle of her morning cycling and lasts throughout the day. She denies any swelling. She reports decreased range of motion compared to her right wrist. She is 29 weeks pregnant and only takes a daily prenatal multivitamin.

Given this information, what is your assessment of the patient's wrist pain? What is the likely etiology of the pain?

What nonpharmacologic and pharmacologic treatment options should be considered?

Based on the information presented, create a care plan for this patient's wrist injury. Your plan should include the following:

(a) The goals of therapy and desired outcomes

(b) A patient-specific therapeutic plan, including nonpharmacologic therapy

(c) A monitoring plan to determine whether goals of therapy have been met and adverse effects avoided

After rehabilitation, the patient should be educated about behavior changes to prevent reinjury.[19] The strength and flexibility exercises learned in the rehabilitation phase should be continued. For overuse injury, correction of biomechanical abnormalities with proper footwear and changes in technique may correct misalignments and imbalances.[2]

In the workplace, repetitive motion can be decreased through proper ergonomic design, improved posture, and redesigning job tasks.[3] In pain of the back or lower extremity, weight loss in overweight or obese patients can help to prevent reinjury or repetitive strain injuries.[16]

OUTCOME EVALUATION

- Use a pain scale to monitor treatment interventions to ensure that pain relief is achieved. Ask the patient to rate pain on a scale of 0 (no pain) to 10 (worst possible pain) both at rest and with movement. Compare the results with baseline pain assessment to monitor the response to therapy. In pediatric patients, use a visual pain scale with facial expressions depicting various degrees of pain.
- Assess range of motion at baseline and after treatment by comparing movement with the unaffected limb and functionality before the injury. Assess functionality by asking patients if they are able to perform activities of daily living or participate in exercise as desired.
- If pain from acute injury does not decrease greatly within 7 to 10 days, further diagnostic evaluation is warranted.

Patient Care Process

Collect Information:

- Establish the timing of injury (if applicable), duration, type and degree of pain, and exacerbating factors. Ask about interference with usual activities or range of motion.
- Ask the patient about exacerbating or alleviating factors. Inquire if the patient has tried any successful or unsuccessful nonpharmacologic or pharmacologic treatments for the current complaint or for this condition in the past.
- Obtain a complete medication history, including prescription and nonprescription drugs and dietary supplement use. Gather patient history, including social history and alcohol use. Inquire about drug allergies and chronic health problems such as asthma. Collect physical assessment and laboratory data when available.
- Inquire about patient preference for systemic (oral) or local (topical) therapy including acceptability of topical medication with frequent application and/or a medicinal odor. Identify the patient's goals, beliefs, lifestyle habits, and socioeconomic factors relevant to development of care plan.

Assess the Information:

- Assess the efficacy, safety, and patient adherence of any nonprescription or prescription medications currently being used for the condition and consider alignment with patient preferences for therapy.
- Based on review of symptoms and timing, assess whether empirical care or diagnostic evaluation is appropriate and whether pharmacologic therapy is warranted.

Develop a Care Plan:

- Develop goals of therapy in collaboration with the patient.
- Determine if referral to another healthcare provider on the team is warranted based on the symptoms provided.
- Recommend nonpharmacologic and pharmacologic therapy appropriate for the specific patient (Tables 61–1, 61–2, and 61–3; Figure 61–1).

Implement the Care Plan:

- Educate the patient on nonpharmacologic therapy for the presenting pain type when appropriate (Tables 61–1 and 61–2).
- Educate on proper use of oral or topical agents selected (Tables 61–3 and 61–4). If a counterirritant is recommended, counsel patients on the irritant effect of the product and recommend washing hands immediately after use and to avoid heating pads. For patients using a capsaicin product, emphasize adherence.
- Coordinate any referrals, when applicable.

Follow-up: Monitor and Evaluate:

- If pain is from an acute injury, assess effectiveness within 7 to 10 days. For chronic pain treated with capsaicin, begin to assess pain control in 2 weeks.
- Evaluate for adherence, adverse effects (systemic or local), and drug interactions.

Patient Encounter 3

An 82-year-old man presents with acute lower back pain complaining of a "pulled muscle." He states that he was at his daughter's house yesterday and tripped on one of his grandson's toys, twisting his back. He reports decreased range of motion, tightness, and tenderness, but denies any nerve pain.

PMH/PSH: Atrial fibrillation, coronary artery disease, hypertension, dyslipidemia.

SH: Nonsmoker, 1 glass of wine on holidays.

Meds: Apixaban 2.5 mg twice daily, lisinopril 10 mg one tablet orally daily, metoprolol XL 50 mg daily, atorvastatin 40 mg one tablet orally daily, aspirin 81 mg one tablet orally daily, multivitamin one tablet orally daily.

Allergies: NKDA

Intolerances: None.

Preferences: No preference to oral or topical medications.

Vital signs: BP 140/92 today, HR 77.

Diagnostic Tests: None.

Pain (numerical rating scale): 3 out of 10. Pain worsens to 4 out of 10 with bending or lifting.

Given this information, what is your assessment of the patient's acute lower back pain? What is the likely etiology of the pain?

What nonpharmacologic and pharmacologic treatment options should be considered?

Based on the information presented, create a care plan for this patient's lower back injury. Your plan should include:

(a) Goals of therapy and desired outcomes

(b) Patient-specific therapeutic plan, including nonpharmacologic therapy

(c) A plan to monitor the outcome of therapy to determine whether goals of therapy have been met and adverse effects avoided

- In patients with chronic low back pain, periodically assess the patient for new signs and symptoms that may warrant further workup.
- Assess adherence to recommended treatments for therapeutic benefit. For all products except capsaicin, assess for acute pain relief within 7 days. For topical capsaicin, assess chronic pain control in 2 weeks.
- Assess medication adverse effects on a regular basis. When NSAIDs and aspirin are used, ask about GI tolerability, bruising, and bleeding. Inquire about local adverse effects, such as burning, when topical counterirritants are used for treatment. When oral muscle relaxants are used, inquire about anticholinergic effects such as xerostomia and blurred vision. Refer to Chapter 35 (Pain Management) for opioid side effects.
- Evaluate adherence to preventative rehabilitation measures such as proper footwear, warm-up before activity, strength training, and proper lifting technique.

Abbreviations Introduced in This Chapter

CNS	Central nervous system
COX	Cyclooxygenase
FDA	Food and Drug Administration
GI	Gastrointestinal
NSAIDs	Nonsteroidal anti-inflammatory drugs
OTC	Over-the-counter
PG	Prostaglandin
RICE	Rest, ice, compression, and elevation

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62

Glaucoma

Daniel O. Clegg, Jr.

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Identify risk factors for the development of primary open-angle glaucoma (POAG) and acute angle-closure glaucoma.
2. Recommend a frequency for glaucoma screening based on patient-specific risk factors.
3. Compare and contrast the pathophysiologic mechanisms responsible for open-angle glaucoma and acute angle-closure glaucoma.
4. Outline the clinical presentation of chronic open-angle glaucoma and acute angle-closure glaucoma.
5. List the goals of managing patients with POAG suspect, POAG, and acute angle-closure glaucoma.
6. Choose the most appropriate therapy based on patient-specific data for open-angle glaucoma, glaucoma suspect, and acute angle-closure glaucoma.
7. Develop a monitoring plan for patients on specific pharmacologic regimens.
8. Counsel patients about glaucoma, drug therapy options, ophthalmic administration techniques, and the importance of adherence to the prescribed regimen.

INTRODUCTION

Glaucoma refers to a spectrum of ophthalmic disorders characterized by neuropathy of the optic nerve and loss of retinal ganglion cells, which typically leads to permanent deterioration of the visual field (peripheral vision) initially and potentially total vision loss (including central vision). It is often, but not always, eye pressure related.[1-3] Table 62–1 describes the general classification of glaucoma. *Glaucoma suspects* are patients with a higher than average risk of developing glaucoma because of the presence of certain clinical findings, including elevated intraocular pressure (IOP) or optic nerve features consistent for glaucoma, risk factors, family history, or racial background. Glaucoma suspects are further classified as open-angle glaucoma suspects or angle-closure glaucoma suspects.

Primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) represent the most common types of glaucoma and therefore are the focus of this chapter. PACG can present clinically as acute angle-closure crisis (AACC). AACC is the sudden obstruction of the trabecular meshwork, which leads to a rapid increase in IOP resulting in pressure-induced optic neuropathy if untreated.[1-4] **KEY CONCEPT** In contrast, patients with POAG typically have a slow, insidious loss of vision, which is often asymptomatic until the latter stage of the disease process. This is contrasted by the course of AACC, which can lead to rapid and painful vision loss that develops over hours to days.

EPIDEMIOLOGY AND ETIOLOGY

It is estimated that nearly 76 million people had glaucoma in 2020, making it the second leading cause of blindness after cataracts. By 2040 this number may increase to greater than 110 million people worldwide.[5] In North America it is estimated that almost 4 million people are affected by POAG, and by 2040 this number will increase to nearly 5 million.[5] The prevalence varies with race and ethnicity, and it is three to five times more prevalent in African Americans than White Americans.[6] The prevalence of POAG increases with age and is rarely seen in patients younger than 40 years.[6,7] The prevalence of POAG suspects is difficult to estimate at this time, but it is expected that 3.5% to 4.5% of White and Hispanic patients older than 40 years have ocular hypertension.[2]

Approximately 20 million people were estimated to have angle-closure glaucoma in 2013, and this is projected to increase to 32 million people by 2040.[5] The prevalence of angle-closure glaucoma is lower than POAG and varies significantly by race and ethnicity. The prevalence is lower in patients of European ancestry (0.4%) but higher in patients of Asian ancestry (1.2%).[5] PACG is also more prevalent with increasing age and among females.[4]

PATHOPHYSIOLOGY

The pathophysiology of glaucomatous neurodegeneration has not been completely elucidated but appears to be caused by both IOP-dependent and IOP-independent factors. Elevated IOP is clearly associated with damage and eventual death of optic nerves; however, optic neuropathy can occur in patients without elevated IOP, which indicates the presence of independent factors that contribute to ganglion cell death.[8,9] The key to understanding the pathophysiology and treatment of glaucoma relies on an understanding of aqueous humor dynamics, IOP, and optic nerve anatomy and physiology.

Aqueous Humor and Intraocular Pressure

IOP maintains the curvature of the cornea which is important for the refractive properties of the eye.[10] The distribution of IOP in

Table 62–1

Glaucoma Classifications[3,4]

Classification	Description
Primary glaucoma	Glaucoma that cannot be attributed to a preexisting ocular or systemic disease.
Secondary glaucoma	Glaucoma that can be attributed to preexisting ocular or systemic disease. Examples include pigment dispersion syndrome, neovascular glaucoma, and pseudoexfoliative syndrome.
Open-angle glaucoma	Glaucoma characterized by normal anterior-chamber angles and glaucomatous changes of the optic disc. Can be further classified as primary or secondary.
Angle-closure glaucoma	Glaucoma characterized by the obstruction of the anterior-chamber angle resulting in either intermittent or progressive elevated IOP with subsequent damage to the optic nerve. Can be further classified as primary or secondary.

the general population is 10 to 21 mm Hg (1.3–2.8 kPa) and is slightly skewed toward higher values. However, caution should be used in assigning this as the "normal range" for IOP because some patients may have optic neuropathy in the "normal range" while for other patients optic neuropathy may be absent at higher IOPs. Elevated IOP is generally considered greater than 21 mm Hg (2.8 kPa).[11]

Aqueous humor is an optically neutral fluid that provides oxygen and nutrition to the avascular lens and cornea. IOP is dependent on the balance between aqueous humor production and outflow from the anterior segment (Figure 62–1A). The anterior segment of the eye is separated by the iris into the posterior and anterior chambers. The ciliary body is a ring-like structure that surrounds and supports the lens. It also produces aqueous humor through the diffusion and ultrafiltration of plasma. The nonpigmented epithelium of the ciliary body secretes the aqueous humor into the posterior chamber. Aqueous humor production can be modified pharmacologically through the α- and β-adrenoceptors, carbonic anhydrase, and sodium and potassium adenosine triphosphatase of the nonpigmented ciliary epithelium.[12,13]

After secretion, the aqueous humor flows from the posterior chamber through the pupil into the anterior chamber. From the anterior chamber, approximately 80% of aqueous humor then exits through the trabecular meshwork while the remaining 20% exits through the uveoscleral pathway.[12,13]

The trabecular meshwork is a lattice of connective tissue that surrounds peripheral edge of the anterior chamber located in the inside intersection of the edge of the cornea and the iris insertion. The size of the trabecular meshwork can be altered by the contraction or the relaxation of the ciliary muscle. Stimulation of muscarinic receptors on the ciliary muscle causes contraction, which in turn causes the pores of the trabecular meshwork to open, increasing aqueous humor outflow into Schlemm canal and the episcleral venous system.[12] The contraction can also be decreased by inhibiting rho kinases that are involved in the regulation of the contractile tone of the trabecular meshwork tissue.[13]

In the uveoscleral pathway, aqueous humor exits the anterior chamber through the iris root and through spaces in the ciliary muscles, which then drain into the suprachoroidal space. Uveoscleral outflow can be pharmacologically modulated by adrenoceptors, prostanoid receptors, and prostamide receptors.[10,14]

Optic Nerve

In the posterior segment of the eye, retinal ganglion cells are responsible for transmitting visual signaling from the retina to the brain. The axons of the retinal ganglion cells converge at the retinal nerve fiber layer to form the optic nerve. The optic nerve head (also called the optic disc) is the portion of the optic nerve that is visible on funduscopic examination. The optic nerve head is typically vertically oval and pink to pale yellow with a depression in the center of the optic nerve, called a physiologic cup, which is formed as the axons converge and exit the eye as a bundle through the lamina cribrosa (Figure 62–2). The optic nerve synapses at the lateral geniculate nucleus in the brain.[8,9,15,16]

Pathophysiology of Open-Angle Glaucoma

In patients with POAG, the cause of elevated IOP is not obvious, as obstruction in aqueous humor outflow is not clinically discernible (Figure 62–1B). Possible causes of this increased IOP may be related to an increase in outflow resistance in the trabecular meshwork.[8,9,13,15]

Glaucomatous optic neuropathy may also occur independent of increased IOP. Pressure independent causes of optic neuropathy include abnormal ocular perfusion, oxidative stress, and inflammation.[8,9,11,15]

Regardless of the underlying cause, elevated IOP initiates several detrimental changes to glial cells, the lamina cribrosa, and retinal ganglion cells. The increase in IOP can lead to alterations in retinal blood flow and axonal transport of neurotrophic factors, resulting in cellular stress of the retinal ganglion cells. This stress activates the glial cells in a manner that leads to inappropriate remodeling of the extracellular matrix. Elevated IOP deforms the lamina cribrosa, which places mechanical strain on the retinal ganglion cells. Chronic elevation of IOP ultimately causes the retinal ganglion cells to undergo apoptosis.[8,9,15,17,18]

Current glaucoma therapies fail to target IOP-independent glaucoma pathophysiologic factors. However, IOP reduction may still be beneficial, as the rate of visual field progression is decreased in many patients who exhibit IOP reduction via medical or surgical modalities.[3,8]

Pathophysiology of Angle-Closure Glaucoma

PACG involves a mechanical obstruction of aqueous humor outflow through the trabecular meshwork by the peripheral iris (Figure 62–1C). Two major mechanisms of trabecular meshwork obstruction by the peripheral iris include pupillary block and an abnormality of the iris called iris plateau. Pupillary block is the more common mechanism of obstruction and results from a complete or functional apposition of the central iris to the anterior lens and is associated with mid-dilation of the pupil. The trapped aqueous humor in the posterior chamber increases pressure behind the iris, causing the peripheral iris to bow forward and obstruct the trabecular meshwork. Plateau iris refers to an anterior displacement of the peripheral iris caused by anteriorly positioned ciliary processes. In this configuration, the peripheral iris bunches as the eye dilates. Both of these mechanisms result in the occlusion of aqueous humor outflow, causing IOP elevation at extreme levels that can lead to vision loss in hours to days.[4,8,19] The degree of iridotrabecular contact (angle closure) can be assessed by visualizing the anatomy of the iridocorneal angle by an examination technique called gonioscopy.

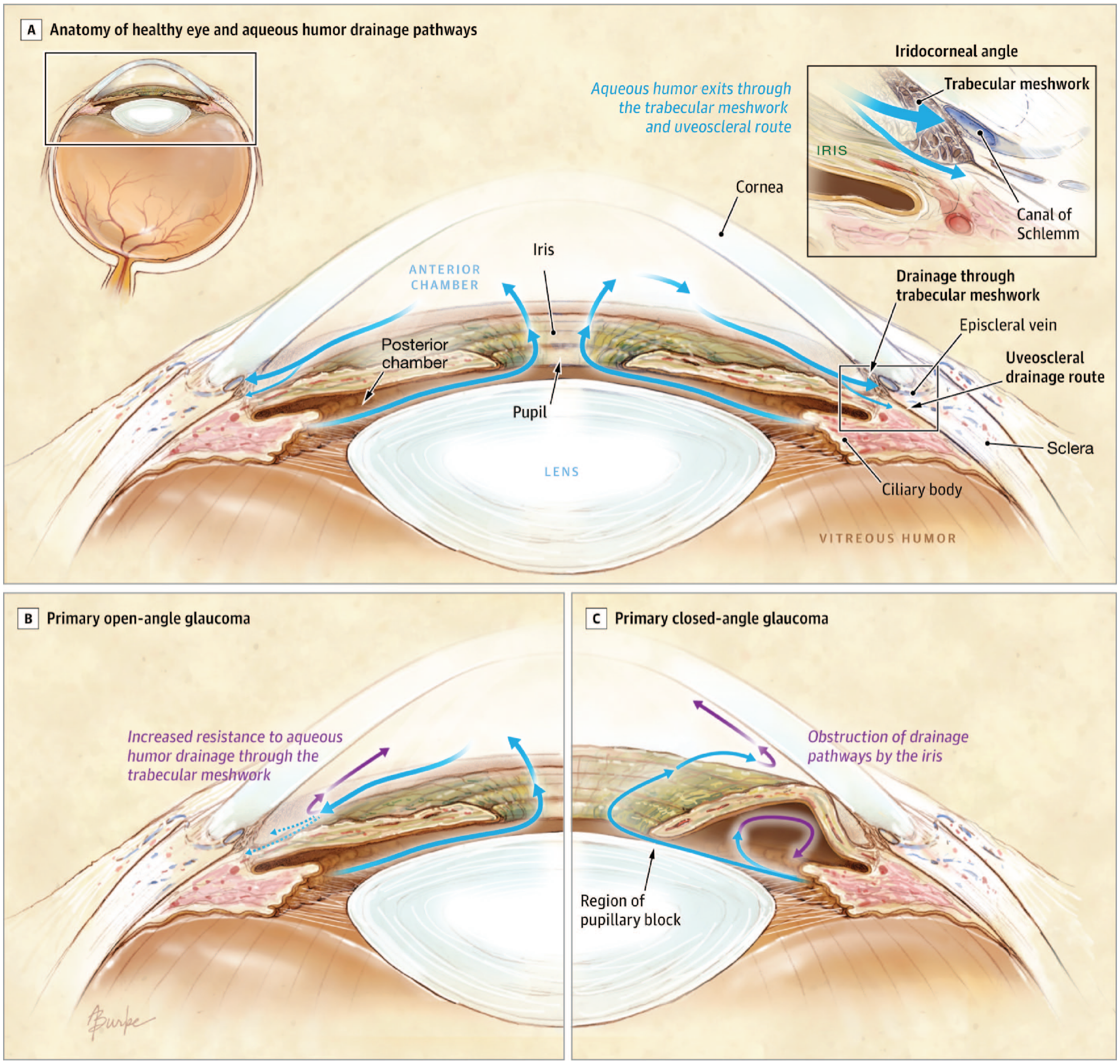
A Anatomy of healthy eye and aqueous humor drainage pathways
Iridocorneal angle
Trabecular meshwork
IRIS
Canal of Schlemm
Aqueous humor exits through the trabecular meshwork and uveoscleral route
Cornea
Iris
ANTERIOR CHAMBER
Posterior chamber
Pupil
LENS
Drainage through trabecular meshwork
Episcleral vein
Uveoscleral drainage route
Sclera
Ciliary body
VITREOUS HUMOR
B Primary open-angle glaucoma
Increased resistance to aqueous humor drainage through the trabecular meshwork
C Primary closed-angle glaucoma
Obstruction of drainage pathways by the iris
Region of pupillary block

FIGURE 62–1. Aqueous humor drainage pathways of healthy and glaucomatous eyes. (Reprinted with permission from Weinreb RN, Aung T, Madeiros FA. The pathophysiology and treatment of glaucoma. JAMA. 2014;311:1901–1911.)

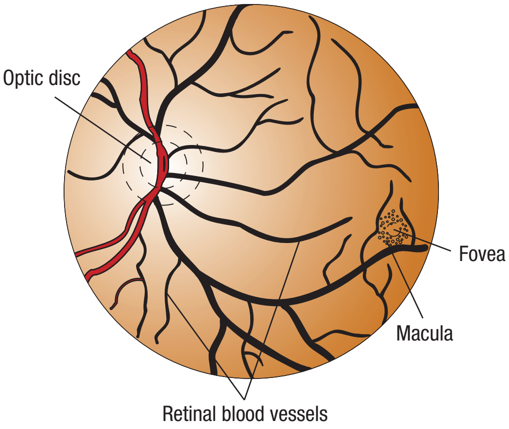
Optic disc
Fovea
Macula
Retinal blood vessels

FIGURE 62–2. Normal fundus of the eye and optic disc and cup.

CLINICAL PRESENTATION AND DIAGNOSIS

Risk Factor Evaluation

For POAG, only 4% to 8% of patients may progress to legal blindness. Vision loss does not occur until there has been significant loss of the retinal ganglion cells. It may take 13 to 16 years for a patient to go blind from glaucoma. A patient's quality of life may not be affected until significant visual field loss is present, and the patient can no longer perform the activities of daily living.[20] **KEY CONCEPT** Practitioners play an important role in eye care by assessing patients for risk factors and referring to an eye care specialist for appropriate screening and evaluation. Risk factor evaluation is essential in determining the frequency of comprehensive eye examinations for patients (Table 62–2).[21] Glaucoma risk factors are also useful in deciding when to start therapy and determining the sequence of pharmacotherapeutic or surgical treatment modalities.[2-4] Table 62–3 lists the major risk factors associated with POAG and PACG.

Patient Encounter, Part 1

CM, a 70-year-old Caucasian woman with a history of congestive heart failure and hypertension, presents to your clinic for her yearly checkup. She states that she is concerned about losing her eyesight because her sister has started losing her vision from glaucoma. She denies changes in her vision.

Meds: Losartan 100 mg orally once daily, metoprolol succinate 50 mg orally once daily, furosemide 20 mg orally once daily

Based on the patient's medical and family history, what risk factors does this patient have for glaucoma?

How often would you recommend that this patient receive a comprehensive eye evaluation?

What objective assessments should be gathered in order to fully evaluate her risk factors for glaucoma?

How often would you recommend that this patient receive a comprehensive eye evaluation?

Table 62–2

Recommended Frequency of Comprehensive Adult Medical Eye Evaluation[21]

Age (Years)	With Risk Factors for Glaucoma	No Known Risk Factors for Ocular Disease
65 or above	1–2 years	1–2 years
55–64	1–2 years	1–3 years
40–54	1–3 years	2–4 years
Under 40	1–2 years	5–10 years

The development of PACG is associated with several anatomical risk factors that lead to shallow anterior chambers. PACG patients may have a thick, anteriorly displaced lens that results from continued growth of the lens and/or cataractous changes. The anterior chamber depth is typically shallower in many individuals with PACG, which predisposes these eyes to anatomically narrower iridocorneal inlets that are a setup for developing critically narrow angles more susceptible to closure (from an enlarging cataractous lens or other insults).[4,19]

Patients with PACG are characterized by at least 180 degrees of iridotrabecular contact, elevated IOP, and ophthalmic examination characteristic of glaucomatous changes. Recurrent attacks or a prolonged acute attack can lead to the development of peripheral anterior synechia, which partially obstructs the flow of aqueous humor through the trabecular meshwork.[4,19]

TREATMENT

Primary Open-Angle Glaucoma

▶ *Desired Outcomes and Goals*

KEY CONCEPT The goals of therapy are to prevent further loss of visual function; minimize adverse effects of therapy and impact on the patient's vision, general health, and quality of life; maintain IOP at or below a pressure at which further optic nerve damage is unlikely to occur; and educate and involve the patient in the management of their disease. KEY CONCEPT Current therapy is directed at altering the flow and production of aqueous humor, which is the major determinant of IOP.

▶ *General Approach*

KEY CONCEPT Because POAG is a chronic, often asymptomatic condition, the decision of when and how to treat patients is difficult, as the treatment modalities are often expensive and have potential adverse effects or complications. Currently lowering

Clinical Presentation and Diagnosis of POAG

General

- Adult onset (usually > 40 years of age)
- Insidious onset with diagnosis often occurring during routine eye examination
- Unilateral or bilateral presentation with asymmetric disease progression

Symptoms

- Severe disease progression may cause peripheral vision loss ("tunnel vision") or paracentral, nasal, and arcuate scotoma (blind spots)

Signs

Ophthalmoscopic examination may reveal:

- Optic nerve head (optic disc) cupping
- Large cup-to-disc ratio
- Diffuse thinning, focal narrowing, or notching of the optic nerve head rim
- Splinter hemorrhages
- Optic nerve head/nerve fiber layer changes occur before visual field changes can be detected

Diagnostic Tests

- Gonioscopy—Anterior-chamber angles are open
- Applanation tonometry—Elevated IOP (> 21 mm Hg [2.8 kPa]). However, POAG can present with signs of optic neuropathy without elevated IOP
- Pachymetry—Corneal thickness less than 540 μm is a risk factor
- Automated static threshold perimetry—visual field defects may present without evidence of vision loss
- Other diagnostic tests—scanning laser polarimetry, confocal scanning laser ophthalmoscopy, and optical coherence tomography

Table 62–3

Risk Factors for Glaucoma[3,4]

POAG	PACG
Elevated IOP	Advancing age
African or Hispanic descent	Asian or Eskimo ethnicity
Family history of glaucoma	Female sex
Older age	**Hyperopia**
Thinner CCT	Shallow anterior chamber
Type 2 diabetes	Family history of angle-closure glaucoma
Low ocular perfusion pressures	
Myopia	

CCT, central corneal thickness; IOP, intraocular pressure; POAG, primary open-angle glaucoma; PACG, primary angle-closure glaucoma.

Table 62–4

Select Nonpharmacologic Treatment Options for POAG[3,4,14]

Treatment Option	Description
Laser Trabeculoplasty	Laser energy aimed at trabecular meshwork Improves aqueous humor outflow
Trabeculectomy	Surgical removal of a portion of the trabecular meshwork Improves aqueous humor outflow Mitomycin C and fluorouracil are used to decrease scarring
Cyclodestructive surgery	Transscleral laser reduces rate of aqueous humor production Reserved for patients who have failed other options
Aqueous shunts	Drainage device that redirects the outflow of aqueous humor through a small tube into an outlet chamber placed underneath the conjunctiva

IOP is the best method to reduce the risk of visual field loss.[1,22] The clinician should evaluate the potential effectiveness, toxicity, and the likelihood of patient adherence for each therapeutic modality. The ideal therapeutic regimen should have maximal effectiveness and patient tolerance to achieve the desired therapeutic response. The American Academy of Ophthalmology (AAO) publishes Preferred Practice Patterns for POAG and POAG Suspect.[2,3]

Before the selection of a therapeutic modality, the target IOP should be determined for each patient. The target IOP ideally represents an IOP range that will slow the progression of optic neuropathy and not simply obtain an IOP in the range of 10 to 21 mm Hg (1.3–2.8 kPa). Currently, the initial target IOP is an estimate, but it should be modified based on the progression of the disease at each follow-up visit (treatment is individualized). **KEY CONCEPT** The AAO recommends an initial target IOP to be set at least 25% lower than the patient's baseline IOP. The target IOP can be set lower (30%–50% of baseline IOP) for patients who already have severe disease, risk factors for disease progression, or have normal-tension glaucoma (NTG).[3,23] Risk factors for progression include high IOP, older age, hemorrhage of the optic disc, large cup-to-disc ratio, thinner central corneal thickness (CCT), and established glaucomatous progression (velocity of disease progression is nonlinear).

Initial IOP control can be achieved by medical, laser, surgical, or combination of these therapies. The AAO guidelines[3] do not provide a specific recommendation on which therapeutic modality should be selected first, but patients in the early stages of glaucoma should receive treatment. In general, medical and laser trabeculoplasty are preferred as early treatment options over surgical as surgical interventions are not without potential intraoperative or postoperative complications.[22] The ophthalmologist will individualize therapy based on the risk and benefits for a specific patient. Table 62–4 describes nonpharmacologic treatment modalities for POAG.[3]

Medical treatment is the most commonly selected therapeutic modality. A well-tolerated ocular antihypertensive, at the lowest concentration, should be selected as the initial mediation (Table 62–5). The prostaglandin analogs are preferred first-line

Clinical Presentation and Diagnosis of Acute Angle-Closure Crisis

General

- Medical emergency due to high risk of vision loss
- Unilateral presentation, but fellow eye is at risk

Symptoms

- Ocular pain
- Red eye
- Blurry vision
- Halos around lights
- Systemic symptoms may develop
  - Nausea/vomiting
  - Abdominal pain
  - Headache
  - Diaphoresis

Signs

- Cloudy cornea caused by corneal edema
- Conjunctival hyperemia
- Pupil semidilated and nonreactive to light
- Firm closed-eye palpation

Diagnostic Tests

- Gonioscopy: Closed anterior chamber angles and possible peripheral anterior **synechiae**
- Applanation tonometry: Elevated IOP (> 21 mm Hg [2.8 kPa], but when symptoms are present, IOP may be > 30 mm Hg [4.0 kPa]).
- **Slit-lamp biomicroscopy**: Shallow anterior-chamber depth. Signs of previous attacks include peripheral anterior synechiae, iris atrophy, and pupillary dysfunction.

Table 62–5

Topical Drugs Used in the Treatment of Open-Angle Glaucoma

Drug	Pharmacologic Properties	Common Brand Names/Generic	Dose Form	Strength (%)	Usual Dose[a]	Mechanism of Action
β-Adrenergic Blocking Agents						
Betaxolol	Relative β_1 selective	Generic	Solution	0.5	One drop twice a day	All reduce aqueous production of ciliary body
		Betoptic-S	Suspension	0.25	One drop twice a day	
Carteolol	Nonselective, intrinsic sympathomimetic activity	Generic	Solution	1	One drop twice a day	
Levobunolol	Nonselective	Betagan/Generic	Solution	0.25, 0.5	One drop twice a day	
Metipranolol	Nonselective	OptiPranolol	Solution	0.3	One drop twice a day	
Timolol	Nonselective	Timoptic, Betimol, Istalol/Generic	Solution	0.25, 0.5	One drop every day—one to two times a day	
		Timoptic-XE/Generic	Gelling solution	0.25, 0.5	One drop every day[a]	
Adrenergic Agonists						
α_2-Adrenergic Agonists						
Apraclonidine	Specific α_2-agonists	Iopidine	Solution	0.5, 1	One drop two to three times a day	Both reduce aqueous humor production; brimonidine known to also increase uveoscleral outflow; only brimonidine has primary indication
Brimonidine		Alphagan P 0.1/ Generic 0.2, 0.15	Solution	0.2, 0.15, 0.1	One drop two to three times a day	
Cholinergic Agonists Direct Acting						
Carbachol	Direct and indirect acting	Carboptic, Isopto Carbachol	Solution	1.5, 3	One drop two to three times a day[a]	All increase aqueous humor outflow through trabecular meshwork
Pilocarpine	Direct acting	Isopto Carpine, Pilocar/Generic	Solution	1, 2, 4	One drop two to three times a day[a] One drop four times a day	
Cholinesterase Inhibitors						
Echothiophate	Indirect acting cholinesterase inhibitor	Phospholine Iodide	Solution	0.125	Once or twice a day	
Carbonic Anhydrase Inhibitors Topical						
Brinzolamide	Carbonic anhydrase type II inhibition	Azopt	Suspension	1	Two to three times a day	All reduce aqueous humor production of ciliary body
Dorzolamide		Trusopt/Generic	Solution	2	Two to three times a day	

(Continued)

Table 62–5

Topical Drugs Used in the Treatment of Open-Angle Glaucoma (*Continued*)

Drug	Pharmacologic Properties	Common Brand Names/Generic	Dose Form	Strength (%)	Usual Dose[a]	Mechanism of Action
Systemic						
Acetazolamide		Generic	Tablet	125 mg, 250 mg	125–250 mg two to four times a day	
		Injection	500 mg/vial	250-500 mg		
		Diamox Sequels	Capsule	500 mg	500 mg twice a day	
Methazolamide		Generic	Tablet	25 mg, 50 mg	25–50 mg two to three times a day	
Prostaglandin Analogs						
Latanoprost	Prostanoid agonist	Xalatan/Generic	Solution	0.005	One drop every night	Increases aqueous uveoscleral outflow and to a lesser extent trabecular outflow
Latanoprostene Bunod	Prostanoid agonist	Vyzulta	Solution	0.024	One drop every night	
Bimatoprost	Prostamide agonist	Lumigan 0.01/ Generic 0.03	Solution	0.01, 0.03	One drop every night	
Travoprost	Prostanoid agonist	Travatan Z / GenericTravoprost	Solution	0.004	One drop every night	
Tafluprost	Prostanoid agonist	Zioptan	Preservative free solution	0.0015	One drop every night	
Rho Kinase Inhibitors						
Netarsudil	Rho Kinase Inhibitor	Rhopressa	Solution	0.02	One drop every night	
Combinations						
Timolol–dorzolamide		Cosopt Generic	Solution	Timolol 0.5/ Dorzolamide 2	One drop twice daily	
Timolol–brimonidine		Combigan	Solution	Timolol 0.5/ Brimonidine 0.2	One drop twice daily	
Brinzolamide–brimonidine		Simbrinza	Suspension	Brinzolamide 1/ Brimonidine 0.2	One drop three times daily	
Netarsudil-latanoprost		Rocklatan	Solution	Netarsudil 0.02/ Latanoprost 0.005	One drop every night	

[a] Use of nasolacrimal occlusion will increase the number of patients successfully treated with longer dosage intervals.

agents since they are the most effective at lowering IOP of both peak and trough measurements by at least 25% of baseline IOP.[24-28] Additionally, these agents lack systemic side effects and are dosed once daily. If monotherapy alone lowers IOP but does not reach target pressure, or there is evidence of progression, then combination therapy or switching to another agent is appropriate. The addition of a second agent from another class generally has an additive effect on IOP reduction. Prostaglandin analogs, timolol, carbonic anhydrase inhibitors, brimonidine, or rho kinase (ROCK) inhibitors are reasonable choices for addition as a second agent.[3,8,11] Combination eyedrops reduce the number of drops that need to be administered. Increasing the concentration or dose frequency can also be tried when possible. An eyedrop's therapeutic agent or inactive excipients, such as preservatives, can cause adverse effects. Benzalkonium chloride is a common eyedrop preservative that has been associated with superficial punctate keratitis, corneal erosion, and conjunctival allergy. Intolerances to preservatives can be resolved by changing to a preservative-free eyedrop.[29] Figure 62–3 presents an algorithm to select and optimize POAG treatment.

A monocular trial can be used to assess the safety and effectiveness of a topical medication before initiation in both eyes; however, monocular drug trials do not always predict the IOP response of the second eye. Ideally, medication effectiveness should be assessed independently using baseline IOP measurements.

▶ *Treatment Considerations for POAG Suspects*

POAG suspects should be considered for topical medication therapy if they are at high risk for developing POAG or have a high IOP in which glaucomatous nerve damage is likely. POAG suspects with evidence of glaucomatous damage or visual field defect have developed POAG and should be treated accordingly.[2] The Ocular Hypertension Treatment Study (OHTS) demonstrated that a 20% decrease in IOP can reduce the progression from ocular hypertension to POAG over a 5-year period. The incidence of progression to POAG in the treatment (4.4%) and control

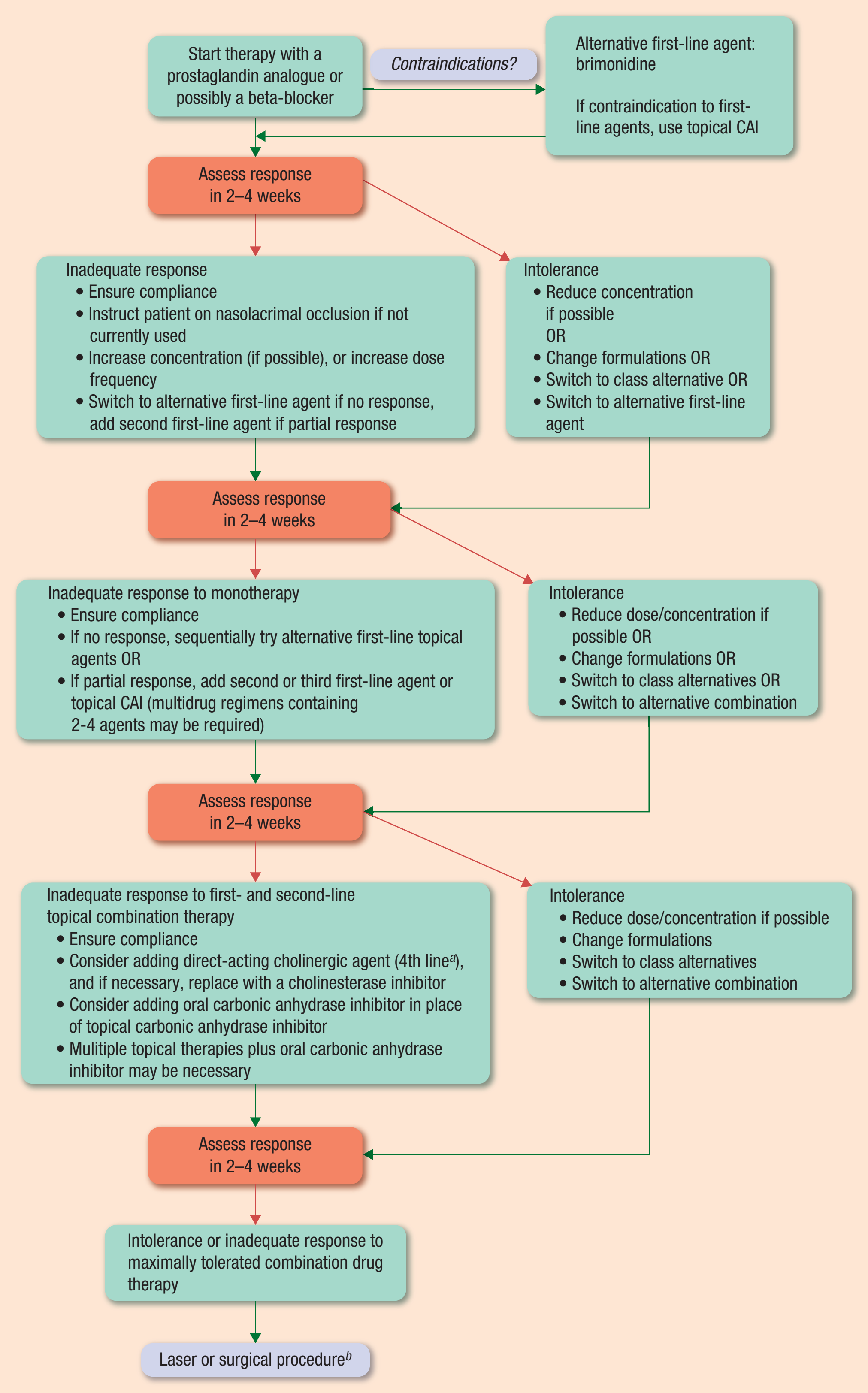
Start therapy with a prostaglandin analogue or possibly a beta-blocker
Contraindications?
Alternative first-line agent: brimonidine
If contraindication to first-line agents, use topical CAI
Assess response in 2–4 weeks
Inadequate response
• Ensure compliance
• Instruct patient on nasolacrimal occlusion if not currently used
• Increase concentration (if possible), or increase dose frequency
• Switch to alternative first-line agent if no response, add second first-line agent if partial response
Intolerance
• Reduce concentration if possible OR
• Change formulations OR
• Switch to class alternative OR
• Switch to alternative first-line agent
Assess response in 2–4 weeks
Inadequate response to monotherapy
• Ensure compliance
• If no response, sequentially try alternative first-line topical agents OR
• If partial response, add second or third first-line agent or topical CAI (multidrug regimens containing 2-4 agents may be required)
Intolerance
• Reduce dose/concentration if possible OR
• Change formulations OR
• Switch to class alternatives OR
• Switch to alternative combination
Assess response in 2–4 weeks
Inadequate response to first- and second-line topical combination therapy
• Ensure compliance
• Consider adding direct-acting cholinergic agent (4th line^a), and if necessary, replace with a cholinesterase inhibitor
• Consider adding oral carbonic anhydrase inhibitor in place of topical carbonic anhydrase inhibitor
• Mulitiple topical therapies plus oral carbonic anhydrase inhibitor may be necessary
Intolerance
• Reduce dose/concentration if possible
• Change formulations
• Switch to class alternatives
• Switch to alternative combination
Assess response in 2–4 weeks
Intolerance or inadequate response to maximally tolerated combination drug therapy
Laser or surgical procedure^b

FIGURE 62–3. Algorithm for the pharmacotherapy of open-angle glaucoma. [a]Fourth-line agents are not commonly used any longer or are commercially unavailable. [b]Most clinicians believe the laser procedure should be performed earlier (eg, after three-drug maximum, poorly adherent patient). (CAI, carbonic anhydrase inhibitor.)

(9.5%) groups was small, which underscores the importance of selecting patients at high risk of progressing to POAG.[30] When medical therapy is indicated, a well-tolerated agent should be selected and optimized following the POAG treatment algorithm (see Figure 62–3). The benefit of therapy should be reassessed in patients who may require third- or fourth-line agents to control IOP. Surgical or laser interventions are not indicated in the treatment of glaucoma suspects.[2]

Primary Angle-Closure Glaucoma

▶ *Desired Outcomes and Goals*

Therapeutic modalities for PACG are targeted at decreasing IOP. The goals of therapy are to preserve visual function by controlling the elevation in IOP, prevent damage to the optic nerve, and manage or prevent an acute attack of angle closure.[4]

▶ *General Approach*

KEY CONCEPT Acute angle-closure crisis is a medical emergency and requires urgent laser or surgical intervention. The treatment of choice for PACG is peripheral laser iridotomy. Laser iridotomy uses laser energy to cut a hole into the iris to alleviate the aqueous humor buildup behind the iris, resulting in reversal of appositional angle closure. Patients currently experiencing an acute angle-closure crisis should receive medical therapy to lower IOP, reduce pain, and reverse corneal edema before the iridotomy. IOP should first be lowered with topical β-blockers, topical α-agonist, prostaglandin $F_{2\alpha}$ analog, systemic carbonic anhydrase inhibitors, or hyperosmotic agents. Once the IOP has been controlled, pilocarpine can be used to break the pupillary block. A topical IOP-lowering agent should be continued to control IOP until laser iridotomy can be performed. Corneal indentation with a cotton-tipped applicator or gonioscopic lens may break pupillary block. If laser iridotomy cannot be performed, then surgical incisional iridectomy is used. Incisional iridectomy is the surgical removal of a small portion of the peripheral iris to allow flow of aqueous humor trapped in the posterior chamber to migrate to the anterior chamber (bypassing the normal flow pattern through the pupil). Topical corticosteroid may be employed to decrease inflammation postoperatively. The fellow eye is at high risk to develop an acute attack and should receive prophylactic iridotomy within a reasonable interval of time. Lens extraction surgery may be another treatment modality as it increases the anterior chamber depth. PACG patients may require chronic medical therapy if the patient has PACG superimposed on preexisting POAG or if synechia formation causes reduced outflow with a continued increase in IOP.[4,8,19]

Pharmacologic Therapy

▶ *Prostaglandin Analogs*

Prostaglandin analogs in typical ophthalmology practice are considered first-line agents along with β-blockers because of their superior efficacy and safety profiles. Many clinicians may choose to use prostaglandin analogs as first line, especially in patients who have an initial requirement to lower IOP by greater than 25%.[27,28,31,32] All four of the available agents currently have an FDA indication for both POAG and ocular hypertension. Latanoprost and travoprost have dosing aids that help patients administer each medication. Travoprost and tafluprost are available as benzalkonium chloride–free solutions.

Latanoprost, travoprost, and tafluprost are analogs of prostaglandin $F_{2\alpha}$ and are agonists of the prostanoid FP receptor, which appears to lower IOP by increasing aqueous humor outflow through the uveoscleral pathway. Bimatoprost is a prostamide analog and appears to lower IOP by activating prostamide receptors in the uveoscleral pathway and possibly through increasing outflow through the trabecular meshwork. The exact mechanism of how uveoscleral outflow is increased is still unclear, but stimulation of prostanoid FP receptors and prostamide receptors in the ciliary body cause remodeling of the extracellular matrix, making it more permeable to aqueous humor, thus increasing aqueous humor outflow through the ciliary muscles. Bimatoprost was recently approved as a 10-mcg anterior chamber implant. This may be an option for patients nonadherent to eyedrops; however, it may be an expensive alternative.[31,33-35]

Latanoprostene bunod 0.024% is a new agent, and when instilled, it is converted to latanoprost and nitric oxide (NO). Latanoprost has action on the uveoscleral pathway, and NO relaxes the trabecular meshwork and Schlemm canal to enhance trabecular outflow.[36] Once-daily latanoprostene bunod demonstrated greater intraocular pressure reduction when compared with twice-daily timolol 0.5% and once-daily latanoprost 0.005%.[37]

Prostaglandin analogs are administered once daily at bedtime and should not be increased to twice daily, as this may decrease effectiveness. Prostaglandin analogs can provide a consistent reduction in IOP over a 24-hour period.[32] For patients nonresponsive to latanoprost, they may respond to bimatoprost, presumably because of the difference in the site of action of each drug.[38,39]

Prostaglandin analogs are well tolerated and rarely cause systemic side effects (headache has been reported). Local effects include conjunctival hyperemia, stinging upon instillation, deepening of the upper eyelid sulcus, **hypertrichosis**, and increase in pigmentation of the iris or the eyelashes. Increases in iris pigmentation occur most commonly in patients with multicolored irides on long-term prostaglandin analog therapy. The mechanism of this effect is by its action on melanocytes of the iris, in which the irides become darker because of increased production of melanin in the iris.[29] Increased iris pigmentation appears to be only a cosmetic effect but may affect your product selection, especially when choosing monocular therapy. Conjunctival hyperemia or engorgement of conjunctival blood vessels is a common adverse effect caused by a vasodilatory effect on scleral blood vessels. It is most prominent early in therapy and usually subsides over time.[29,31]

Prostaglandin analogs should be used with caution in certain patients, since they may worsen anterior uveitis and herpetic keratitis. Cystoid macular edema has been reported during treatment with prostaglandin analogs; therefore, use caution in patients with intraocular inflammation, **aphakia**, **pseudophakia** with a history of intraoperative complications (eg, torn posterior lens capsule), or with risk factors for macular edema.[29]

Counsel patients prescribed prostaglandin analogs on potential adverse effects and appropriate administration. Instruct patients receiving latanoprost or tafluprost to refrigerate unopened medication. Once open, latanoprost may be stored at room temperature for 6 weeks. Tafluprost single-use containers may be stored at room temperature for up to 30 days.

▶ *β-Adrenergic Antagonists*

Topical β-adrenergic antagonists (β-blockers) are considered a second-line agent after the prostaglandin analogs for the treatment of POAG unless contraindications are present.[3,8] Topical β-blockers decrease IOP by reducing the formation of aqueous humor made by the ciliary body, which results in a 20% to 35% reduction in IOP.[27,28,31,32] Timolol, levobunolol, and carteolol are nonselective for β_1- and β_2-adrenergic receptors, whereas betaxolol has β_1-selective properties.[31,32] Betaxolol reduces IOP to a lesser extent than the nonselective β-blockers, but part of its efficacy may be related to a neuroprotective mechanism independent of IOP reduction.[40]

Topical β-blockers are typically administered twice daily. A gel-forming solution of timolol is indicated once-daily dosing. Tachyphylaxis may occur in 20% to 50% of patients on monotherapy with a β-blocker, resulting in the need for a different agent or combination therapy. Patients on concurrent systemic β-blockers may experience less IOP reduction than patients on only topical β-blockers.[31,32]

β-Blockers can cause significant systemic adverse effects through nasolacrimal drainage and subsequent systemic absorption in the mucus membranes of the nasal-pharyngeal cavity. This route bypasses first-pass hepatic metabolism resulting in pharmacologically significant serum drug concentrations.[41] Bronchospasm is the most common pulmonary effect of topical β-blockers. Pulmonary edema, status asthmaticus, and respiratory arrest have been reported with β-blockers as well. Cardiovascular effects include bradycardia, hypotension, and congestive heart failure exacerbation. As with systemic β-blockers, topical β-blockers have also been reported to cause depression and hyperlipidemia and mask symptoms of hypoglycemia. The β_1-selective properties of betaxolol may cause less exacerbation of pulmonary disease. Despite the intrinsic sympathomimetic activity demonstrated by carteolol, this does not translate to a clinically significant decrease in pulmonary or cardiovascular adverse effects. Topical β-blockers are generally contraindicated in patients with asthma, chronic obstructive pulmonary disease (COPD), sinus bradycardia, second- or third-degree heart block, cardiac failure, and hypersensitivity to the product.[29,32,41]

Stinging upon instillation is the most common adverse effect. Other local adverse effects include conjunctivitis, keratitis, dry eyes, and uveitis.[29,31]

Counsel patients prescribed topical β-blockers on the nasolacrimal occlusion technique to decrease systemic absorption.

α_2-Adrenergic Agonists Brimonidine and apraclonidine are α_2-adrenergic agonists that decrease IOP by reducing aqueous humor production. Brimonidine has a higher selectivity to the α_2-receptor than apraclonidine and has a dual mechanism of action by increasing uveoscleral outflow.[31,32] Apraclonidine is indicated for the prevention and treatment of postsurgical IOP elevations but is rarely used. Brimonidine lowers IOP by 14% to 25%. Peak IOP-lowering effect is similar to that of timolol, but the trough IOP-lowering effect is less than that of timolol.[26,27] Brimonidine may exhibit a neuroprotective effect and has been shown to delay visual field progression compared with timolol, but there is insufficient evidence it prevents retinal ganglion cell death.[42]

Brimonidine is typically used as an adjunctive agent in combination with other agents and is usually administered every 8 hours. A 12-hour dosing schedule may be employed when used in combination therapy. Brimonidine-purite 0.1% and 0.15% solution (Alphagan-P) has similar efficacy compared with the brimonidine 0.2% solution, because the purite solution's higher pH allows for more drug to penetrate the cornea.[31,32] Localized side effects include blepharoconjunctivitis, conjunctivitis, and ocular allergy. Systemic side effects include headache, dry mouth, and fatigue.[29,31,32]

The frequency of dosing and local adverse effects may lead to nonadherence in some patients. Counsel patients using brimonidine on the nasolacrimal occlusion technique to reduce systemic adverse effects and to improve efficacy.[31,32]

▶ *Rho Kinase Inhibitors*

Netarsudil and ripasudil are novel, potent ROCK inhibitors dosed once daily in the evening. ROCK inhibition decreases intraocular pressure by limiting adhesions within the trabecular meshwork and contraction of the ciliary muscle, facilitating aqueous humor outflow by increasing the meshwork pore size. Other minor pathways of pressure reduction include decreasing episcleral venous pressure and production of aqueous humor. The most common ocular adverse effect is conjunctival hyperemia. Systemic adverse effects are uncommon.[43] Combination of netarsudil and latanoprost is available as a once-daily product.

▶ *Carbonic Anhydrase Inhibitors*

Carbonic anhydrase inhibitors decrease aqueous humor production by inhibition of the carbonic anhydrase isoenzyme II located in the ciliary body. In the eye, carbonic anhydrase catalyzes the conversion of H_2O and CO_2 to HCO_3^- and H^+, a significant step in aqueous humor production. Carbonic anhydrase inhibitors are available in systemic and topical preparations.[31,32]

Topical Carbonic Anhydrase Inhibitors Dorzolamide and brinzolamide are the topical carbonic anhydrase inhibitors in production. Both are administered every 8 hours and are used as adjunctive therapy or as monotherapy for patients who cannot tolerate first-line therapies. Nasolacrimal occlusion may allow for a 12-hour dosing interval. They lower peak and trough IOP by 17% to 20%.[27,28,31,32]

Local side effects include burning, stinging, itching, foreign body sensation, dry eyes, and conjunctivitis. Brinzolamide may have fewer side effects since the drug is in a neutral pH solution. Dorzolamide has been reported to cause irreversible corneal decompensation. Dysgeusia has been reported with each agent. Both topical carbonic anhydrase inhibitors are sulfonamides and should be used with caution in patients with history of sulfonamide hypersensitivity.[29,31,32,44]

Systemic Carbonic Anhydrase Inhibitors There are two systemic carbonic anhydrase inhibitors: acetazolamide and methazolamide. These agents effectively lower IOP by 20% to 30% but are reserved as third-line to fourth-line agents because of their significant adverse effects. They are typically used as bridge therapy from maximal medical therapy to laser or surgical intervention or to control IOP in the perioperative period following a laser or surgical ocular procedure. The systemic carbonic anhydrase inhibitors can also be used to lower IOP in acute angle-closure glaucoma. Acetazolamide has an IV formulation that can be used in patients who are experiencing nausea due to the angle-closure attack.[4,31,32]

The systemic carbonic anhydrase inhibitors are associated with significant adverse effects that include paresthesias of the hands and feet, nausea, vomiting, and weight loss. Patients can develop systemic acidosis, hypokalemia, hyponatremia, and nephrolithiasis due to the inhibition of renal carbonic anhydrase. Sulfonamide allergy, renal failure, hepatic insufficiency, COPD, and decreased serum potassium and sodium levels are all contraindications of systemic carbonic anhydrase inhibitor therapy. Blood dyscrasias from bone marrow suppression have been reported and include agranulocytosis, aplastic anemia, neutropenia, and thrombocytopenia.[31,32]

▶ *Cholinergic Agents*

Cholinergic agents (also called parasympathomimetics or miotics) at one time were the first class of agents to treat glaucoma. The class can be divided into direct-acting cholinergic agents and indirect-acting cholinergic agents.

Patient Encounter, Part 2

CM was referred to an ophthalmologist for a comprehensive eye evaluation. The ophthalmology report reveals the patient has an IOP (as assessed by applanation tonometry) of 17 mm Hg (2.3 kPa) in the right eye and 19 mm Hg (2.5 kPa) in the left eye. Gonioscopic examination reveals open anterior angles in both eyes. Ophthalmoscopy reveals cupping of the optic discs in both eyes. Visual field examination reveals a nerve fiber bundle defect consistent with glaucoma in the left eye.

What is your assessment of this patient's glaucoma type?

What pharmacologic and nonpharmacologic treatment modalities are available for this patient?

Direct-Acting Cholinergic Agents Pilocarpine directly stimulates the muscarinic (M_3) receptors of the ciliary body, which causes contraction of the ciliary muscle. This results in the widening of spaces in the trabecular meshwork, which causes an increase in aqueous humor outflow and reduces IOP by 20% to 30%.

Pilocarpine requires administration four times daily, since the duration of IOP-lowering effect is approximately 6 hours. Pilocarpine is available in 1%, 2%, and 4% concentrations. Higher concentrations may be needed for patients with dark irides to obtain adequate IOP reduction.[31] Pilocarpine is considered a fourth-line agent for POAG. In the treatment of PACG, it is important to delay use until IOP has been controlled, because pilocarpine could worsen angle closure by causing anterior displacement of the lens. Once IOP is controlled, pilocarpine can be used to break pupillary block by instilling one drop applied twice in an hour.

The adverse effects of pilocarpine are caused by the induction of miosis. The contraction of the ciliary muscle causes the lens to displace forward, which can cause accommodation spasm and myopia, which can lead to brow ache. Pupillary constriction can also affect night vision. Pilocarpine should be avoided in patients with severe myopia as it increases the risk of developing retinal detachment. Systemic effects may occur at higher concentrations including nausea, vomiting and diarrhea, and bradycardia.[29]

Indirect-Acting Cholinergic Agents Echothiophate iodide inhibits acetylcholinesterase, which increases the acetylcholine available to stimulate the muscarinic (M_3) receptors of the ciliary body. This product is given twice daily and has similar efficacy to pilocarpine in the degree of IOP reduction. The side effect profile is similar to that of pilocarpine; however, it can deplete systemic cholinesterases and pseudocholinesterases and may cause the formation of cataracts. This agent should be discontinued at least 1 week prior to surgical procedures requiring general anesthesia. Succinylcholine and some local anesthetics are metabolized by pseudocholinesterases; therefore, depletion of this enzyme by echothiophate may lead to toxic effects. This product is typically used when other topical agents have failed and are limited to patients with aphakia or pseudophakia.[31]

▸ *Hyperosmotics*

Glycerin, isosorbide, and mannitol are hyperosmotic agents that increase the osmolality of blood. These agents create an osmotic gradient that draws water from the vitreous humor, thus decreasing IOP. The resulting dehydration of the vitreous humor may cause posterior movement of the lens, which then causes the anterior chamber to deepen, thus opening the anterior angle. If the patient is not vomiting, glycerin (1–1.5 g/kg of a 50%) solution and isosorbide (1.5–2 g/kg) can be given orally. Isosorbide is preferred in patients with diabetes because it is not metabolized into glucose. If the patient has nausea or vomiting, mannitol (20%) can be given IV at a dose of 1 to 2 g/kg over 45 minutes. The hyperosmotic agents are rapid acting, reaching peak effect in 30 to 60 minutes. Headache and thirst are common complaints. Patients who are already dehydrated are at risk of developing CNS dehydration, which can lead to coma. These agents should be used with caution in patients with renal or cardiovascular disease, as extracellular water is increased.[32,45]

SPECIAL CONSIDERATIONS: DRUG-INDUCED GLAUCOMAS

Medications have the potential to cause or exacerbate both POAG and PACG; however, PACG is more likely to be exacerbated by medications than POAG. The use of medications with anticholinergic or sympathomimetic properties can precipitate angle closure. Medications with anticholinergic properties include first-generation antihistamines, tricyclic antidepressants, and antipsychotics. Medications with sympathomimetic properties include phenylephrine and pseudoephedrine. PACG patients who have been treated with laser iridotomy can usually use these agents without causing an exacerbation. Sulfa-based drugs, such as topiramate, acetazolamide, and hydrochlorothiazide, cause swelling of the ciliary body, which causes an anterior displacement of the lens, resulting in a decrease in anterior-chamber depth. Patients with open or closed anterior angles can experience elevated IOP from these drugs. Controlled POAG is rarely exacerbated by anticholinergics and sympathomimetics unless the patient is concomitantly at risk for angle closure. For uncontrolled or untreated POAG, the risk–benefit ratio should be considered before employing these agents. Corticosteroids, through any route of administration, can exacerbate POAG. Corticosteroids increase IOP by causing obstruction of the trabecular meshwork with extracellular material. The increase in IOP appears to increase with potency and intraocular penetration. Ophthalmic corticosteroid preparations carry the highest risk of increasing IOP. However, all administrated routes have been shown to raise IOP in some patients. The onset and extent of IOP elevation is dependent on the specific corticosteroid, dose, route, and frequency. Generally, corticosteroid-induced IOP elevation occurs within a few weeks of beginning steroid therapy. In most cases, the IOP lowers spontaneously to baseline within a few weeks to months upon stopping the steroid. In rare instances, the IOP

Patient Encounter, Part 3

The practitioner and CM agree to start medication therapy. Develop a patient-specific care plan.

Address the patient's (a) drug-related needs, (b) goals of therapy, (c) potential pharmacologic therapies, and (d) plan for follow-up of therapy.

List the monitoring parameters for effectiveness and safety for the chosen therapy.

Explain how you would counsel the patient on the chosen therapy, including the administration of an ophthalmic preparation.

remains elevated. Some patients exhibit clinically significant and dangerously high IOP as a result of steroid use.[46]

OUTCOME EVALUATION

Primary Open-Angle Glaucoma

Evaluate patients 2 to 4 weeks after the initiation or alteration of medical therapy. The clinician should elicit the status of ocular health since the last visit, systemic medical history, medication history, and presence of systemic and ocular adverse effects of medications. IOP measurement, visual acuity assessment, and slit-lamp biomicroscopy at every POAG follow-up visit are necessary. The frequency of visual fields and optic nerve evaluation depends on whether IOP is controlled, the length of time IOP has been controlled, and whether there is progression of the disease. Patients who are at target IOP and have no disease progression should have optic nerve head evaluation and visual field testing every 6 to 12 months. Patients with disease progression and/or who are not at target IOP should receive follow-up evaluation every 1 to 6 months. Assess the patient's ability to use topical eyedrops.[3] (See Application of Ophthalmic Solutions or Suspensions textbox.) Finally, evaluate the patient's adherence to their medical regimen. Nonadherence among patients on topical medical therapy ranges from 5% to 80%. Suspect nonadherence in patients who have visual field and optic nerve progression despite a low IOP measurement, as patients may be more adherent to their medical regimen before their visit. Pharmacy refill histories may be useful in assessing adherence but do not confirm that the patient is actually taking the regimen as prescribed.[47] Specific patient factors related to the risk of nonadherence may include health literacy, medication cost, complicated medication regimens, adverse effects, and ethnicity.[48] Using adherence aids, prescribing the least complex regimen, and educating patients about their glaucoma are ways to reduce nonadherence.[49] Consider providing an eyedrop instillation aid for patients that have dexterity and/or coordination problems.[50]

KEY CONCEPT Target IOP should be revised based on the course of the disease and rate of progression (so-called "velocity of disease"). Adjust therapy if the patient fails to reach target IOP. Patients who have achieved target IOP yet have progressive damage of the optic nerve or worsening of their visual fields should have further adjustment of therapy. Evaluate these patients further for possible reasons of continued disease progression. Consider determining the diurnal pattern of IOP and looking for signs of poor ocular perfusion pressure. Establish a lower target IOP. Adjust therapy in patients who are intolerant, nonadherent, or develop contraindications to their drug therapy regimen. Consider increasing the target IOP and reducing drug therapy for patients who have stable disease and who have maintained a low IOP; closely follow these patients to assess their response.[3]

Primary Angle-Closure Glaucoma

Follow-up of acute angle-closure crisis occurs in the postoperative period. Evaluate the patency of the iridotomy and IOP in the

Patient Care Process

Collect Information:

- Obtain a past medical history, inquiring about previous and current medical problems with eyes.
- Obtain a complete medication history for use of prescription, nonprescription, and dietary supplements.
- Review the medical record for ophthalmic examination findings (applanation tonometry, visual acuity, gonioscopy, visual fields, optic nerve evaluation, pachymetry, and so on).
- Identify socioeconomic factors and health beliefs that affect access to medical care and medications.
- Have patient demonstrate or explain how to instill ophthalmic medications.

Assess the information:

- Determine any recent change or difficulty with vision.
- Determine risk factors for glaucoma.
- Review prescriptions, nonprescriptions, and natural products and determine any potential to exacerbate glaucoma or interact with glaucoma medications.
- Determine presence of ocular or systemic adverse effects from glaucoma medications.
- Determine if patient has achieved goal IOP and if there is evidence of disease progression based on ophthalmic examination findings.
- Identify barriers to medication adherence such as low health literacy, socioeconomic challenges, and physical limitations.

Develop a Care Plan:

- Select medication therapy that will likely achieve target IOP with minimal adverse effects and financial burden.
- Use combination glaucoma eyedrops when possible to improve adherence.
- Safely and appropriately discontinue or minimize the use of medications that could increase IOP.

Implement the Care Plan:

- Educate patient about changes in ophthalmic medication regimen.
- Address patient concerns about glaucoma and its treatment.
- Educate patient on importance of medication adherence and proper instillation and have them demonstrate their technique.
- Educate patient on potential adverse effects, reinforcing proper instillation technique as a strategy to minimize local and systemic adverse effects.

Follow-up: Monitor and Evaluate:

- Follow-up in 2 to 4 weeks to reassess progression of glaucomatous damage, medication effectiveness on IOP, medication adherence, and adverse effects to medication therapy.
- Review interval medical history.
- Perform or review ophthalmic examination findings.
- Determine the need for additional treatment modalities.
- Consider altering follow-up interval based on the progression and control of the disease.

Application of Ophthalmic Solutions or Suspensions

1. Clean hands with soap and water.
2. Avoid touching the dropper tip with your fingers or against your eye to maintain sterility of product; shake dropper bottle if product is a suspension.
3. Tilt head back; pull down the lower eyelid with index finger.
4. Hold the dropper bottle with other hand as close as possible without touching the eye. The dropper should be pointing toward the eye with remaining fingers bracing against the face.
5. Gently squeeze the bottle so that one drop is placed into the pocket.
6. Close eye (do not squint) for 2 to 3 minutes to allow for the maximum corneal penetration of drug.
7. Use a tissue to wipe away excess liquid.
8. Replace and retighten the cap to the dropper bottle.
9. Wait at least 5 minutes before instilling another ophthalmic drug preparation.
10. Application of some ophthalmic preparations (suspension and gels) may cause blurring of vision.

postoperative period. Perform gonioscopy and optic nerve head evaluation if not already performed. Stable patients with PACG should be evaluated at least annually, specifically for the presence of peripheral anterior synechia and optic neuropathy. Treat patients according to POAG guidelines if they have underlying POAG or areas of peripheral anterior synechia with the presence of optic neuropathy.[4]

Abbreviations Introduced in This Chapter

POAG	Primary open-angle glaucoma
PACG	Primary angle-closure glaucoma
IOP	Intraocular pressure
CCT	Central corneal thickness
NTG	Normal tension glaucoma
AAO	American Academy of Ophthalmology

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63

Minor Ophthalmic and Otic Disorders

Lauren R. Biehle and Michelle L. Hilaire

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Differentiate between the various ophthalmic disorders based on patient-specific information.
2. Choose an appropriate treatment regimen for an ophthalmic disorder.
3. Discuss the product differences that direct the selection of ophthalmic medications.
4. Assess when further treatment is required based on patient-specific information.
5. Recommend an ophthalmic monitoring plan given patient-specific information, a diagnosis, and a treatment regimen.
6. Educate patients about ophthalmic disease states and appropriate drug and nondrug therapies.
7. Review common otic disorders and appropriate drug and nondrug therapies.

INTRODUCTION

This chapter provides an overview of common ophthalmic and otic disorders and their treatments. **KEY CONCEPT** Many ophthalmic disorders are benign or self-limited, but the clinician must be able to distinguish conditions that lead to serious morbidity, including blindness. Preserving both visual function and cosmetic appearance is the goal.[1] The clinician must understand when referral is appropriate and the proper time frame for follow-up, based on the patient-specific condition. Healthcare professionals should also be aware of common otic disorders that may be encountered.

OCULAR INJURIES

Etiology and Epidemiology

Ophthalmic problems encompass 3% of all emergency department visits.[2] Corneal abrasions are the most common eye injury in children. Scratches, objects, and aggressive eye rubbing may damage the cornea.[3] Healthcare practitioners must know the proper treatment for ocular emergencies and the time frame for follow-up in order to prevent further morbidity (Table 63–1).

CORNEAL ABRASIONS

Treatment

Desired Outcomes

- Complete healing of the corneal abrasion with no scarring or vision impairment
- Prevent infection and pain
- Prevent corneal loss or corneal transplant

General Approach to Treatment

The five layers of the cornea contain no blood vessels but are nourished by tears, oxygen, and aqueous humor. Minor corneal abrasions, also called corneal epithelial defects, heal quickly—typically within 24 hours.[4] Moderate abrasions take 24 to 72 hours to heal. Deep abrasions may scar the cornea. This rarely results in sufficient visual impairment to require corneal transplant. Patients should be instructed not to rub the eye if a corneal abrasion is present. Do not use eye patches to treat uncomplicated corneal abrasion.[3]

Corneal Abrasion Prevention[3]

- Wear eye protection during sports
- Wear industrial safety lenses
- Carefully fit and place contact lenses

Pharmacologic Therapy

Topical NSAIDs Topical nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the need for oral analgesics, but there is not strong evidence available to support their use in the management of corneal abrasions.[4] Available ocular NSAIDs are diclofenac, ketorolac, nepafenac, and bromfenac. The usual dose for

Table 63–1

Ophthalmic Emergencies: Time to Follow Up by Ophthalmologist

Immediate Consult Required	Within 24 Hours
Acute chemical burn	Acute angle-closure glaucoma
Acute, painless loss of vision	Blood in the eye (hyphema)
Blunt trauma to eye	Corneal ulcer
Foreign body in eye	Macular edema
Orbital cellulitis	Sudden congestive proptosis (bulging of eye forward)
Retinal detachment	

Adapted from Shah SM, Khanna CL. Ophthalmic emergencies for the clinician. Mayo Clin Proc. 2020;95(5):1050–1058.

Clinical Presentation and Diagnosis of Corneal Abrasions[3]

Symptoms

- Photophobia
- Pain with eye or eyelid movement
- Foreign body sensation (or gritty feeling)
- Recent ocular trauma

Signs

- Excessive tearing
- Blepharospasm
- Blurred vision
- Conjunctival injection ("red eye")

Diagnostic Test

Use sterile fluorescein dye strips and visualize the cornea under a cobalt-blue filtered light; abrasions appear green; ensure that no foreign body remains in the eye or under eyelid.

diclofenac and ketorolac is one drop four times daily; nepafenac is dosed one to three times daily, and bromfenac is dosed once or twice daily. Use topical NSAIDs with caution in patients with clotting disorders or those who are on systemic NSAIDs or warfarin therapy. Adverse effects typically include discomfort upon administration and conjunctival hyperemia or itching.[4]

Topical Antibiotics Infection slows the healing of a corneal abrasion; therefore, prophylactic antibiotics are often used. However, antibiotic-steroid ophthalmic products are not recommended as the steroid may slow healing of the abrasion. Patients should be asked if any contaminated matter could have entered the eye as this can lead to bacterial keratitis. Discontinue the use of contact lenses until the abrasion is healed and the antibiotic course complete. **KEY CONCEPT** In patients who do not wear contacts, antibiotics active against Staphylococcus, such as erythromycin ointment or trimethoprim-polymyxin B solution, are appropriate choices. In contact lens wearers, choose an ophthalmic antibiotic that has activity against Pseudomonas aeruginosa, such as gentamicin or a fluoroquinolone.[3]

▶ *Outcome Evaluation*

1. Reevaluate patients in 24 hours.
2. If symptoms worsen, recheck for foreign bodies.
3. Refer to ophthalmologist if[3]:
   - Contact lens wearers
   - Decreased vision
   - Lack of improvement or worsening symptoms

OTHER OCULAR INJURIES: TREATMENT

Traumatic Injuries

Attempt to remove loose foreign bodies by gentle irrigation with artificial tears or sterile saline. If removal is successful, a topical broad-spectrum antibiotic, such as erythromycin, will prevent infection. If irrigation is unsuccessful, only ophthalmologists should complete mechanical removal of foreign objects. Protect the eye from further injury with a metal eye shield or a paper cup taped over the eye while awaiting the ophthalmologist.[2]

Splash Injuries and Chemical Exposure

Instruct patients by phone to immediately irrigate the eye with water or saline continuously for at least 15 minutes before seeking a clinician. Irrigation dilutes and removes the chemical agent and is the best way to decrease ocular tissue damage. Patients should then seek immediate care from an ophthalmologist or emergency facility.[5]

Loss of Vision

A variety of disorders may lead to rapid, painless, monocular or binocular vision loss. These include central retinal artery occlusion, acute narrow-angle glaucoma, trauma, and others.[6] The differential diagnosis is complex and should be undertaken by an emergency department or ophthalmologist.

HORDEOLUM

A hordeolum is a common bacterial infection of an oil-producing gland of the eyelid that can be described as external (also called a stye) or internal. Patients will often present with a tender swollen mass and redness of the affected area. *Staphylococcus aureus* is the most common bacteria to cause a hordeolum.[7] A comparison of characteristics and treatment options for external and internal hordeola can be found in Table 63–2.

CONJUNCTIVITIS

Etiology

Conjunctivitis, also known as red eye, is one of the most common ophthalmic complaints seen by clinicians. An inflamed conjunctiva is the most common cause of red eye.[8] Conjunctivitis cases are most commonly viral in nature. Both viral and

Table 63–2

Comparison of Internal and External Hordeola[7,23,24]

Characteristic	External Hordeolum (Stye)	Internal Hordeolum
Gland	Infection of the Zeis tear gland	Infection of the Meibomian gland
Location	Occurs on eyelid margin	Interior of eyelid
Cause	Often caused by *S. aureus*	Often caused by *S. aureus*
Supportive care	Warm compresses can provide symptom relief	Warm compresses can provide symptom relief
Antibiotics required	Not required	May be required
		Options include topical erythromycin ophthalmic ointment, oral dicloxacillin, or oral trimethoprim–sulfamethoxazole
	Not required, patients may experience recurrent hordeola	If large or unresolving hordeola, patients should be referred to an ophthalmologist for possible incision/drainage

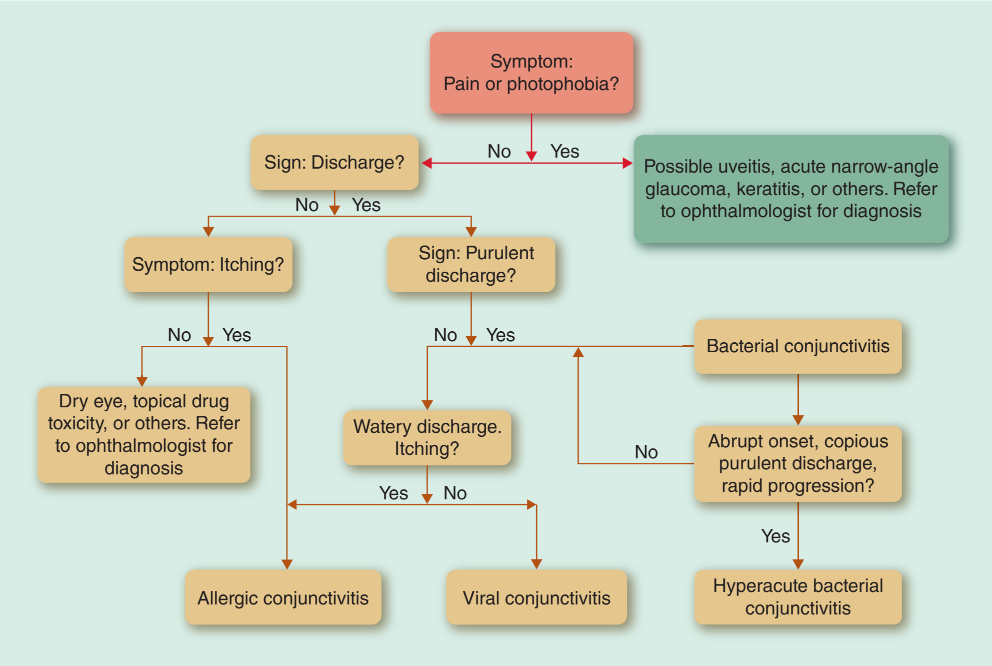
Symptom: Pain or photophobia?
No
Yes
Sign: Discharge?
Possible uveitis, acute narrow-angle glaucoma, keratitis, or others. Refer to ophthalmologist for diagnosis
No
Yes
Symptom: Itching?
Sign: Purulent discharge?
No
Yes
No
Yes
Bacterial conjunctivitis
Dry eye, topical drug toxicity, or others. Refer to ophthalmologist for diagnosis
Watery discharge. Itching?
No
Abrupt onset, copious purulent discharge, rapid progression?
Yes
No
Yes
Allergic conjunctivitis
Viral conjunctivitis
Hyperacute bacterial conjunctivitis

FIGURE 63–1. Differential diagnosis for red eye.

bacterial conjunctivitis are highly contagious. The most common symptoms indicating bacterial conjunctivitis rather than viral are adherence of the eyelids upon waking and presence of mucopurulent discharge. The most common symptom differentiating allergic conjunctivitis from bacterial or viral is itching.[9] Use the differential diagnosis algorithm shown in Figure 63–1 to determine the proper treatment or need for referral.

BACTERIAL CONJUNCTIVITIS

Etiology and Pathophysiology

The primary cause of acute bacterial conjunctivitis (ABC) is gram-positive organisms, *S. aureus, Streptococcus pneumoniae*, and gram-negative *Haemophilus influenzae*.[6] *Pseudomonas* may be a cause of ABC in contact lens wearers.[8] *S. aureus* is a more common cause in adults, while *S. pneumoniae* and *H. influenzae* are more common in children.[8] KEY CONCEPT The pathogens are rarely cultured unless the case is unresponsive to treatment.[6] Patients with bacterial conjunctivitis lasting 4 weeks or more should be referred to an ophthalmologist.[9]

Hyperacute bacterial conjunctivitis is associated with gonococcal *(Neisseria gonorrhoeae)* infections in sexually active patients. Prompt workup and treatment is required, as corneal perforation can occur.[6,8]

Treatment

▶ *Desired Outcomes*

- Complete resolution of the bacterial conjunctivitis
- Prevent adverse consequences of the infection
- Preserve functionality of the eye

▶ *General Approach to Treatment*

ABC may be treated with broad-spectrum antibiotics. Although the condition is usually self-limiting, antibiotic treatment decreases the spread of disease to others and prevents extraocular infection. Additionally, treatment may help decrease the risk of corneal ulceration or other complications that affect sight. Finally, treatment speeds recovery.[6,8]

▶ *Pharmacologic Therapy*

The choice of an antibiotic agent for ABC is largely empiric. The initial treatment needs to include *Staphylococcus* coverage, and cost and side effect profile may be pertinent.[6] In general, ointments are a good dosage form for children. Adults may prefer drops because they do not interfere with vision.

Many broad-spectrum topical antibiotics are approved to treat ABC (Tables 63–3 and 63–4).

- First-line treatments include polymyxin B/trimethoprim solution, polymyxin B with bacitracin ointment, or erythromycin ointment as these provide activity against *S. aureus.*
- The aminoglycosides (tobramycin and gentamicin) are alternatives but have incomplete gram-positive coverage and can cause corneal epithelial toxicity.[8]
- Sulfacetamide has significant resistance and is not highly effective.
- If infection occurs in contact lens users, recurs or is severe, a topical fluoroquinolone is recommended to provide activity against *Pseudomonas*.[8] Moxifloxacin, gatifloxacin, and besifloxacin are newer ophthalmic fluoroquinolones and may have less resistance.[10]
- Treat hyperacute bacterial conjunctivitis with a single dose of intramuscular ceftriaxone 1 g in combination with topical antibiotics and refer the patient to an opthalmologist.[8]
- If concurrent blepharitis is present, add a lid hygiene regimen to antibiotic treatment.[6]

Outcome Evaluation

Significant improvement of acute bacterial conjunctivitis should be seen within 1 week.[8]

Table 63–3

Adult Bacterial Conjunctivitis Dosing Guidelines for Topical Ophthalmic Antibiotics[25]

Azithromycin 1% solution	Days 1 and 2: 1 drop twice daily Days 3–7: 1 drop once daily
Ciprofloxacin 3.5 mg/mL solution	Days 1 and 2: 1–2 drops every 2 hours while awake Days 3–7: 1–2 drops every 4 hours while awake
Ciprofloxacin 0.3% ointment	Apply a ½ in (~1 cm) ribbon of ointment 3 times daily for 2 days, then twice daily for next 5 days
Erythromycin 0.5% ointment	Apply a ½ in (~1 cm) ribbon of ointment up to 6 times daily
Gatifloxacin 0.5% solution	Days 1 and 2: 1 drop every 2 hours while awake up to 8 times daily Days 3–7: 1 drop 4 times per day while awake
Gentamicin 0.3% solution	1–2 drops every 4 hours. In severe infections, may use up to 2 drops every hour
Gentamicin 0.3% ointment	Apply a ½ in (~1 cm) ribbon of ointment 2–3 times daily
Levofloxacin 0.5% solution	Days 1 and 2: 1–2 drops every 2 hours while awake, up to 8 times per day Days 3–7: 1–2 drops every 4 hours while awake, up to 4 times daily
Moxifloxacin 0.5% solution	1 drop 2 times a day for 7 days (Moxeza) 1 drop 3 times a day for 7 days (Vigamox)
Ofloxacin 0.3% solution	Days 1 and 2: 1–2 drops every 2–4 hours while awake Days 3–7: 1–2 drops 4 times daily
Polymyxin B with bacitracin ointment	Apply a ½ in (~1 cm) ribbon of ointment every 3–4 hours for 7–10 days
Polymyxin B/trimethoprim solution	1 drop every 3 hours for 7–10 days
Sulfacetamide 10% ointment	Apply a ½ in (~1 cm) ribbon of ointment every 3–4 hours and at bedtime
Sulfacetamide 10% solution	1–2 drops every 2–3 hours for 7–10 days
Sulfacetamide 10% ointment	Apply a ½ in (~1 cm) ribbon of ointment every 3–4 hours and at bedtime
Tobramycin 0.3% ointment	Mild-to-moderate infections: Apply a ½ in (~1 cm) ribbon of ointment 2–3 times daily; severe infections: Apply every 3–4 hours
Tobramycin 0.3% solution	Mild-to-moderate infections: 1–2 drops every 2–4 hours Severe infections: Initially, 2 drops every hour

Data from Lexi-Drugs Online™. Lexi-Comp Online™. Hudson (OH): Lexi-Comp, Inc.; 2020. Available from: http://online.lexi.com. Accessed: August 16, 2020.

Table 63–4

Pediatric Bacterial Conjunctivitis Dosing Guidelines for Topical Ophthalmic Antibiotics

Azithromycin 1% solution	Children 1 year of age or older: Days 1 and 2: 1 drop twice daily, 8–12 hours apart Days 3–7: 1 drop once daily
Ciprofloxacin 3.5 mg/mL solution	Children 1 year of age or older, days 1 and 2: 1–2 drops every 2 hours while awake Days 3–7: 1–2 drops every 4 hours while awake
Ciprofloxacin 0.3% ointment	Children 2 years of age or older: Apply a ½ in (~1 cm) ribbon of ointment 3 times daily for 2 days, then twice daily for next 5 days
Erythromycin 0.5% ointment	Apply a ½ in (1 cm) ribbon of ointment up to 6 times daily
Gatifloxacin 0.3% solution	Children 1 year of age or older, days 1 and 2: 1 drop every 2 hours while awake up to 8 times daily Days 3–7: 1 drop every 4 hours while awake
Gentamicin 0.3% solution	1–2 drops every 4 hours. In severe infections, may use up to 2 drops every hour
Gentamicin 0.3% ointment	Apply a ½ in (~1 cm) ribbon of ointment 2–3 times daily; up to every 3–4 hours
Levofloxacin 0.5% solution	Children 1 year of age or older, days 1 and 2: 1–2 drops every 2 hours while awake, up to 8 times daily Days 3–7: 1–2 drops every 4 hours while awake, up to 4 times daily
Moxifloxacin 0.5% solution	Children 4 months of age or older: 1 drop 2 times per day for 7 days Children 1 year of age or older: 1 drop 3 times a day for 7 days
Ofloxacin 0.3% solution	Children 1 year of age or older, days 1 and 2: 1–2 drops every 2–4 hours while awake Days 3–7: 1–2 drops 4 times daily
Polymyxin B with bacitracin ointment	Apply a ½ in (~1 cm) ribbon of ointment 4 times daily for 7–10 days
Polymyxin B/trimethoprim solution	Infants and children 2 months of age or older: 1 drop every 3 hours for 7–10 days
Sulfacetamide 10% ointment	Apply a ½ in (~1 cm) ribbon of ointment every 3–4 hours and at bedtime
Sulfacetamide 10% solution	1–2 drops every 2–3 hours for 7–10 days
Tobramycin 0.3% ointment	Infants and children 2 months of age or older: Mild-to-moderate infections: Apply an approximately ½ in (~1 cm) ribbon 2–3 times daily Severe infections: Apply every 3–4 hours
Tobramycin 0.3% solution	Infants and children 2 months of age or older: Mild-to-moderate infections: 1–2 drops every 4 hours Severe infections: Initially, 2 drops every hour

Data from Lexi-Drugs Online™. Lexi-Comp Online™. Hudson (OH): Lexi-Comp, Inc.; 2020. Available from: http://online.lexi.com. Accessed August 16, 2020.

Patient Encounter 1

This morning, a 42-year-old male kindergarten teacher presents with eye redness and frequent clear watery discharge. His symptoms started in his left eye 2 days ago and then moved into both eyes. He is not having eye pain or itching, and his symptoms are not affecting his vision. He asks if he needs an antibiotic eyedrop and if he should continue wearing his contact lenses.

What is the probable diagnosis?

Please differentiate between bacterial, hyperacute bacterial, viral, and allergic causes based on physical assessment.

What is a reasonable treatment regimen?

What do you recommend for the patient to do with his contact lenses?

What nonpharmacologic measures should be employed to prevent spreading?

VIRAL CONJUNCTIVITIS

Etiology

Viral conjunctivitis is commonly caused by adenovirus and is often called "pink-eye."[8] Adenovirus is easily spread through daycare centers, nursing homes, swimming pools, camps, and contaminated fingers and medical instruments.[9] Patients often present with an upper respiratory tract infection or recent exposure to viral conjunctivitis.[8] **KEY CONCEPT** Viral conjunctivitis is usually self-limiting, resolving within 2 weeks.[8]

Treatment

Desired Outcomes

- Complete resolution of the viral conjunctivitis
- Prevent adverse consequences of the infection
- Avoid spreading infection to others

Nonpharmacologic Therapy

KEY CONCEPT Nonpharmacologic measures are critical to prevent the spread of viral conjunctivitis. Cold compresses may relieve symptoms.[6,8] Patients should not share towels or other contaminated objects, should avoid close contact with other people, and avoid swimming for 2 weeks.[8,9] Current contact lenses in the infected eyes and their lens case should be discarded. Take care in the medical setting to thoroughly decontaminate instruments and wash hands.[8,9]

Pharmacologic Therapy

Patients may obtain further symptomatic relief by using artificial tears.[8,9] If artificial tear solutions sting, recommend a preservative-free formula.

Topical antivirals are not used to treat adenovirus conjunctivitis. Topical antibiotics are unnecessary and should not be used for a viral infection and to help prevent the development of antibiotic resistance.[9]

Patients with severe subepithelial infiltration may require a topical steroid. However, topical steroids may cause serious ocular complications, increase the period of viral shedding, and may worsen herpetic conjunctivitis, which has similar symptoms as viral conjunctivitis.[9] Only ophthalmologists should prescribe topical steroids.[8]

Outcome Evaluation

Refer patients who do not see improvement within 7 to 10 days or with visual loss to an ophthalmologist to rule out herpetic and other infectious processes.[8,9]

ALLERGIC CONJUNCTIVITIS

Etiology and Clinical Presentation

Ocular allergy is a broad term that includes several diseases with the hallmark symptom of itching, often accompanied by tearing, conjunctival swelling, photophobia, and stringy or sticky mucoid discharge.[11] Allergic conjunctivitis affects up to 40% of patients.[12] Seasonal ocular allergy is the most common type of allergic conjunctivitis. Often, the patient's history is positive for atopic conditions including allergic rhinitis, asthma, or eczema.[8] Perennial allergic conjunctivitis has similar but less severe symptoms and may not be tied to a specific time of year. Finally, conjunctivitis medicamentosa is a drug-induced form of allergic conjunctivitis caused by overuse of topical vasoconstricting agents and sometimes polypharmacy from use of multiple topical glaucoma eyedrops.[11]

Pathophysiology

The conjunctiva of the eye is often the initial site of contact with an environmental allergen. Mast cell degranulation occurs, and the earliest mediator is histamine, which causes itching, redness, and swelling.[12] Leukotrienes and prostaglandins cause cellular infiltration and increased mucus secretion along with chemosis, resulting in conjunctival vasodilation.

Treatment of ocular allergy is aimed at slowing or stopping these processes. Antihistamines block the histamine receptors, prevent histamine release from the mast cells, and stop eosinophil activity.[12] Mast cell stabilizers inhibit the degranulation of mast cells, preventing mediator release. Some topical agents have multiple mechanisms of action, combining antihistaminic, mast cell stabilization, and anti-inflammatory properties (Tables 63–5 and 63–6).[12]

Treatment

Desired Outcomes

- Relief of current allergic symptoms
- Prevention of future allergic symptoms
- No adverse effects from treatment

Table 63–5

Mechanisms of Action of Ocular Allergy Drugs

Drug	Mechanisms
Azelastine	H_1-receptor antagonist
Cromolyn sodium	Mast cell stabilizer
Epinastine	H_1- and H_2-receptor antagonist, mast cell stabilizer
Ketorolac	Inhibitor of prostaglandin synthesis
Ketotifen	H_1-receptor antagonist, mast cell stabilizer, eosinophil inhibitor
Lodoxamide	Mast cell stabilizer
Loteprednol	Corticosteroid
Naphazoline	Decongestant, vasoconstrictor
Nedocromil	Mast cell stabilizer, eosinophil inhibitor
Olopatadine	H_1-receptor antagonist, mast cell stabilizer
Tetrahydrozoline	Decongestant, vasoconstrictor

Data from Lexi-Drugs Online™. Lexi-Comp Online™. Hudson (OH): Lexi-Comp, Inc.; 2020. Available from: http://online.lexi.com. Accessed August 16, 2020.

Table 63–6

Pediatric and Adult Dosing and Common Side Effects of Ocular Allergy Drugs

Drug	Dosing	Common Side Effects
Azelastine 0.05%	Children 3 years of age or older and adults: 1 drop in affected eye(s) twice daily	Ocular stinging, bitter taste, headache
Cromolyn sodium 4%	Children 4 years of age or older and adults: 1–2 drops in each eye 4–6 times daily	Ocular stinging
Epinastine 0.05%	Children 3 years of age or older and adults: 1 drop in each eye twice daily	Ocular burning, ocular itching, cold symptoms
Ketorolac 0.5%	Children 3 years of age or older and adults: 1 drop 4 times a day	Ocular stinging, irritation
Ketotifen 0.025%	Children 3 years of age or older and adults: 1 drop in affected eye(s) twice daily	Red eyes, headache, rhinitis
Lodoxamide 0.1%	Children 2 years of age or older and adults: 1–2 drops in affected eye(s) 4 times daily, for up to 3 months	Ocular stinging, discomfort, foreign body sensation
Loteprednol 0.2%	Adults only: 1 drop in affected eye(s) 4 times daily	Elevated intraocular pressure, cataracts, secondary ocular infections, systemic side effects possible
Naphazoline 0.012%, 0.03%, 0.1%	0.1%: 1–2 drops into affected eye(s) every 3–4 hours as needed 0.012% or 0.03% solution: 1–2 drops into affected eye(s) up to 4 times daily	Burning, stinging on instillation; mydriasis
Nedocromil 2%	Children 3 years of age or older and adults: 1–2 drops in each eye twice daily	Headache, ocular stinging, unpleasant taste, nasal congestion
Olopatadine 0.1%, 0.2%	Children 3 years of age or older and adults (0.1%): 1 drop in affected eye(s) 2 times daily with minimum 6–8-hour interval between doses Children 2 years of age or older and adults (0.2%): 1 drop in affected eye(s) once daily	Headache, blurred vision, ocular stinging
Tetrahydrozoline 0.05%	1–2 drops in affected eye(s) up to 4 times daily	Burning, stinging on instillation; mydriasis

Data from Lexi-Drugs Online™. Lexi-Comp Online™. Hudson (OH): Lexi-Comp, Inc.; 2020. Available from: http://online.lexi.com. Accessed August 16, 2020.

▶ *Nonpharmacologic Therapy*

The primary treatment for ocular allergy is removal and avoidance of the allergen.[8,9] For conjunctivitis medicamentosa, discontinue the offending medication. Patients should be instructed to avoid rubbing their eyes. Apply cold compresses several times daily to reduce redness and itching and to provide symptomatic relief.[11]

▶ *Pharmacologic Therapy*

KEY CONCEPT Use a step-care approach for the treatment of allergic conjunctivitis.

- Step 1: Nonmedicated, artificial tears solution. The solution dilutes or removes the allergen, providing relief while lubricating the eye. The artificial tear solutions may be refrigerated to provide additional topical relief.[13] Solutions are applied two to four times daily as needed. Ointments may be used in the evenings to further moisturize the surface of the eye. Preservative-free formulations may be tried if other products sting or burn, or if the artificial tears need to be used frequently throughout the day.
- Step 2: Topical antihistamine or antihistamine/decongestant combination. Decongestants are vasoconstrictors that reduce redness and seem to have a small synergistic effect with the antihistamine. Topical decongestants used in combination products include naphazoline and tetrahydrozoline. Topical decongestants burn and sting on instillation and commonly cause mydriasis, especially in patients with lighter-colored eyes. Topical decongestant use should be limited to less than 10 days to avoid rebound congestion.
- Step 3: A mast cell stabilizer or a multiple-action (antihistamine-mast cell stabilizer) agent. Use mast cell stabilizers, including cromolyn or nedocromil, prophylactically throughout the allergy season—they are not used for acute relief of symptoms. Full response may take 4 to 6 weeks.
- Step 4: Short-term topical corticosteroids and immunotherapy.[11,12]

Topical antihistamine-mast cell stabilizers are recommended before oral agents in step therapy due to the increased risk of systemic side effects with oral drugs. Topical antihistamines provide faster relief of ocular symptoms. Topical antihistamine-mast cell stabilizers include alcaftadine, azelastine, bepotastine, epinastine, ketotifen, and olopatadine. Topical NSAID ketorolac tromethamine is approved for ocular itching, though it is used less commonly than topical antihistamines.[12]

Outcome Evaluation

Monitor patients for relief of symptoms. Ensure an adequate trial of each agent. Refer severe cases that do not respond to an ophthalmologist.

BACTERIAL KERATITIS

Epidemiology

Thirty thousand cases of microbial keratitis occur annually in the United States.[14] Microbial keratitis encompasses bacterial, fungal, and *Acanthamoeba* keratitis.[14] Only bacterial keratitis, the most common form, is discussed here.

Pathophysiology

Bacterial keratitis is a broad term for a bacterial infection of the cornea including corneal ulcers and corneal abscesses. The cornea in a healthy eye has natural resistance to infection, making bacterial keratitis rare. However, many factors may predispose a

Patient Encounter 2

ST is a 71-year-old woman who presents with eye complaints. She states her eyes are watering off and on and feel like they have sand in them. She has been wearing her glasses, rather than her usual contact lens use. She is able to look up at the light on the ceiling and denies eye pain or itching. She denies any discharge from the eye, except the feeling that they water occasionally. She states now that the spring temperatures have increased; she has recently turned on the fans in her apartment. She tried using artificial tears one time, but they stung, and she did not continue use of them.

Past medical history:

- GERD
- Migraines
- Insomnia

Social history:

- Alcohol use: denies
- Tobacco: 1 pack per day
- Illicit drug use: denies

Medications:

- Doxepin 6 mg at bedtime
- Ibuprofen 400 mg PRN headaches
- Pantoprazole 40 mg Q AM

Which symptoms would distinguish dry eye from conjunctivitis?

What risk factors may contribute to ST's dry eye?

What nonpharmacologic therapies should be recommended for this patient?

What pharmacologic therapies should be recommended for this patient?

Which dosage forms should be recommended for this patient?

How should the patient be monitored?

patient to bacterial infection by compromising the defense mechanisms of the eye (Table 63–7).[14]

The most common pathogens in bacterial keratitis are *Pseudomonas* (including *P. aeruginosa*) and other gram-negative rods, staphylococci, and streptococci.[14] If the keratitis is related to the use of contacts, *Pseudomonas* and *Serratia marcescens* are the most common pathogens.[14] **KEY CONCEPT** Untreated bacterial keratitis can result in corneal scarring and potential loss of vision. Corneal perforation may occur which may require emergent corneal transplant, and the patient could lose the eye.[14] Central corneal scarring may result in vision loss even after successful eradication of the organism.[14]

Clinical Presentation and Diagnosis of Bacterial Keratitis[8,14]

General

The rate of progression of signs and symptoms varies depending on the infecting organism. A differential diagnosis for keratitis must include viral, fungal, and nematodal infections in addition to bacterial causes.

Symptoms

- Photophobia
- Rapid onset of ocular pain

Signs

- Red eye
- Conjunctival discharge
- Decreased vision

Laboratory Tests

Culture if keratitis is severe or sight-threatening, chronic, or unresponsive to broad-spectrum antimicrobial therapy.

Table 63–7

Risk Factors for Bacterial Keratitis

Exogenous Factors

- Contact lenses
- Loose sutures from ocular surgeries
- Previous corneal surgery
- Previous ocular or eyelid surgery
- Trauma, including foreign bodies, chemical and thermal injuries, and local irradiation

Ocular Surface Disease

- Abnormal lid anatomy or function
- Misdirection of eyelashes
- Ocular infection (eg, conjunctivitis, blepharitis)
- Tear film deficiencies

Systemic Conditions

- Atopic dermatitis
- Connective tissue disease
- Diabetes mellitus
- Gonococcal infection
- Immunocompromised
- Stevens-Johnson syndrome
- Substance abuse
- Vitamin A deficiency

Ocular Medications

- Anesthetics
- Antimicrobials
- Contaminated ocular medications
- Glaucoma medications
- Preservatives
- Steroids
- Topical NSAIDs

Corneal Epithelial Abnormalities

- Corneal epithelial edema
- Predisposition to recurrent erosion of the cornea
- Viral keratitis (eg, herpes simplex or zoster keratitis)

Data from Lin A, Rhee MK, Akpek EK, et al. Bacterial Keratitis Preferred Practice Pattern®. Ophthalmology. 2019;126(1):P1–P55.

Treatment

▶ *Desired Outcomes*[14]

- Resolution of infection and corneal inflammation
- Reduced corneal pain
- Restored corneal integrity with minimal scarring
- Restored visual function

▶ *General Approach to Treatment*

All cases of suspected bacterial keratitis require prompt ophthalmology consultation to prevent permanent vision loss.[8]

▶ *Pharmacologic Therapy*

Dosage Considerations Topical antibiotic drops are preferred. Consider subconjunctival antibiotics if compliance is a concern. Systemic therapy is useful in cases of systemic infection (eg, gonorrhea) or if the sclera is infected. Reserve ointments for minor cases or adjunctive nighttime therapy.[14]

Drug Choice Start topical broad-spectrum antibiotics empirically. Use a loading dose for severe keratitis (Table 63–8). Single-drug therapy with a fluoroquinolone is as effective as combination therapy. Resistance is seen with some fluoroquinolones, choose moxifloxacin or gatifloxacin in severe keratitis cases.[14] Antibacterials should be continued until positive response, then tapered. Fortified antibiotic therapy is an option for severe or unresponsive cases but may increase toxicity to the cornea and surrounding tissues. Fortified antibiotics are compounded products that are a higher concentration than the commercially available formulations.

Topical corticosteroids are employed in some cases of bacterial keratitis. The suppression of inflammation may reduce corneal scarring. However, local immunosuppression, increased ocular pressure, reduced epithelial healing and reappearance of the infection are disadvantages to their use. Topical steroids may be beneficial in bacterial keratitis if initiated early (within 72 hours of antibiotic therapy) but may lead to worse outcomes in keratitis caused by fungi or *Acanthamoeba*.[15]

Table 63–8

Pharmacologic Therapies for Bacterial Keratitis[14]

Organism	Drug
Unknown or multiple types of organisms	Cefazolin 50 mg/mL *and* tobramycin/ gentamicin 9–14 mg/mL *or* Fluoroquinolones (various strengths)
Gram-positive cocci	Cefazolin 50 mg/mL *or* Vancomycin[a] 10–50 mg/mL *or* Bacitracin[a] 10,000 international unit *or* Fluoroquinolones (various strengths)
Gram-negative rods	Tobramycin 9–14 mg/mL *or* Gentamicin 9–14 mg/mL *or* Ceftazidime 50 mg/mL *or* Fluoroquinolones (various strengths)
Gram-negative cocci	Ceftriaxone 50 mg/mL *or* Ceftazidime 50 mg/mL *or* Fluoroquinolones (various strengths)

Adult Topical Dosing

Severe keratitis: Loading dose every 5–15 minutes for the first hour, then every 15 minutes to 1 hour around the clock. Less severe keratitis may use less frequent dosing.

[a] Use for resistant *Enterococcus* and *Staphylococcus* species and penicillin allergy. Due to the absence of gram-negative activity, do not use vancomycin or bacitracin for single-agent empiric therapy in bacterial keratitis.

Data from Lin A, Rhee MK, Akpek EK, Amescua G, Farid M, Garcia-Ferrer FJ, et al. Bacterial Keratitis Preferred Practice Pattern®. Ophthalmology. 2019;126(1):P1–P55.

Outcome Evaluation[14]

- Symptomatic improvement is indicative of therapeutic efficacy.
- Adjust treatment based on culture and sensitivity reports.
- Modify the treatment regimen if the patient does not show improvement within 48 hours.
- Gram-negative keratitis will have increased inflammation in the first 24 to 48 hours, even on appropriate therapy.
- Taper therapy based on clinical response.
- Reculture if negative clinical response; discontinue antibiotics 12 to 24 hours before culturing for best results.
- Contact lenses wearers should be educated about the increased risk of infection overnight and continuous wear and the importance of adherence to contact lens hygiene.

DRY EYE

Epidemiology and Etiology

Dry eye is a frequent cause of eye irritation. The lack of a single diagnostic test for the condition limits the available epidemiologic data. Dry eye affects millions worldwide, being more frequent in elderly patients.[16] The risk factors for dry eye are listed in Table 63–9. Dry eye that is left untreated can cause loss of vision, structural damage, an increased risk for infection, and compromised efficacy of ocular surgery.[17]

Pathophysiology

The surface of the eye and the tear-secreting glands work together as an integrated unit that refreshes the tear supply and clears away used tears. Dry eye may be caused by impaired tear secretion and/or increased tear evaporation.[17]

Dysfunction of tears may be caused by aging, systemic inflammatory diseases, a decrease in androgen hormones, surgery, ocular surface diseases, systemic diseases, or medications that affect the efferent cholinergic nerves. Dysfunctional tear film may result in an inflammatory response on the ocular surface called keratoconjunctivitis sicca.[17]

Table 63–9

Risk Factors for Dry Eye[17]

- Androgen deficiency
- Antihistamine use
- Connective tissue disease
- Estrogen replacement therapy
- Female gender
- Hematopoietic stem cell transplantation
- Hepatitis C infection
- LASIK and refractive excimer laser surgery
- Low dietary intake of omega-3 fatty acids
- Older age
- Radiation therapy
- Vitamin A deficiency

Data from Akpek EK, Amescua G, Farid M, Garcia-Ferrer FJ, Lin A, Rhee MK, et al. Dry Eye Syndrome Preferred Practice Pattern®. Ophthalmology. 2019;126(1):P286–P334.

Table 63–10

Associated Conditions That Cause or Worsen Dry Eye[17]

Ocular Conditions	Environmental Factors
Blepharitis	Air travel
Eyelid malposition	Air conditioning or heating
Lagophthalmos	Contact lenses
Meibomian gland dysfunction	Exogenous irritants or allergens
Systemic Diseases	Prolonged use of computer or reading
Amyloidosis	Reduced humidity
Bell palsy	Smoke exposure
Epstein-Barr virus	Wind and/or use of fans
Graft-versus-host disease	**Local Trauma**
Hemochromatosis	Injury/scarring
Hepatitis C infection	Orbital surgery
Human immunodeficiency virus infection	Radiation
Lymphoma	**Medications**
Neuromuscular Diseases	Anticholinergics
Ocular mucous membrane pemphigoid	Antidepressants
Parkinson disease	Antihistamines
Rosacea	β-Blockers
Rheumatoid arthritis	Diuretics
Sarcoidosis	Hormone therapy
Scleroderma	Systemic retinoids
Sjögren syndrome	Frequent administration of ophthalmic medication
Stevens-Johnson syndrome	
Systemic lupus erythematosus	

Data from Akpek EK, Amescua G, Farid M, Garcia-Ferrer FJ, Lin A, Rhee MK, et al. Dry Eye Syndrome Preferred Practice Pattern®. Ophthalmology. 2019;126(1):P286–P334.

Clinical Presentation and Diagnosis of Dry Eye[16,17]

General

Many other ocular diseases have similar symptoms. Patients with suggestive symptoms without signs should be placed on a treatment trial. Repeated observations may be required for a clinical diagnosis.

Symptoms

- Dry or foreign body sensation
- Mild itching
- Burning or stinging
- Photophobia
- Ocular irritation or soreness
- Blurry vision and/or variable vision
- Contact lens intolerance
- Diurnal fluctuation or symptoms worsening later in the day

Signs

- Redness
- Mucus discharge
- Increased blink frequency
- Intermittent tearing

Other Diagnostic Tests

- The tear break-up time test assesses the stability of precorneal tear film. Break-up times of less than 10 seconds are considered abnormal.
- Ocular surface dye staining assesses the ocular surface and will show blotchy areas in the dry eye.
- Schirmer test evaluates aqueous tear production but is not diagnostic. Results of 5 mm or less are considered abnormal.
- Assess corneal sensation if trigeminal nerve dysfunction is suspected.
- Consider an autoimmune disorder if significant dry eyes, other signs and symptoms, or family history are present.

Environmental causes (Table 63–10) and an abnormal blink reflex are common causes of increased evaporative loss of tears and worsening of dry eye.[17]

Treatment

Desired Outcomes[17]

- Relief of the symptoms of dry eye
- Maintain or improve visual acuity
- Prevention of long-term adverse effects from dry eye

General Approach to Treatment

KEY CONCEPT Dry eye is a chronic condition. Symptoms can be improved with treatment, but unless dry eye is secondary to a disease, it is not usually curable. Because of this, patient education is important, and a periodic reassessment of the efficacy of the treatment is appropriate. If the patient is unresponsive to treatment, refer to an ophthalmologist for additional options. If the dry eye is secondary to a systemic disease, the disease should be managed by the appropriate medical specialist.[17]

Nonpharmacologic Therapy

Behavioral and environmental modifications may significantly improve dry eye, especially in mild cases. Patients should be counseled to increase their frequency of blinking, use eyelid hygiene and warm compresses, and stop smoking. Reduce air drafts and consider adding a humidifier in low-humidity areas. Schedule regular breaks from computer work, other electronic screens, or reading. These activities promote decreased blinking and can increase dry eye symptoms. Lower the computer screen to below eye level to decrease lid aperture. Evaluate medication profile and therapeutically substitute medications that do not exacerbate dry eye. Moisture chamber spectacles or goggles may reduce tear evaporation.[16,17]

If pharmacologic and other therapies are not sufficient, punctal occlusion or lateral tarsorrhaphy may be an option for more severe cases.[16,17] Punctal occlusion is the plugging of the punctal drainage sites with collagen or silicone plugs. Lateral tarsorrhaphy sutures portions of the lid margins together to decrease evaporative tear loss.

Pharmacologic Therapy

The mainstay of treatment for dry eye is artificial tears. Artificial tears augment the tear film topically by increasing viscosity and provide symptom relief. If a patient uses artificial tears more than four times daily, or develops an allergy to ophthalmic preservatives, recommend a preservative-free formulation. Artificial tears are available in gel, ointment, and emulsion forms that provide a longer duration of relief. Ointment use is appropriate at bedtime as it may cause blurry vision.[17]

Preliminary data suggest dietary or supplemental intake of omega-3 fatty acids may be beneficial. Omega-3 fatty acids may block the production of inflammatory cytokines and proinflammatory mediators.[16,17]

Anti-inflammatory agents may be used in conjunction with artificial tears. The first approved agent was cyclosporine emulsion. Cyclosporine emulsion increases tear production in some patients. Cyclosporine emulsion may require several months for full results, so it should not be used for acute relief.[16]

An additional treatment for the signs and symptoms of dry eye is twice-daily lifitegrast 5% ophthalmic solution. Lifitegrast is a lymphocyte function-associated antigen-1 (LFA-1) antagonist. LFA-1 is a protein that interacts with an intracellular adhesion molecule (ICAM-1). ICAM-1 may be overexpressed in patients with dry eye disease and can promote inflammation of the ocular surface. By blocking the interaction of LFA-1 to ICAM-1, lifitegrast may reduce ocular surface inflammation. The duration of therapy in clinical trials was 12 weeks. The most common adverse effects of lifitegrast include eye irritation, distortion of taste, and reduced visual acuity.[18,19] Use of topical corticosteroids for short periods (2 weeks) may suppress inflammation and ocular irritation symptoms but should be used with caution.[17] (Table 63–11).

Table 63–11

Pharmacologic Therapies for Dry Eye[17]

Drug	Dosing
Cyclosporine ophthalmic emulsion 0.05%	1 drop in each eye twice daily
Lifitegrast 5% ophthalmic solution	1 drop in each eye twice daily
Loteprednol etabonate suspension 0.5%	1–2 drop(s) in affected eye(s) 4 times daily; short term use only

Data from Akpek EK, Amescua G, Farid M, Garcia-Ferrer FJ, Lin A, Rhee MK, et al. Dry Eye Syndrome Preferred Practice Pattern®. Ophthalmology. 2019;126(1):P286–P334.

Outcome Evaluation[17]

- Monitor patient for relief of symptoms and ocular damage.
- Periodically reassess the patient's compliance with therapy and understanding of the disease.

Patient Care Process: Dry Eye

Collect information:

- Collect relevant information about medical history of dry eye.
- Collect information about the patient's signs and symptoms related to dry eye.
- Collect relevant information about the patient's behaviors, such as smoking, and environmental risk factors for dry eye.
- Collect an updated medication list including prescription medications, nonprescription medications, herbal products, and dietary supplements.

Assess information:

- Assess the patient's signs and symptoms of dry eye for potential need for referral.
- Assess the patient's reported behaviors and environmental risk factors for potential intervention.
- Assess each medication in the patient's medication list for appropriateness and risk of exacerbation of dry eye.

Develop a care plan:

- Address the patient's risk factors for dry eye, including potential nonpharmacologic interventions related to smoking and other environmental risk factors.
- Address the patient's medication-related problems and optimize the patient's medication therapy by recommending alternatives to medications that can exacerbate symptoms of dry eye.
- Determine an appropriate care plan based on the patient's frequency of symptoms. The care plan may include treatment options such as over-the-counter formulations of artificial tears, omega-3 fatty acids, or prescription therapies such as cyclosporine or lifitegrast.
- Plan to counsel the patient on appropriate use of ophthalmic solutions that may be utilized as part of the recommended therapy for dry eye.

Implement a care plan:

- Engage the patient in discussion about his/her risk factors for dry eye, including potential nonpharmacologic interventions related to smoking and other environmental risk factors.
- Recommend alternatives to medications that can exacerbate symptoms of dry eye.
- Initiate an appropriate care plan based on the patient's frequency of symptoms. The care plan may include treatment options such as over-the-counter formulations of artificial tears, omega-3 fatty acids, or prescription therapies such as cyclosporine or lifitegrast.
- Counsel the patient on appropriate use of ophthalmic solutions with the steps below:
    - Wash hands before and after instilling medication(s) into the eye.
    - Contact lenses should be removed prior to instilling eye medication, and the patient should wait 10 minutes before reinserting contact lenses.
    - Do not touch the tip of the container with anything.
    - Use of **nasolacrimal occlusion** decreases systemic absorption and may increase ocular bioavailability of the drug. After instilling the eyedrop, the patient should close the eye and press a finger gently against the nasolacrimal duct (tear duct) for 2 to 3 minutes.
    - Contribute to the coordination of care by referring the patient to an ophthalmologist if self-care is not appropriate.

Monitor and Evaluate:

- Monitor patient for relief of symptoms and ocular damage.
- Assess adherence and recommend alternative formulations of artificial tears if necessary.
- Periodically reassess the patient's compliance with therapy and understanding of the disease.

Patient Encounter 3

BE, a 45-year-old Black man, presents with an irritation to his right ear that started about 24 hours ago. He has recently started wearing new waterproof headphones when he does his intense cardiovascular workouts and swimming at a local pool for his triathlon training. PMH: seasonal allergies

PE:

BP 130/76 mm Hg

P 72 beats/min

R 16 breaths/min

Ht. 6′6″ (198 cm)

Wt. 215 lb (98 kg)

Medications:

- Cetirizine 10 mg daily as needed for allergies
- Multivitamin daily

Does BE have any potential risk factors for acute otitis externa?

What pharmacologic options are available?

What nonpharmacologic therapies could BE do to decrease the likelihood of this happening again?

- Cyclosporine or lifitegrast may take up to 3 months for full improvement.
- If a patient presents with vision loss, moderate or severe pain, corneal ulceration, or a lack of response to therapy, refer the patient to an ophthalmologist for prompt evaluation.

DRUG-INDUCED OCULAR DISORDERS

Many systemic medications can cause ocular adverse effects. Patients presenting with ocular complaints should have their medication profile evaluated.

OTIC DISORDERS

OTITIS EXTERNA

Epidemiology and Etiology

KEY CONCEPT Acute otitis externa (AOE), or what is commonly referred to as swimmer's ear, is an infection of the external auditory canal that potentially involves diffuse inflammation that may extend distally to the pinna and proximally to the tympanic membrane.[20,21] Otitis externa has a lifetime prevalence of approximately 10% and can be considered chronic rather than acute if it lasts 3 months or longer.[20]

A diffuse acute otitis media is diagnosed by a rapid onset, generally within 48 hours, in the past 3 weeks of symptoms and signs of inflammation such as intense or disproportionate tenderness of the tragus, pinna, or both.[21] Patients with a nonintact tympanic membrane, tympanostomy tube, diabetes, immunocompromised state, or prior radiotherapy are at risk for more serious infections and are not treated the same as an uncomplicated acute otitis externa.

Pathophysiology

In North America, the vast majority of acute otitis externa cases are bacterial caused by pathogens such as *P. aeruginosa* and *S. aureus*.[20,21] Otitis externa can be polymicrobial, and it should be treated with topical antibiotics if uncomplicated.[21]

Otitis externa can be caused by a variety of different factors such as water exposure, self-cleaning, soapy deposits, alkaline eardrops, dermatologic conditions, trauma, sweating, allergies, genetics, climate, and stress.[21]

Treatment

▶ *Desired Outcomes*

- Relief of the symptoms of otitis externa
- Prevention of long-term adverse effects from otitis externa

▶ *General Approach to Treatment/ Nonpharmacologic Therapy*

Removing obstructing cerumen; using acidifying eardrops shortly before swimming, after swimming, at bedtime, or all three; drying the ear canal with a hair dryer; using ear plugs while swimming; and avoiding trauma to the external auditory canal are recommended by the guidelines as therapy options for preventing otitis externa.[21]

▶ *Pharmacologic Therapy*

Otitis externa in a patient with a perforated tympanic membrane needs to be treated with medications that are not ototoxic as compared to an uncomplicated case. There are not significant differences in efficacy of the topical agents; therefore, patient and provider preferences, cost, adherence, and adverse effects are priority.[21] Refer to Table 63–12 for common otic preparations.

Cortisporin (bacitracin, neomycin, polymyxin B, hydrocortisone) is typically used first in patients with an intact tympanic membrane. Ofloxacin and ciprofloxacin/dexamethasone (Ciprodex) are used with a perforated tympanic membrane or if it cannot be visualized. A total of 7 to 10 days of topical therapy is recommended.[21] Also, pain is very common with otitis media, and it needs to be managed accordingly. Anesthetic otic drops are not recommended for pain management. If there is no improvement with the drops within 48 to 72 hours, then the diagnosis of otitis externa should be reviewed.

Outcome Evaluation

- Monitor patient for relief of symptoms and otic damage.

Table 63–12

Pharmacologic Therapies for Otitis Externa

Drug	Considerations
Acetic acid 2.0% solution	Pain and irritation, may be less effective beyond a week of treatment; not with perforated tympanic membrane
Acetic acid 2.0%, hydrocortisone 1.0% solution	Pain and irritation; not with perforated tympanic membrane
Ciprofloxacin 0.2%, hydrocortisone 1.0% solution	Twice daily adequate
Ciprofloxacin 0.3%, dexamethasone 0.1% solution	Twice daily adequate
Neomycin, polymyxin B, hydrocortisone solution	Ototoxic; four times daily; not with perforated tympanic membrane
Ofloxacin 0.3% solution	Twice daily adequate, potentially daily

Adapted from Schaefer P, Baugh RF. Acute otitis externa: an update. Am Fam Physician. 2012;86(11):1055–1061; Rosenfeld RM, Schwartz SR, Cannon CR, et al. Clinical practice guideline: acute otitis externa. Otolaryngol Head Neck Surg. 2014;150(1 Suppl):S1–S24.

CERUMEN IMPACTION

Epidemiology and Etiology

One of the most common reasons for patients seeking care for auditory problems is obstruction of the ear. Ear canal obstruction is most commonly caused by cerumen. Twelve million people in the United States annually seek care for cerumen impaction, 8 million cerumen removal procedures occur annually, and "…one in 10 children, 1 in 20 adults and more than one-third of the geriatric and developmentally delayed populations…" have excessive or impacted cerumen.[22]

Pathophysiology

Obstruction can lead to more serious problems including hearing loss, tinnitus, fullness, itching, otalgia, discharge, odor, and cough. Hearing loss can range from 5 to 40 dB depending on the degree of occlusion of the canal with cerumen.[22] Cerumen impaction can also prevent a provider from viewing the external auditory canal and/or tympanic membrane and performing auditory diagnostic tests that are vital components of any physical examination. Common symptoms include pain, itching, sensation of fullness, tinnitus, odor, drainage, and cough.

Treatment

▶ *Desired Outcomes*

- Relief of the symptoms of cerumen impaction

▶ *General Approach to Treatment*

Prevention of cerumen impaction includes education in proper ear hygiene. Proper ear hygiene does not include using cotton-tipped swabs to clean ears. Cotton-tipped swabs have been implicated in increasing cerumen impaction.[22] Alcohol or hydrogen peroxide drops or irrigation, topical earwax-softening agents, and irrigation are all potential options for secondary prevention of impacted cerumen.[22]

Only patients who are symptomatic should receive treatment. Patients with cerumen that prevent assessment of the ear should also be treated. Treatment for cerumen impaction may include cerumenolytic agents, irrigation, or manual removal.[22] Cerumenolytics work by thinning the cerumen to decrease the need for irrigation and manual removal. All cerumenolytic agents have been shown to be equally efficacious including water. The different cerumenolytic agents available include water based, oil based, and non-water- and nonoil based. Water-based agents work by breaking up the cerumen while oil-based preparation soften without breaking up the cerumen. Irrigation uses a jet of warm water to flush out the cerumen. A curette, probe, hook, forceps, or suction may be used for manual removal. All treatment regimens have been shown to be efficacious and none are preferred over another.

Side effects, although rare, can occur with treatment for cerumen impaction. Some side effects include tympanic membrane perforation, ear canal laceration, infection of the ear, bleeding, or hearing loss. The number of side effects from cerumen impaction treatment that occur in the United States is around 8000 yearly.[22]

Outcome Evaluation

- Monitor patient for relief of symptoms from excess cerumen.

Abbreviations Introduced in This Chapter

ABC	Acute bacterial conjunctivitis
NSAID	Nonsteroidal anti-inflammatory drug

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Nose, Mouth, and Throat Disorders

Alexandra Hintz, Phu Trinh, and Luke Dearden

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Compare and contrast clinical presentations of various nose, mouth, and throat disorders.
2. Identify common medications that cause xerostomia and sialorrhea.
3. Evaluate when pharmacologic treatment is necessary for treatment of nose, mouth, and throat disorders.
4. Compare and contrast the mechanisms of action of common medications used to treat nose, mouth, and throat disorders.
5. Develop a treatment plan, including nonpharmacologic and pharmacologic interventions, for the treatment of nose, mouth, and throat disorders.
6. Educate patients about nose, mouth, and throat disorders and the pharmacologic and nonpharmacologic therapies used to treat them.
7. Create a monitoring plan for treatment of nose, mouth, and throat disorders.

NONALLERGIC RHINITIS

Introduction

Allergic rhinitis refers to inflammation of the nasal mucous membrane when exposed to allergens. In contrast, nonallergic rhinitis (NAR) refers to a condition of chronic symptoms of nasal congestion and rhinorrhea, unrelated to a specific allergen.[1] Symptoms may be constant or may only present for a brief period of time. Symptoms may develop and resolve year-round. NAR can be divided into acute rhinitis, chronic rhinitis, atrophic rhinitis, and vasomotor rhinitis. NAR was previously referred to as nonallergic vasomotor or vasomotor rhinitis but was renamed because of a lack of evidence showing a vascular origin. The pathophysiology of NAR is complex and mainly unknown.

Epidemiology and Etiology

NAR is thought to be associated with dysregulation of sympathetic, parasympathetic, and nociceptive nerves innervating the nasal mucosa. Rhinitis affects roughly 20% of the population of industrialized countries.[2] Annual healthcare costs for this average $1.9 billion in the United States. Symptoms occur most commonly between 30 and 60 years of age and affect women more than men.[2]

Clinical Presentation and Diagnosis

KEY CONCEPT NAR is clinically diagnosed by performing a complete medical history, physical examination, and diagnostic testing to rule out other possibilities.[3] The most important factor in attaining a proper diagnosis of NAR is a comprehensive medical history and complete physical. Common symptoms that present with both allergic rhinitis (see Chapter 65) and NAR are headache, facial pressure, postnasal drip, coughing, and throat clearing.[3-5] Environmental triggers may also affect NAR, such as strong odors, cold air exposure, alcohol, tobacco smoke, and/or spicy foods to name a few.[6] If a skin test is performed, patients will typically have a negative skin test and serum antibodies for relevant allergens.[6]

Treatment

▶ *Desired Outcomes*

Minimize or prevent symptoms and prevent long-term complications.

▶ *General Approach to Treatment*

The best overall treatment of NAR is the avoidance of an identified trigger while utilizing medical therapy as an adjunct option. Management of NAR first requires educating the patient on avoiding environmental triggers. Once the causative allergens and the specific symptoms are identified, management consists of three possible approaches: allergen avoidance, nonpharmacologic therapy, and pharmacotherapy for prevention or treatment of symptoms. Limiting exposure to factors such as perfumes, tobacco, spicy foods, and various cleaning items may significantly reduce symptoms. A stepwise approach is implemented when using pharmacologic agents.[1]

▶ *Nonpharmacologic Therapy*

Avoiding environmental triggers, preventing poor air quality in home, avoidance of offending allergen, avoidance of tobacco smoke, avoidance of house dust mites, and saline rinses are nonpharmacologic options to utilize for treatment of NAR.

▶ *Pharmacologic Therapy*

Generally, patients with chronic NAR are less responsive to pharmacologic therapy than those with allergic rhinitis. Topical agents often have better efficacy in these patients compared to oral formulations. Typically, treatment avoids oral agents. **KEY CONCEPT** Use

Patient Encounter 1

LJ is a 39-year-old man who presents with a runny nose, congestion, sneezing, itchy eyes for the past 2 weeks. He states that he has to blow his nose several times throughout the day and that his mucus is clear. He denies any sinus pressure and cough. Upon a thorough workup, the patient does not have any triggers that produces these symptoms.

Past medical history:

- Hypertension
- Diabetes
- GERD

Social history:

- Alcohol use: 1 to 2 drinks/week
- Tobacco: denies (wife smokes)
- Illicit drug use: denies

Which symptoms does LJ present to suggest nonallergic rhinitis?

What environmental or medical risk factors may contribute to LJ's symptoms?

What nonpharmacologic therapies should be recommended for this patient?

What pharmacologic therapies should be recommended for this patient?

a stepwise pharmacologic approach for management of NAR (Table 64–1). Topical nasal corticosteroids are often first-line treatment, especially for those with congestion and obstruction.[1,7] Topical anticholinergics, such as ipratropium, may be used as first line for those experiencing rhinorrhea.[1,7] Topical antihistamines have a limited role in NAR. However, they may be helpful in patients with rhinorrhea and nasal congestion.[1,7]

Outcome Evaluation

Major outcomes to evaluate include quality of life, the efficacy and tolerability of treatment, and patient satisfaction. Nasal symptom scores may be utilized to assess outcomes and health-related quality of life. Patient-reported instantaneous and reflective total nasal symptom scores have been used to assess the level of efficacy of

Table 64–1

Pharmacologic Doses of Medications for Nonallergic Rhinitis[1,4,5,7]

Drugs	Brand Names	Dosages	Special Populations	Adverse Effects
Topical Antihistamines				
Azelastine	Astepro	1–2 sprays twice daily	Pediatrics: 5–11 years: 1 spray twice daily	Headache, drowsiness
Olopatadine	Patanase	2 sprays twice daily	Pediatrics: 6–11 years: 1 spray twice daily	
Topical Decongestants				
Oxymetazoline (OTC)	Afrin, various	2–3 sprays twice daily		Epistaxis, headache, cough, pharyngitis, rhinitis medicamentosa
Phenylephrine (OTC)	Various	2–3 sprays every 4 hours	Pediatrics: > 12 years: 0.25%–0.5% 2–3 sprays every 4 hours 6–12 years: 0.25% 2–3 sprays every 4 hours 2–6 years: 0.125% 1 drop every 2–4 hours	
Intranasal Steroid				
Beclomethasone	Beconase AQ, Qnasl	1–2 inhalations in each nostril twice daily (Beconase AQ) 2 inhalations (160 mcg) in each nostril once daily (Qnasl)	Pediatric: Beconase AQ: 6–11 years: 1 inhalation in each nostril twice daily Qnasl: 4–11 years: 1 inhalation (40 mcg) in each nostril once daily	
Budesonide	Rhinocort Aqua	1 spray each nostril daily; max: 4 sprays/day		
Fluticasone (OTC)	Flonase, various	2 sprays in each nostril once daily	Pediatrics: > 4 years: 1 spray in each nostril daily (Flonase)	
Topical Antimuscarinics				
Ipratropium	Atrovent	2 sprays in each nostril 2–4 times a day	Pediatrics: 5–11 years: 2 sprays in each nostril 2–3 times a day	Epistaxis, nasal drying

Data from Lexi-Drugs Online™. Lexi-Comp Online™. Hudson, OH: Lexi-Comp, Inc.; 2017. Available from: http://online.lexi.com.proxy.hsc.unt.edu. Accessed August 7, 2020.

Patient Care Process: Nonallergic Rhinitis

Collect information:

- Duration of symptoms
- Any concomitant signs and symptoms
- Medication list
- Past medical history (eg, other conditions, medications trialed in past, triggers to allergens)
- Social history (eg, smoking history/exposure to secondhand smoke, occupation)
- Perform physical examination
- Perform skin prick test, if allergic rhinitis suspected

Assess information:

- Determine whether the rhinitis is allergic or nonallergic.
- Determine whether the rhinitis is acute or chronic.
- Assess potential causes of NAR and identify any underlying conditions.

Develop a care plan:

- Select nonpharmacologic therapy (eg, avoiding environmental triggers, preventing poor air quality in home, avoidance of offending allergen, avoidance of tobacco smoke, avoidance of house dust mites, and saline rinses).
- If symptoms do not resolve with nonpharmacologic therapy, select pharmacologic treatment targeted toward the predominant symptom (eg, corticosteroids for congestion and obstructive symptoms, anticholinergic medications for rhinorrhea, antihistamines for rhinitis).

Implement a care plan:

- Educate the patient regarding nonpharmacologic treatment for NAR.
- Counsel patients regarding any new medications used to treat NAR.
- Counsel patient when to follow-up if symptoms do not resolve.

Follow-up:

- Monitor for resolution of NAR.

treatment. Instantaneous scores refer to assessment of symptoms within 1 hour or less. Reflective scores refer to assessment of symptoms over the 12 hours prior to the recording of the score. Scores are given on a 0 to 3 scale, with 0 being no symptoms, 1 being mild symptoms, 2 being moderate symptoms, and 3 being severe symptoms. The main goal is to minimize or prevent symptoms, and success will be driven by a collaborative effort with the patient and the clinician.

POSTNASAL DRIP/UPPER AIRWAY COUGH SYNDROME

Introduction

Postnasal drip is the drainage of secretions from the nose or paranasal sinuses into the pharynx.[8] The ACCP Clinical Practice Guidelines recommends the term upper airway cough syndrome (UACS) be used, rather than postnasal drip, for patients with chronic cough related to upper air abnormalities.[8] UACS includes all upper airway abnormalities causing cough. Increased mucous production that drips to the back of the throat may be the leading cause. Cough reflex is related to inflammatory conditions of the nose and sinuses.

Pathophysiology

Clinical studies have suggested that the pathogenesis of cough from UACS is due to the mechanical stimulation of the afferent limb of the cough reflex in the upper airway.[9] Stimulation by secretions from the nose and sinuses may cause cough. Patients with UACS-induced cough may have a more sensitive cough reflex in the upper airway. Causes of UACS may include colds, flu, allergies, sinus infection or sinusitis, nasal obstruction, rhinitis (allergic, nonallergic, chronic), pregnancy, medications, deviated septum, changes in weather, certain foods, and fumes.

Clinical Presentation and Diagnosis

The clinical presentation of patients with UACS includes cough, drainage in throat, nasal congestion, and nasal discharge. Patients may report having the sensation of having something drip down the throat or frequent throat clearing.[8,9] Medical histories often have findings of an upper respiratory illness or wheezing. Diagnosis of UACS-induced cough should be determined by consideration of symptoms, physical examination, radiographic findings, and response to therapy.

Treatment

▶ *Desired Outcomes*

Minimize or prevent symptoms of cough and respiratory issues.

▶ *General Approach to Treatment*

KEY CONCEPT The general approach to treatment of UACS is to treat the patient's presenting symptoms as well as any underlying causes. Identifying UACS may be difficult. Respiratory tract infections are the most common cause of acute cough. Chronic cough may stem from asthma, UACS, bronchitis, and gastroesophageal reflux disease (GERD). If a patient presents with cough with concurrent dyspnea, the patient should be evaluated by a medical provider.

▶ *Nonpharmacologic Therapy*

Options for patients in treatment of UACS are nasal saline irrigation, vaporizers, humidifiers, reduction of exposure to dust, and utilization of HEPA air filters. If patient has chronic cough that is related to GERD, options include diet modifications for weight loss in overweight or obese patients, elevating the head of the bed and avoiding meals within 3 hours of bedtime.

Patient Care Process: Postnasal Drip/Upper Airway Cough Syndrome

Collect information:

- Duration of cough, drainage in throat, nasal congestion, and nasal discharge
- Any concomitant signs and symptoms
- Medication list
- Past medical history (eg, other conditions, medications trialed in past)
- Social history (eg, smoking history/exposure to secondhand smoke, occupation)
- Perform physical examination

Assess the information:

- Determine whether cough contributed to conditions or triggers (eg, colds, flu, allergies, sinus infection or sinusitis, nasal obstruction, pregnancy, medications, deviated septum, changes in weather, certain foods, and fumes).
- Assess potential causes of cough and identify any underlying conditions.

Develop a care plan:

- Select nonpharmacologic therapy (eg, nasal saline irrigation, vaporizers, humidifiers, reduction of exposure to dust, and utilization of HEPA air filters).
- If symptoms do not resolve with nonpharmacologic therapy, select pharmacologic treatment (eg, intranasal glucocorticoids, oral and nasal antihistamines, oral decongestants, or oral leukotriene receptor antagonists).

Implement the care plan:

- Educate the patient regarding nonpharmacologic treatment for UACS.
- Counsel patients regarding any new medications used to treat UACS.
- Counsel patient when to follow up if symptoms do not resolve.

Follow-up: monitor and evaluate

- Monitor patient for resolution of UACS.
- Reevaluate the patient if UACS does not improve or worsens.

► *Pharmacologic Therapy*

For patients experiencing cough attributed to allergic rhinitis, empiric therapy of intranasal glucocorticoids may be effective in symptom reduction within the first few days. However, maximal effect may take up to 2 weeks to achieve. Therapy is continued for approximately 3 months if patient responds.[10] Other options for cough due to allergic rhinitis includes oral and nasal antihistamines, oral decongestants, oral leukotriene receptor antagonists, and other agents. See Chapter 65 for more details on the medications and dosing.

When cough may be linked to nonallergic rhinitis, an oral first-generation antihistamine or a combined antihistamine decongestant may be trialed. First-generation antihistamines are preferred over second-generation antihistamines due to the stronger anticholinergic effect.

Other options include intranasal azelastine, glucocorticoid, and ipratropium. Lack of improvement after 1 to 2 weeks of empiric therapy suggests UACS is not the cause of cough.[10]

Outcome Evaluation

Patients may have more than one cause for chronic cough and may only resolve when all causes treated concurrently. Treatments for cough may be stopped once cough has resolved while closely monitoring and observing the patient.

DYSGEUSIA

Introduction

Dysgeusia refers to taste and smell disorders that can lead to decreased quality of life due to decreased detection of aroma and flavors of foods, as well as fragrances in the environment.[1] Consequences of dysgeusia include consuming spoiled foods, injury or death from delayed detection of environmental hazards, and reduced nutritional intake.[11] Dysgeusia may also be a symptom related to COVID-19; please refer to Chapter 74 for more information.

Epidemiology and Etiology

A study performed by the United States National Health and Nutrition Examination Survey (NHANES) showed that 12.4% of US adults 40 years or older had some degree of olfactory dysfunction.[12] Advanced age was associated with increasing prevalence of both taste and smell disorders. Dysgeusia is more prevalent in elderly patients who are hospitalized and institutionalized (13.9%) than in those living in the community (3.2%).[13] Medications that can cause dysgeusia are macrolides, antimycotics, fluoroquinolones, protein kinase inhibitors, angiotensin-converting enzyme (ACE) inhibitors, statins, and proton pump inhibitors (PPIs).

Clinical Presentation and Diagnosis

Patients may be reluctant to disclose a history of smell impairment unless there is a specific complaint. Underreporting of this phenomenon may lead to undiagnosed dysgeusia and nontreatment. Symptoms may include a decreased ability to taste and smell. Patients may also complain of having an unpleasantly sweet, bitter, metallic, or salty taste. Patients who experience any of these symptoms warrant further evaluation. Diagnosis may include a smell or taste test, imaging, laboratory studies, and a thorough history and physical examination.[11] Office smell or taste tests such as the University of Pennsylvania Smell Identification Test (UPSIT) may identify symptoms associated with dysgeusia. Other tests include threshold, discrimination, identification test (TDIT), chemosensory tests, butanol threshold tests, whole-mouth taste tests, spatial tests, flavor discrimination tests, and somatosensory tests.

Treatment

► *Desired Outcomes*

The main goal of treatment is to restore the sense of taste and smell, if able.

► *General Approach to Treatment*

Treatment depends on etiology; nasal sinus diseases are the most common olfactory disorders to cause dysgeusia. Nasal sinus

Patient Care Process: Dysgeusia

Collect information:

- Duration of dysgeusia
- Any concomitant signs and symptoms
- Medication list
- Past medical history (eg, other conditions, medications tried in past)
- Social history (eg, smoking history/exposure to secondhand smoke, alcohol use, occupation)
- Physical examination

Assess the information:

- Determine whether loss of taste and smell can be attributed to medications or conditions (eg, advanced age).
- Identify potential causes of dysgeusia and identify any underlying conditions.

Develop a care plan:

- Select nonpharmacologic therapy (eg, removing exposure to allergens, desensitization therapy, surgery to remove offending obstruction when medical therapy for nasal and sinus disease ineffective, mouth rinses, and smell training).
- Select pharmacologic treatment (eg, intranasal glucocorticoids, antihistamines, or leukotriene inhibitors) if symptoms do not resolve with nonpharmacologic therapy.

Implement the care plan:

- Educate the patient regarding nonpharmacologic treatment for dysgeusia.
- Counsel patients regarding any new medications used to treat dysgeusia.
- Counsel patient when to follow up if symptoms do not resolve.

Follow-up: monitor and evaluate

- Monitor patient for resolution of dysgeusia.
- Reevaluate the patient if dysgeusia does not improve or worsens.
- Refer to specialist if symptoms persist.

diseases may be either obstructive or nonobstructive. Obstructive disorders require relief of the obstruction and the treatment of infection, if present in the patient. Patients without obstruction may have damage to olfactory receptors due to inflammation. Physicians should refer patients to a smell and taster disorder center or to an otolaryngologist if the patient's quality of life is significantly decreased.

▶ *Nonpharmacologic Therapy*

Nonpharmacologic therapy consists of removing exposure to allergens, desensitization therapy, surgery to remove offending obstruction when medical therapy for nasal and sinus disease is ineffective, mouth rinses, and smell training.

▶ *Pharmacologic Therapy*

Intranasal glucocorticoids are useful in treatment of dysgeusia with rhinitis, nasal edema, and polyps.[11] Examples include two sprays in each nostril twice daily of either beclomethasone dipropionate 42 mcg, flunisolide 25 mcg, or mometasone furoate 50 mcg. Antihistamines may be useful for patients experiencing dysgeusia accompanied with allergic rhinitis (see Chapter 65 for options). Leukotriene inhibitors, such as montelukast 10 mg by mouth once daily, are beneficial in patients with nasal polyps, anosmia, and hyposmia.[14]

Outcome Evaluation

Patients may recover from dysgeusia when sense of taste and smell recovers. Improvements may be seen after treatment is initiated if damage is reversible. Performing tests above to assess sense of taste and smell will identify improvement.

EPISTAXIS

Introduction

Epistaxis refers to the loss of blood from tissues that line the inside of the nose. Anterior bleeds are the most common at 90%, which occurs in the Kiesselbach plexus, a vascular watershed area of nasal septum.[15] Posterior bleeds may lead to more severe cases which is caused by the posterolateral branches of the sphenopalatine artery.[15]

Epidemiology and Etiology

Causes of epistaxis may be due to trauma, medications (eg, anticoagulants, nonsteroidal anti-inflammatory drugs [NSAIDs], and nasal steroids), bleeding disorders, vascular conditions, neoplasms, hypertension, alcohol, allergies, or heart failure.[15,16] Patients may experience epistaxis at any age; however it is common in patients under the age of 10 and patients between 45 and 65 years of age.[15] Hospitalizations increase with age. Seasonal changes may also affect the incidence of epistaxis. Factors include incidence of upper respiratory infections, allergic rhinitis, and mucosal changes associated with fluctuations in temperature and humidity.[16]

Clinical Presentation and Diagnosis

Nosebleeds will be evident by performing an assessment of the patient. Patients may undergo coagulation studies, an initial tamponade procedure, or physical examinations to identify causes. Distinguishing between anterior and posterior bleeds may be performed by placing bilateral anterior nasal packing and them examining the patient. Continued bleeding may suggest a posterior bleed which will require hospitalization with cardiac monitoring.

Treatment

▶ *Desired Outcomes*

Locating the source of bleeding and stopping the bleeding to prevent further complications.

▶ *General Approach to Treatment*

Initial management includes compression of nostrils and plugging the affected nostril with cotton or gauze. The patient

Patient Care Process: Epistaxis

Collect information:

- Severity and duration of epistaxis
- Any concomitant signs and symptoms
- Medication list
- Past medical history (eg, other conditions)
- Social history (eg, smoking history/exposure to secondhand smoke, alcohol use, occupation)
- Perform physical examination

Assess the information:

- Determine whether nosebleeds are caused by medications or conditions (eg, anticoagulants, NSAIDs, nasal steroids, bleeding disorders, vascular conditions, neoplasms, hypertension, alcohol, allergies, or heart failure).
- Assess potential causes of epistaxis and identify any underlying conditions.
- Determine whether bleeding requires hospitalization.

Develop a care plan:

- Initially select compression of nostrils and plugging affected nostril with cotton or gauze.
- If above does not control bleeding, select nasal packing, balloon catheters, electrocautery, thrombogenic foams and gels, vasoconstriction with pharmacologic agents, or tranexamic acid if patient has a refractory case by a medical professional.

Implement the care plan:

- Educate the patient regarding when to seek medical attention.
- Educate the patient on initial management of compression and plugging of nostrils.

Follow-up: monitor and evaluate:

- Monitor patient for resolution of epistaxis.
- Monitor if hospitalization is required.

should then sit up straight and lean forward slightly. Do not have the person lie down or tilt the head backward. With thumb and index finger, firmly pinch the nose just below the bone up against the face. Apply pressure for 5 minutes. If bleeding continues after 5 minutes, repeat process. **KEY CONCEPT** Call a healthcare provider if a nosebleed does not stop after 10 minutes of home treatment, if the patient is having difficulty breathing, uses blood thinners, or has a nosebleed after a severe head injury.[16]

▶ *Nonpharmacologic Therapy*

Nasal packing, which includes nasal tampons or gauze packing, is a common option for treatment of epistaxis. This includes ribbon gauze impregnated with petroleum jelly or polymyxin B-bacitracin zinc-neomycin ointment, or petroleum jelly and 3% bismuth tribromophenate (Xeroform). Nasal balloon catheters are also often utilized, but mainly in more severe posterior bleeding. Electrocautery is used in larger vessels that are found to be the cause of the bleed. Electrocautery is utilization of a special electrical tool to cauterize blood vessels in the nose. Electrocautery must be performed with caution to avoid excessive destruction of health tissues.

▶ *Pharmacologic Therapy*

Oxymetazoline nasal spray often is utilized to manage single anterior bleeds due to its vasoconstriction properties. Patients may utilize oxymetazoline two to three sprays in each nostril twice daily. Vasoconstriction using 4% cocaine solution or phenylephrine 0.25% to 1% solution topically may manage single anterior bleeds, but use is limited. Cocaine is a controlled substance and with cardiovascular effects. Phenylephrine also has cardiovascular effects when absorbed systemically. If bleeding is more severe, local anesthetics such as 4% cocaine or tetracaine or 2% lidocaine solution should be used. Lastly tranexamic acid may be utilized in refractory cases. A Merocel tampon saturated with 500 mg of the IV formulation of tranexamic acid is used to treat this form of epistaxis.[16] Thrombogenic foams and gels such as Quixil fibrin glue, Floseal thrombin gel, Surgicel, Gelfoam, and Avitene are all products that may be used for controlling epistaxis.[16]

Outcome Evaluation

Determining the origin of bleeding is paramount to treatment success. Nosebleeds that are managed in the outpatient setting will stop after proper treatment. If origin is suspected to be posterior, hospitalization is required.

COLD SORES

Introduction, Epidemiology, and Etiology

Cold sores are reoccurring, painful lesions caused by the herpes simplex virus type 1 (HSV-1) and most commonly present on the vermillion border of the lip. Approximately 48% of the US population is seropositive for HSV-1, which is usually transmitted via oral secretions or direct contact with a lesion.[17] Cold sores are the most common manifestation of HSV-1.

Pathophysiology

Upon initial infection, HSV-1 rapidly replicates at the site of contact, which may lead to illness (including a lesion) within days of transmission. It resides in the sensory neurons where it remains for life. Although HSV-1 lies dormant for most of the time, cold sores can reoccur upon viral reactivation. Reactivation is often associated with identifiable triggers including sun exposure, stress, or immunodeficiency.[18]

Clinical Presentation and Diagnosis

Cold sores are often first identifiable by a prodrome tingling sensation at the site of lesion development.[18] If left untreated, the lesion rapidly develops leading to pain and inflammation. Blisters often form and lyse, creating ulceration, scabbing, and finally healing. The entire process may last up to 2 weeks. Diagnosis occurs via clinical evaluation; however, most patients are capable of self-diagnosis.

Treatment

▶ *Desired Outcomes*

The two primary goals of cold sore treatment are:

1. Shorten the duration of, or eliminate, the lesion while limiting pain or discomfort.
2. If prophylaxis is indicated, reduce lesion reoccurrence to allow for improved quality of life.

Depending on the frequency of virus reactivation, the cold sore severity, and other patient-specific factors, successful treatment can include chronic prophylaxis or episodic treatment with oral antivirals, most commonly acyclovir or valacyclovir. No treatment, in the case of mild cases, is also an acceptable approach.

► *Episodic Treatment*

As-needed antiviral treatment upon onset of symptoms:

- All treatment with antivirals should be initiated as early as possible, ideally during the prodrome phase.
- Appropriate for less frequent reactivation, or if the patient can clearly identify prodrome symptoms.

► *Prophylactic Treatment*

Daily suppressive antiviral treatments are appropriate when:

- Patient does not have prodrome (cannot tell when symptoms are initially appearing).
- Episodes cause significant disfigurement or pain.
- Reoccurrence is associated with significant systemic complications, which could include fever, malaise, or ocular involvement.
- Patient is immunocompromised (eg, HIV, malignancies).
- Patient-specific factors, including quality of life and cost.

► *Nonpharmacologic Therapy*

Avoiding triggers (if easily identifiable) can be moderately successful. Excessive sun exposure is a commonly reported trigger and may be mitigated via sunscreen or SPF lip balm.[19] Additional triggers could include fatigue, stress, trauma to the affected region, or illness. Some triggers (eg, stress or illness) may be more difficult to avoid than others, and pharmacologic therapy may be required.

► *Nonprescription Pharmacologic Therapy*

Numerous over-the-counter (OTC) products containing topical pain relievers (eg, benzocaine, menthol) and skin protectants are marketed as cold sore treatments. Although they may provide symptomatic relief, they are often costly and do not treat the underlying infection. Docosanol prevents viral entry into the host cell and is the only topical antiviral product available OTC. It has demonstrated ability to reduce lesion duration in certain studies, though results are largely inconsistent.[20]

► *Prescription Pharmacologic Therapy*

KEY CONCEPT Oral antivirals, including acyclovir, famciclovir, and valacyclovir disrupt DNA synthesis of the herpes simplex virus and are highly effective for treatment and suppression, especially when started early in the disease course.[20] These agents are well-tolerated and are used first line, especially when the patient reports significant disruption in daily life. While all three oral antiviral medication are equally effective for the episodic treatment of cold sores, acyclovir and valacyclovir are also used regularly for prevention (Table 64–2).[21]

Outcome Evaluation

Episodic treatment with oral antivirals can completely eliminate lesion formation if initiated early enough. However, even if initiated after lesion formation, treatment can significantly lessen the cold sore duration, discomfort, and severity. No routine monitoring is recommended with episodic treatment.

Daily prophylaxis is successful if cold sore reactivation is reduced to a level acceptable with the individual patient's lifestyle. Assess hepatic and renal function at least annually.

XEROSTOMIA AND SIALORRHEA

Introduction, Epidemiology, and Etiology

Xerostomia (dry mouth) is a nonspecific symptom resulting from salivary gland hypofunction.[22] Hypofunction may be disease related. Sjögren syndrome, for example, is an autoimmune disease

Table 64–2

Pharmacologic Treatment Used for Cold Sores

Drug	OTC/Rx	Episodic	Prophylaxis	Pros and Cons
Oral Antivirals				
Acyclovir	Rx	**Adults:** 400 mg TID for 5–10 days **Peds:** 20 mg/kg TID for 5–10 days. Max 400 mg/dose	400 mg BID	• Low cost • Frequent dosing • Safe for chronic suppression
Famciclovir	Rx	**Adults:** 500 mg orally twice daily for 5–10 days (initial) **OR** 1500 mg once (recurrent) **Peds:** Dosing not established	N/A	• Simple dosing regimen • Higher cost, reduced availability
Valacyclovir	Rx	**Adults/Peds:** 2 g BID for 1 day	500 mg daily	• Simple dosing regimen • Higher cost • Safe for chronic suppression
Topical Antivirals				
Acyclovir 5% ointment/cream	Rx	Apply 5 times daily for 4 days	N/A	• Limited effectiveness
Docosanol 10% cream	OTC	Apply 5 times daily until healed	N/A	• No prescription required • Consistent effectiveness not established • Higher cost
Penciclovir 1% cream	Rx	Apply every 2 hours while awake for 4 days	N/A	• Limited effectiveness • Frequent dosing

Patient Care Process: Cold Sores

Collect information:

- About the onset of the cold sore, including possible triggers
- About the history related to cold sores (eg, how frequently do cold sores occur, severity, and what treatment has been tried)
- About past medical history (eg, is the patient immunocompromised)
- About social history (eg, how does the cold sore affect the patient's quality of life)

Assess the information:

- Determine whether the patient will require episodic treatment, preventive treatment, or no treatment.
- Assess potential triggers and evaluate nonpharmacologic way to prevent cold sore onset.

Develop a care plan:

- If patient presents with a recently active or oncoming cold sore, initiate oral antiviral (valacyclovir, acyclovir, or famciclovir).

Implement the care plan:

- Recommend avoidance of triggers, if identifiable.
- Educate the patient to take the oral antiviral during the prodrome phase of the cold sore, if possible.

Follow-up: monitor and evaluate:

- Monitor patient for complete lesion healing.
- Discuss preventive therapy with oral antivirals (acyclovir or valacyclovir), if cold sores occur frequently, are severe, or greatly affect the patient's quality of life.

that reduces salivary gland function directly. Dry mouth, however, is also commonly a side effect of medications, including anticholinergics, opioids, antidepressants, and many others (Table 64–3). Prolonged salivary gland hypofunction leads to deterioration of dental hygiene including dental caries, oral candidiasis, halitosis, and gingivitis. Dry mouth resulting from medication use must also be commonly managed within a palliative care setting.

Sialorrhea (drooling) is also a nonspecific symptom that may result from salivary gland dysfunction; however, it is more commonly attributed to neuromuscular dysfunction.[23] Patients at the end of life, as well as those with Parkinson disease, cerebral palsy, stroke, and amyotrophic lateral sclerosis (ALS) are most likely to experience sialorrhea. Nevertheless, antipsychotics (particularly clozapine) and benzodiazepines can contribute to drooling as well. The primary risk associated with drooling is aspiration pneumonia.

Upon presentation for drooling or dry mouth, a thorough history and medication reconciliation must be obtained.

Table 64–3

Medications That Commonly Cause Dry Mouth

Medication Class	Examples of Medications
Anticholinergic medications	Diphenhydramine (Benadryl), oxybutynin (Ditropan), solifenacin (Vesicare), tolterodine (Detrol)
Antidepressants	**SNRIs**—duloxetine (Cymbalta), venlafaxine (Effexor) **SSRIs**—sertraline (Zoloft), fluoxetine (Prozac), paroxetine (Paxil), citalopram (Celexa), escitalopram (Lexapro) **Tricyclics**—amitriptyline (Elavil), nortriptyline (Pamelor)
Antipsychotics	**Atypical**—aripiprazole (Abilify), olanzapine (Zyprexa), quetiapine (Seroquel) **Typical**—haloperidol (Haldol), chlorpromazine (Thorazine), fluphenazine (Prolixin)
Opioids	Fentanyl (Duragesic), tramadol (Ultram), buprenorphine (Subutex), morphine (MS Contin)
Muscle relaxants	Baclofen (Lioresal), tizanidine (Zanaflex), cyclobenzaprine (Flexeril)

Treatment

▶ *Xerostomia Overview*

KEY CONCEPT A critical first step in treating xerostomia should include a thorough review of medications. Elimination of an offending agent should take priority, if possible. Table 64–3 includes a list of common medications that contribute to dry mouth. If elimination of the offending agent is not possible, or xerostomia is not related to medication, nonpharmacologic and pharmacologic options are available and will be discussed below (Table 64–4).

▶ *Sialorrhea Overview*

For sialorrhea, the medications should also be reviewed, primarily looking for clozapine use. Other atypical antipsychotics and benzodiazepines may also contribute to sialorrhea. If medication use is ruled out as the primary cause, treatment should be centered around pharmacologic management, especially if aspiration is a risk. Pharmacologic management is outlined in Table 64–4.

Desired Outcomes

▶ *Xerostomia*

Treatment of xerostomia aims to alleviate symptoms and prevent complications such as dental caries, periodontal disease, halitosis, salivary gland calculi, dysphagia, and oral candidiasis.

▶ *Sialorrhea*

Treatment of sialorrhea aims to control drooling to maintain quality of life and prevent aspiration.

Nonpharmacologic Therapy

Oral hygiene minimizes the long-term risks associated with dry mouth and also decreases the risks of aspiration associated with sialorrhea. Appropriate dental care needs to be prioritized and should include[22]:

1. Brushing teeth with fluoride toothpaste at least twice per day. For those at high risk of dental cavities use fluoride 1.1% gel daily. Alternatively, 5% fluoride varnish or 38% silver diamine fluoride can be applied at a dentist's office every 3 months.
2. Using alcohol-free mouthwash to decrease bacteria and eliminate halitosis.

Table 64–4

Pharmacologic Treatments for Xerostomia and Sialorrhea[24]

Indication	Medication	Dosage Form	Dosing Regimen	Mechanism
Xerostomia	Artificial saliva	**Spray** (Aquoral, Mouth Kote, Oasis Spray) **Orally disintegrating tablet or lozenge** (SalivaSure, Caphosol, Salivate Rx) **Liquid** (Biotene, Numoisyn, Oasis Mouthwash) **Gel** (Biotene Oral Balance Gel)	Use as needed	Topical lubricant that mimics saliva
Xerostomia (Sjögren syndrome)	Cevimeline (Evoxac)	Tablet	30 mg orally TID	Cholinergic agonist
	Pilocarpine (Salagen)	Tablet	5 mg orally QID	Cholinergic agonist
Sialorrhea	Glycopyrrolate (Cuvposa, Glycate)	Oral liquid Injection	0.1 mg sublingually as needed OR 0.2 mg subcutaneously every 4–6 hours (palliative care)	Anticholinergic agent
	Atropine (Isopto Atropine)	Ophthalmic 1% drops (used orally)	1–2 drops placed under the tongue as needed	Anticholinergic agent
	Tropicamide (Mydriacyl)	Ophthalmic 1% drops (used orally)	1–2 drops placed under the tongue as needed	Anticholinergic agent

3. Appropriate denture care, if applicable.
4. Avoid carbonated soft drinks or other sugary foods/beverages where possible.

Proactiself-care to stimulate saliva secretion also include the following:

1. Ensure hydration with water or sugar-free liquids. Avoid caffeine, nicotine, or alcohol.
2. Chew on sugar-free gum or suck on sugar-free hard candies/lozenges.
3. Avoid "mouth-breathing" by making sure the nasal passage is clear.
4. Use humidifiers in dry environments if necessary.

Pharmacologic Therapy

▶ *Xerostomia*

Pharmacologic therapy for dry mouth should be pursued if offending medication cannot be reduced or discontinued, and if nonpharmacologic therapy is inadequate. Artificial saliva is most commonly used, is available over the counter, and is associated with little risk.[25] Dry mouth that is a result of medication use rarely requires cholinergic agonists (pilocarpine or cevimeline), however they are likely to be required in the setting of Sjogren syndrome.[22] Doses for pilocarpine and cevimeline can be found in Table 64–4.

▶ *Sialorrhea*

Atropine ophthalmic drops, up to two drops four times daily, used sublingually are first-line treatment for sialorrhea, especially in the setting of palliative care. If atropine is unavailable, tropicamide ophthalmic drops should be used. Additional options include oral anticholinergic medications including glycopyrrolate, scopolamine, or benztropine.[23]

Outcome Evaluation

Treatment of dry mouth and drooling should be evaluated regularly by the patient's primary care and dental teams. Evaluation should include swallowing assessment, physical inspection, and presence of infection (candidiasis for dry mouth or aspiration pneumonia for drooling). Successful treatment involves improving patient's quality of life and elimination of complications.

Patient Care Process: Medication-Related Xerostomia

Collect information:

- Accurate medication list
- Past medical history, including onset and duration of xerostomia

Assess the information:

- Determine which medications are most likely to cause xerostomia.

Develop a care plan:

- Discontinue or reduce the dose of medications that could exacerbate xerostomia, if possible.
- Select nonpharmacologic options (eg, chewing sugar-free gum) to stimulate saliva.
- If medications are unable to change, and nonpharmacologic therapy is ineffective, select appropriate pharmacologic treatment, beginning with artificial saliva products.

Implement the care plan:

- Educate the patient regarding any nonpharmacologic therapies.
- Educate regarding the importance of dental hygiene, and ensure the patient is engaged with a dentist, if applicable.
- Monitor for worsening of other disease states if treating medication is discontinued or reduced.

Follow-up: monitor and evaluate:

- Monitor patient for improved salivary production.
- Reevaluate the patient if xerostomia does not improve or worsens.

APHTHOUS STOMATITIS (CANKER SORES)

Introduction, Epidemiology, and Etiology

Canker sores are common, recurrent, and painful ulcerative lesions that develop on the oral mucosa. In North America, about 20% of people experience canker sores. While sores may develop infrequently in most, some experience near continuous ulcer activity. The sores tend to occur most frequently in younger individuals and typically occur less and less as one ages.

Pathophysiology

The cause of canker sores is largely unknown, though are thought to occur as a result of immune dysregulation.[26] However, it is likely a combination of numerous factors that may include food allergies, micronutrient deficiencies, and infection. There is evidence that trauma (eg, chewing on insides of cheeks) and stress are triggers.[27]

Clinical Presentation and Diagnosis

Diagnosis is made via physical examination, as canker sores are distinct, round, ulcerations with an erythematous rim surrounding a yellowish center. They are painful and may make eating or drinking uncomfortable. Typically, they are between 3 and 6 mm in diameter. Ulcers are classified into three groups[28]:

1. Minor ulcers, less than 1 cm, usually 3 to 5 mm (most common).
2. Major ulcers greater than 1 cm.
3. Herpetiform ulcers, 1 to 2 mm, present in clusters.

The disease course from onset to healing lasts between 10 and 14 days.

Treatment

Unlike cold sores, there is not a widely effective treatment option available for canker sores. Approach to management should focus on prevention, if possible, and symptomatic management. Most canker sores do not require treatment and are self-limiting.

Patient Encounter 2

A community pharmacist is approached in the store by a 30-year-old woman who has questions about treatments for a "painful and embarrassing cold sore." Upon observation the pharmacist recognizes the cold sore is quite noticeable, has already blistered, lysed, and has scabbed over. The patient reveals that she is a saleswoman, and the cold sore has decreased her confidence when interacting with potential clients. She has been battling this cold sore for 8 days.

Realizing that this cold sore is diminishing this patient's confidence, and possibly damaging her career, what are the most important questions to ask?

What treatment strategy is appropriate to recommend for this patient's current cold sore?

What strategy should be discussed with this patient for cold sore reoccurrences?

▶ *Desired Outcomes*

The primary goals of canker sore treatment are to:

1. Reduce lesion duration and limit pain or discomfort.
2. Reduce lesion frequency to allow for improved quality of life.

▶ *Nonpharmacologic Therapy*

Similar to cold sores, avoidance of triggers (if easily identifiable) can be moderately successful. Avoiding trauma (chewing on inside cheek, dental restorations, hard candies) should be prioritized. Maintaining appropriate dental hygiene may also reduce reoccurrence. In the case of an active ulcer, acidic and spicy foods can increase irritation and should be avoided if possible.

▶ *Pharmacologic Therapy*

Pharmacologic therapy is not curative and is aimed to reduce duration and relieve pain.

Pain Relief Topical anesthetics, namely lidocaine 2% viscous solution, are first-line pain relievers and are applied directly to the lesion. Additional topical anesthetics, including benzocaine and dyclonine as mouth rinses, gels, or lozenges are widely available over the counter.

First-Line Treatment KEY CONCEPT Moderate-to-high-potency topical corticosteroids contribute to quicker ulcer healing and are first-line treatment for individuals who require disease-modifying treatment.[29] These should be initiated as early as possible within the disease course. Dexamethasone elixir (0.5 mg/5 mL) is commonly swished for 5 minutes and spit four times daily. Other high- or mid-potency topical corticosteroids including clobetasol 0.05% ointment and triamcinolone 0.1% may be applied directly to the lesions three times daily. Notably, the ulcer should be thoroughly dried with gauze prior to application.[29]

Oral treatment in Complex Aphthosis Oral treatment should be reserved for complex cases, including lesions greater than 1 cm in diameter and when oral ulcerations occur simultaneously with genital ulcerations. The drug of choice should be oral prednisone 20 to 40 mg daily for up to 7 days.[30] Alternatively, dapsone 25 to 50 mg daily or colchicine 0.6 mg daily has been used, though there is limited evidence demonstrating their effectiveness. Oral prednisone, in combination with the previously mentioned topical corticosteroids, is a first-line treatment.

Treatment of Secondary Infection Although the pathophysiology of canker sores is unlikely of infectious origin, secondary candida infection is possible in severe cases. For this, chlorhexidine rinse, nystatin, or clotrimazole troches are indicated.

Outcome Evaluation

Most canker sores completely resolve without treatment after 10 to 14 days. In cases where topical corticosteroids are needed, no routine monitoring is recommended.

COUGH

Introduction

Cough is the single most common complaint for which patients seek medical care in the primary care setting. It can present due to a number of underlying causes of either infectious or noninfectious origin.

Patient Care Process: Canker Sores

Collect information:

- Onset of the canker sore.
- History related to canker sores (eg, how frequently do they occur, severity, and what treatment has been tried).
- How does the canker sore affect the patient's quality of life?

Assess the information:

- Determine whether the canker sore will require pain relief, topical treatment, or no treatment.

Develop a care plan:

- Select nonpharmacologic therapy as applicable (eg, avoidance of acidic and spicy foods).
- Select topical pain relievers.
- Select a topical corticosteroid if quality of life is significantly hindered.

Implement the care plan:

- Educate the patient regarding any nonpharmacologic therapies.
- Educate that the canker sore will likely heal without treatment in 10 to 14 days.
- Counsel patient when to follow up if symptoms do not resolve.

Follow-up: monitor and evaluate:

- Monitor patient for resolution of canker sore.
- Follow up as necessary for additional episodes.
- Educate the patient that severity and frequency of canker sores lessen as age increases.

Pathophysiology

Cough is an important defense mechanism that the body uses to clear the airways of excessive secretions and foreign material. A complex sensorimotor reflex arc is activated when cough receptors are irritated by stimuli such as accumulated secretions, postnasal drip, or inflammation.[31]

Clinical Presentation and Diagnosis

Cough is classified based on duration of symptoms (Table 64–5). When assessing cough, it is important to gather an accurate patient history with information regarding any environmental or occupational factors and travel exposures as these may be contributing factors to the cough. It is also important to assess whether there are any red flags that could possibly indicate a life-threatening condition (eg, hemoptysis, prominent dyspnea, etc.). If present, these should be addressed and evaluated immediately.[32]

Treatment

▶ *Desired Outcomes*

1. Treat the underlying cause of the cough when possible (refer to appropriate chapters in this book for more information).
2. Promote the safe use of OTC products when used for symptomatic treatment of cough.
3. In patients with an ineffective cough, clear the airways of tenacious secretions and prevent complications such as pneumonia.[33]

▶ *General Approach to Treatment*

When treating the underlying cause of cough, recommendations are consistent with guidance for specific disease states. For example, treatment of cough due to upper airway cough syndrome (UACS) should be treated as discussed in the section of this chapter "Postnasal Drip/Upper Airway Cough Syndrome," and treatment of cough due to an upper respiratory tract infection (URTI) should be treated as discussed in Chapter 72. KEY CONCEPT OTC cough and cold products should be safely chosen based on patient-specific factors, preferably with guidance from a healthcare professional. A description of the most common cough medications as well as some patient considerations can be found in Table 64–6.

In pediatric patients, treatment of cough with OTC medications should generally be avoided, especially in those under the age of 2 years. Per the American College of Chest Physicians (CHEST) guidelines, when cough medications are used for pediatric patients

Table 64–5

Common Etiologies for Cough Based on Classifications[33]

Classification	Duration	Possible Causes
Acute	< 3 weeks	**Most common causes** URTI, also known as the common cold **Other causes** Life-threatening diagnoses: pneumonia, severe exacerbation of asthma or COPD, PE, heart failure Non–life-threatening diagnoses: LRTI, asthma, **bronchiectasis**, UACS, COPD
Subacute	3–8 weeks	Same life-threatening and non–life-threatening diagnoses as acute cough Postinfectious cough GERD Bronchitis
Chronic	> 8 weeks	**Most common causes** UACS secondary to rhinosinusitis Asthma NAEB GERD **Other causes** Smoking ACE inhibitors

ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; LRTI, lower respiratory tract infection; NAEB, nonasthmatic eosinophilic bronchitis; PE, pulmonary embolism; UACS, upper airway cough syndrome, URTI, upper respiratory tract infection

Table 64–6

Common Medications used for Cough Treatment

Drug	Dosing	Considerations
Antihistamines		
Diphenhydramine (Benadryl)	Oral: 25 mg every 4–6 hours or 50 mg every 6–8 hours as needed	Primarily reduce postnasal drip; do not directly suppress cough
Loratadine (Claritin)	Oral: 10 mg once daily	There are several antihistamines (See Table 64–4), but diphenhydramine (first generation) is commonly used for cough. Second-generation antihistamines, such as loratadine, may be preferred due to less sedating side effects Avoid first-generation antihistamines in elderly patients due to anticholinergic side effects such as sedation, blurry vision, dry mouth, constipation, and urinary retention
Decongestants		
Phenylephrine (Sudafed PE Sinus Congestion)	Oral: 10 mg every 4 hours as needed	Primarily reduce postnasal drip; do not directly suppress cough
Pseudoephedrine (Sudafed Sinus Congestion)	Oral: 30–60 mg every 6 hours as needed	Oral decongestants should not be used for longer than 7 days Use with caution in patients with cardiovascular disease, including hypertension
Opioid Agonists		
Codeine with promethazine (Schedule V controlled substance)	Oral: 5 mL (promethazine 6.25 mg/codeine 10 mg) every 4–6 hours (max 30 mL [promethazine 37.5 mg/codeine 60 mg] per 24 hours)	Effective for cough suppression but used primarily for severe cough due to the risk for respiratory depression Avoid use in pediatric patients < 12 years old
Expectorant		
Guaifenesin XR (Mucinex)	Oral: 600–1200 mg every 12 hours as needed	The primary mechanism of action is to remove mucus by reducing viscosity
Antitussives		
Benzonatate (Tessalon Perles) (Rx only)	Oral: 100–200 mg 3 times daily as needed	There have been reports of serious hypersensitivity reactions with benzonatate, such as bronchospasm, laryngospasm, and cardiovascular collapse
Dextromethorphan (Delsym)	Oral: 10–20 mg every 4 hours or 20–30 mg every 6–8 hours; XR: 60 mg twice daily (max 120 mg/24 hours)	Dextromethorphan can reduce cough severity by decreasing the sensitivity of cough receptors and interrupting cough impulse transmission Dextromethorphan comes in several formulations such as capsules, liquid, lozenges, suspensions, syrups, strips, and gel Higher doses of dextromethorphan can increase risk of serotonin syndrome when used with other serotonergic agents. It also carries an increased risk for abuse/misuse which can lead to death, brain damage, etc.

Data from Lexi-Drugs Online™. Lexi-Comp Online™. Hudson, OH: Lexi-Comp, Inc.; 2017. Available from: http://online.lexi.com. Accessed August 8, 2020.

under the supervision of a healthcare professional, dextromethorphan has proven superior to honey for symptom relief; however, honey may provide more relief in comparison to diphenhydramine or placebo.[34] It is also important to note certain safety concerns within the pediatric population. For example, honey should not be used in children less than 1 year old due to the risk of infantile botulism, and medications containing codeine should be avoided in all children due to the risk of respiratory distress.[35]

▶ *Nonpharmacologic Therapy*

Nonpharmacologic therapies that are often used for treatment of cough include the use of a neti pot, mentholated chest rub, honey, demulcents, cough drops, gelatin, and chicken soup. The evidence for these therapies in the treatment of acute cough from the common cold were reviewed in the 2017 CHEST guidelines, but no specific recommendations were made regarding their effectiveness.[35] If honey is used for pediatric patients, the amount of honey given during clinical trials has been dependent on patient age with those between the ages of 2 to 5 years receiving ½ teaspoon, ages 6 to 11 receiving 1 teaspoon, and ages 12 to 18 receiving 2 teaspoons.[36] Additionally, nonpharmacologic therapies should target underlying conditions when applicable (eg, lifestyle modifications for GERD, smoking cessation, etc.). In patients with cystic fibrosis who have an ineffective cough, airway clearance techniques, such as chest physiotherapy or oscillating devices, are often used, but the effect on long-term outcomes is not known.[33]

▶ *Pharmacologic Therapy*

See Table 64–6.

Outcome Evaluation

Monitor patients with chronic cough for symptom resolution after 4 to 6 weeks of optimal treatment. If symptoms persist, consider further investigations.[32]

CROUP

Introduction

Croup is a distinct cough that occurs primarily in children between 6 months and 3 years of age and is most prominent during the fall

Patient Care Process: Cough

Collect information:

- Duration of cough
- Signs and symptoms related to cough
- Past medical history
- Occupational or environmental exposures
- Current medication list

Assess the information:

- Whether the cough is acute, subacute, or chronic.
- Determine severity and acuity of cough to determine need for immediate investigation or hospital admission (ie, any "red flags" that could suggest a life-threatening illness).
- Assess potential causes of cough (eg, infectious, underlying conditions, occupational exposures).
- Assess appropriateness of medication list by ensuring adequate control of underlying conditions and identifying medications that could potentiate cough.
- Ensure patient is an appropriate candidate for OTC medications (eg, avoid cough/cold medications in children lees than 2 years; avoid NSAIDs in patients with cardiovascular history).

Develop a care plan:

- Select appropriate nonpharmacologic therapy as applicable (eg, smoking cessation).
- Optimize therapy for underlying conditions that could potentiate cough.
- Discontinue medications that could potentiate cough.
- Select appropriate treatment of cough symptoms when applicable (eg, antibiotics for bacterial infection).

Implement the care plan:

- Educate the patient regarding any nonpharmacologic therapies.
- Counsel patients regarding indication, duration, directions, adverse effects, and any other applicable information for new medications used to treat cough.
- Advise patient when to follow up if symptoms do not resolve.

Follow-up: monitor and evaluate

- Monitor patient for relief of cough symptoms.
- Monitor patient for safety of new medications used to treat cough.
- Reevaluate patient if symptoms do not resolve after 4 weeks of optimal treatment.

and winter months. It is typically caused by viruses, and the most common viral pathogens are parainfluenza viruses (types 1–3).[37]

Pathophysiology

Croup develops when immune responses to an infection cause swelling in the larynx, trachea, and bronchi. This leads to obstruction of the upper airway and consequent inspiratory stridor and barking cough.[37]

Clinical Presentation and Diagnosis

Croup is primarily a clinical diagnosis. It is characterized by a high-pitched, whistling sound when breathing in (stridor) and a barking cough. Symptoms typically develop abruptly, peak after 24 to 48 hours, and then spontaneously resolve within 1 week.[37]

Treatment

▶ *Desired Outcomes*

1. Achieve symptom improvement within 4 hours of treatment.
2. Achieve complete resolution of symptoms within 1 week.

▶ *General Approach to Treatment*

Treatment of croup is determined by severity of the illness. Scoring systems, such as the Westley Croup Score, are sometimes used to assess the severity of croup. Westley Croup Scores are based on level of consciousness, cyanosis, stridor, air entry, and retractions with higher scores indicating worse croup severity. Patients with mild illness can often be managed at home after receiving a single dose of a corticosteroid, usually dexamethasone, orally or parenterally. Patients with moderate or severe illness should receive a single dose of a corticosteroid along with nebulized epinephrine. Oxygen can also be given if the patient is hypoxic.[37]

▶ *Nonpharmacologic Therapy*

Because croup symptoms can be exacerbated by emotional distress, it can be helpful to minimize agitation in a symptomatic child. Humidified air inhalation has traditionally been used for croup management, but studies have not demonstrated a statistically significant effect on croup scores or hospital admissions when used in patients with moderate croup.[37]

▶ *Pharmacologic Therapy*

Outcome Evaluation

Patients with mild croup can be sent home after receiving a single dose of a corticosteroid if they are stable with no stridor. Patients with moderate or severe croup should be observed for up to 4 hours after receiving treatment. If symptoms do not improve, hospitalization should be considered (Table 64–7).[37]

SORE THROAT

Introduction

Sore throat is a common complaint in the outpatient setting. It is most commonly attributed to pharyngitis, which is inflammation of the mucous membranes of the oropharynx. It is characterized by throat pain, especially when swallowing. This chapter focuses mainly on supportive management of viral and noninfectious sore throat, which does not require antibiotic treatment. For a detailed description of bacterial pharyngitis treatment, please see Chapter 75, Upper Respiratory Tract Infection.

Epidemiology and Etiology

Pharyngitis is a very common complaint, accounting for over 2% to 5% of all primary care visits and approximately 1.8 million annual visits to the emergency room.[38,39] The etiology of sore throat is generally categorized as either infectious or noninfectious, with

Table 64–7

Medications Used for Croup Treatment

Drug	Dosing
Dexamethasone	0.15–0.60 mg/kg orally or parenterally, single dose[38]
Nebulized epinephrine	Up to 0.5 mL of racemic epinephrine 2.25% or Up to 5 mL of L-epinephrine 1:1000; repeat as needed[38]

infectious being the most common origin. Most infectious causes (50%–80%) are viral in nature while a smaller portion (5%–36%) are caused by the bacteria group A β-hemolytic streptococci (GAS). The most common viral pathogens include rhinovirus, coronavirus, influenza, parainfluenza, and adenovirus while less common viral causes include herpes, Epstein-Barr virus, and human immunodeficiency virus (HIV).[39]

Examples of noninfectious causes of sore throat include allergic rhinitis or sinusitis, postnasal drainage, irritation from smoke exposure or dry air, and GERD.[39] Less commonly, severe sore throat can indicate epiglottitis, which is a potentially life-threatening inflammation of the epiglottis, most frequently caused by *Haemophilus influenza* type B (HiB).[40]

Patient Care Process: Croup

Collect information:

- Demographic information (eg, age)
- Onset of cough
- Observe the nature of the cough (eg, stridor, barking cough)

Assess the information:

- Distinguish croup from other etiologies such as cough from bacterial infection.
- Assess severity of the croup as either mild, moderate, or severe by examining level of consciousness, cyanosis, stridor, air entry, and retractions (ie, Westley Coup Score).

Develop a care plan:

- Select a single dose of a corticosteroid such as dexamethasone.
- For patients who have moderate or severe croup, select nebulized epinephrine in addition to dexamethasone.
- Consider giving oxygen if indicated.

Implement the care plan:

- Administer the medications (ie, dexamethasone with or without nebulized epinephrine).
- Counsel parents about the illness.
- Counsel parents on when symptom resolution can be expected.
- Counsel parents on when to seek medical attention if necessary.

Follow-up: monitor and evaluate

- Monitor patient for relief of croup symptoms.
- If patient is stable with no stridor after receiving treatment, consider sending the child home.
- Consider hospitalization if symptoms do not improve.

Clinical Presentation and Diagnosis

Sore throat can be associated with several different etiologies. While symptoms alone cannot determine the etiology of sore throat, understanding symptoms that are commonly associated with different etiologies can help focus the evaluation and exclude life-threatening illnesses (Table 64–8). Different tools, such as the Centor Score, can be used to estimate the probability that the etiology is GAS (see Chapter 75 for more detail).[39]

Treatment

▶ *Desired Outcomes*

1. Treat the underlying cause of sore throat when possible.
2. Avoid improper use of antibiotics.
3. Alleviate pain associated with sore throat.

▶ *General Approach to Treatment*

Patients with signs or symptoms suggesting life-threatening illnesses from severe or invasive infections and upper airway obstruction should be referred to the emergency room immediately. Patients determined to have epiglottitis should have their airway immediately secured and then transferred to an intensive

Table 64–8

Concomitant Symptoms With Sore Throat Based on Etiology

Etiology	Possible Symptoms
Life-threatening illnesses ("red flags")[39]	Respiratory distress Neck pain or stiffness Unilateral throat pain **Trismus**
Epiglottitis[40]	High fever Severe sore throat Difficulty or painful swallowing Shortness of breath Stridor Drooling
Viral infection[38]	Cough Rhinorrhea Conjunctivitis Fatigue Diarrhea Redness or swelling in the back of the throat
GAS infection[39]	Acute onset Fever Tonsillar exudates **Cervical adenopathy**
Fungal infection[38]	Loss of taste Mouth numbness White curd-like plaques Smooth red patches
Tonsillitis[41]	Swollen tonsils Tonsillar exudates Tender lymph nodes Fever Sore throat/difficulty swallowing Bad breath

GAS, group A β-hemolytic streptococci.

Patient Encounter 3

LM is a 10-year-old girl who presents to the pharmacy with her mom. Her mom states they are on their way home from the doctor's office where LM was just diagnosed with influenza A. The mother, who seems agitated that the doctor did not give her daughter any antibiotics to help with the pain, holds up a product with "flu" on the label and asks you if it will help her daughter's sore throat. After looking at the product, you find that it contains aspirin, chlorpheniramine, and dextromethorphan.

Is the product that LM's mother has an appropriate treatment option for LM? Why or why not?

If not, what other medications could you recommend to help with symptomatic relief of LM's sore throat?

What nonpharmacologic recommendations could LM's mother try to ease the sore throat pain?

What would be the best way to address this mother's frustrations with not receiving antibiotics for her daughter?

care unit (ICU). For infectious causes of epiglottis, antibiotics such as second- or third-generation cephalosporins are typically given to cover HiB and then adjusted as needed based on culture and sensitivity results.[40]

Patients with signs or symptoms suggesting tonsillitis should be referred to their primary care provider. Removal of the tonsils (ie, tonsillectomy) is typically reserved patients who have at least seven episodes per year, five episodes per year for 2 consecutive years, or three episodes per year for 3 consecutive years.[41]

For uncomplicated sore throat, the underlying cause should be the target of therapy. Bacterial etiologies should be treated with antibiotics (see Chapter 75), but infectious causes of viral origin will resolve with supportive care alone. Supportive care usually involves pain relief using oral and topical analgesics as well as nonpharmacologic measures.[38] Often, antibiotics are inappropriately prescribed for viral or noninfectious sore throat, largely due to patient concerns of pain. Managing patient's sore throat pain may help to alleviate patient concern and discourage improper antibiotic prescribing.

▶ *Nonpharmacologic Therapy*

Nonpharmacologic therapies used for symptomatic relief of sore throat most commonly involve consuming hot or cold foods and beverages such as tea with honey, soups, melted ice chips, or popsicles. Patients can also use salt-water rinses. Avoiding triggers that cause sore throat, such as secondhand smoke, is also helpful. If a sore throat is due to dry air, a humidifier can also be used. There is very little literature supporting these recommendations, but they are likely not harmful.

▶ *Pharmacologic Therapy*

There is currently a lack of evidence-based recommendations for therapeutic management of noninfectious sore throat. Data from nonantibiotic treatments of infectious sore throat is often extrapolated for treatment of noninfectious sore throat. **KEY CONCEPT** Pharmacologic treatment for sore throat typically includes a systemic oral analgesic with or without a topical agent for pain relief (Table 64–9).[38]

Single-dose oral corticosteroids (OCS), such as dexamethasone, can reduce the duration of pain in sore throat; however, the

Table 64–9

Oral and Topical Analgesics

Drug	Dosing	Considerations
Oral Analgesics		
Acetaminophen (Tylenol)	Oral: 325–650 mg every 4–6 hours (max 4 g/day)	Oral analgesics have a slower onset of action but longer duration of action compared to topical analgesics Both acetaminophen and NSAIDs have demonstrated benefits such as sore throat pain relief; however, patient-specific factors must be considered (eg, avoid NSAIDs in patients with high risk of cardiovascular or GI adverse effects)[39] Aspirin is contraindicated in pediatric patients <18 years old who have or are recovering from chickenpox or flu symptoms due to the risk of Reye syndrome
Acetaminophen/caffeine (Excedrin Tension Headache)	Oral: 1 g/130 mg every 6 hours as needed (max 3 g/390 mg per 24 hours)	
Ibuprofen (Advil)	Oral: 200–400 mg 3–4 times daily (max 3200 mg/day)	
Aspirin (Bayer Aspirin)	Oral: 325 mg to 1 g every 4–6 hours as needed (max 4000 mg/day)	
Topical Analgesics		
Phenol (Chloraseptic)	Lozenges: Use 2 lozenges every 2 hours as needed Spray: Apply one spray to the affected area, keep in place for 15 seconds, then expectorate; may repeat every 2 hours as needed Rinse: Gargle or swish for 15 seconds, then expectorate; repeat every 2 hours as needed (max 12 times/day)	Quicker onset of action and shorter duration than oral analgesics The phenol lozenges can be used in pediatric patients starting at age 6, the spray starting at age 3, and the rinse starting at age 4 months (if using Ulcerease with a clean swab).
Benzocaine (Hurricaine, Cepacol)	Lozenge (with menthol): Allow 1 lozenge to dissolve slowly; may repeat every 2 hours as needed Spray: Apply one spray on affected area or throat up to 4 times daily	
Menthol (Vicks VapoDrops)	Drops: Dissolve 1 drop slowly in the mouth; repeat every 2 hours as needed	

Data from Lexi-Drugs Online™. Lexi-Comp Online™. Hudson, OH: Lexi-Comp, Inc.; 2017. Available from: http://online.lexi.com. Accessed August 8, 2020.

Patient Care Process: Sore Throat

Collect information:

- Past medical history (eg, allergic rhinitis or sinusitis, postnasal drainage, irritation from smoke exposure or dry air, GERD)
- Current medication list
- Concomitant signs and symptoms to determine etiology of sore throat

Assess the information:

- Assess severity of sore throat to exclude potentially life-threatening causes such as epiglottis.
- Assess potential causes of sore throat (eg, infectious or noninfectious).
- Ensure patient is an appropriate candidate for OTC medications (eg, avoid NSAIDs in patients with high cardiovascular or gastrointestinal risk).

Develop a care plan:

- Select nonpharmacologic therapy as applicable (eg, tea with honey, soups, melted ice chips, popsicles).
- Avoid antibiotic therapy for noninfectious causes of sore throat.
- Determine medications that could potentiate sore throat.
- Select appropriate treatment of sore throat symptoms when applicable (eg, oral analgesics with or without topical analgesics) based on patient-specific factors.

Implement the care plan:

- Discontinue medications that could potentiate sore throat if possible.
- Educate the patient regarding any nonpharmacologic therapies.
- Institute treatments determined to be appropriate.
- Counsel patients regarding indication, duration, directions, adverse effects, and any other applicable information for OTC medications.

Follow-up: monitor and evaluate

- Monitor patient for relief of sore throat symptoms.
- Monitor patient for safety of new medications used to treat sore throat.
- Refer the patient for further investigation if symptoms do not resolve after 7 to 10 days.

absolute benefit is lower in patients with less severe sore throat. Therefore, OCS are generally reserved for symptomatic relief of severe sore throat.[42] Other treatments that have been studied for sore throat, specifically in the postoperative setting, include inhaled fluticasone propionate, intravenous dexamethasone, lidocaine, ketamine gargle, topical NSAIDs, and perioperative amylmetacresol/dichlorobenzyl lozenges.[43] These agents do not have a clear place in therapy for routine treatment of sore throat. There is inconsistent evidence for the management of sore throat using alternative treatments such as zinc, herbals, and acupuncture. Ibuprofen 25-mg lozenges have proven effective in clinical trials for relief of sore throat; however, the lozenge formulation is not yet available.[44]

Outcome Evaluation

Most cases of pharyngitis spontaneously recover within 7 to 10 days. Symptoms associated with streptococcal pharyngitis typically resolve after 24 to 72 hours of antibiotics.[39] If symptoms do not improve, patients should be reevaluated for other underlying causes of sore throat.

LARYNGITIS

Introduction

Laryngitis is defined as inflammation of the larynx and vocal fold mucosa. Dysphonia, or impaired voice production, is the most common sign of laryngitis. Most episodes of laryngitis are acute, which can be defined as lasting less than 3 weeks.[45] Chronic episodes, which last longer than 3 weeks, can also occur. While there are several different possible etiologies, this chapter will focus on the most common causes of both acute and chronic laryngitis.

Epidemiology and Etiology

Dysphonia-related disorders, such as laryngitis, are very common and can produce direct costs somewhere between \$577 and \$953 per patient per year.[46]

Acute laryngitis is self-limited and most often caused by voice misuse, URTIs, or the influence of weather conditions.[46] Infectious causes are usually due to viral pathogens such as parainfluenza, rhinovirus, influenza, and adenovirus. However, bacterial causes have also been identified in acute laryngitis.

Chronic laryngitis is most commonly caused by voice overuse but can also be caused by irritants such as purulent sinus drainage or tobacco.[46] Laryngitis is associated with GERD and is considered an extraesophageal syndrome; however, it is important not to assume GERD as the sole cause since laryngitis can have multiple etiologies.[47] Other less common etiologies of chronic dysphonia can be neurologic (eg, Parkinson disease, spasmodic dysphonia), musculoskeletal (eg, muscle tension dysphonia), rheumatologic (eg, rheumatoid arthritis), or pulmonary (eg, chronic obstructive pulmonary disease [COPD]).[46]

Clinical Presentation and Diagnosis

Physical examination and patient history are essential to identify both acute and chronic causes of laryngitis (Table 64–10). If dysphonia is associated with red flags such as stridor, neck mass, unexpected weight loss, or concomitant neurologic symptoms, the patient should be further evaluated using laryngoscopy to visualize the larynx. In less alarming scenarios, laryngoscopy is only necessary if dysphonia does not improve or resolve after 4 weeks of observation.[46]

Other symptoms can be observed in combination with dysphonia and can be used in assessing the underlying cause of laryngitis. For example, patients with acute laryngitis resulting from an infection will experience symptoms that are consistent with an URTI. Patients who have laryngitis that is associated with GERD will typically have concomitant manifestations that are characteristic of esophageal syndrome (Table 64–10).[47]

Table 64–10

Assessment of Patients Presenting With Laryngitis

Signs/symptoms	Throat discomfort, change in voice, cough, dysphagia, secretion If caused by infection: Sore throat, painful swallowing, rhinorrhea, dyspnea, postnasal discharge, and congestion[46] If associated with reflux: Heartburn, chest pain, regurgitation, dysphagia[47]
Physical examination[46]	Full head and neck examination Evaluation of patient's voice Inspection and palpation of the neck for masses or lesions Observation of swallowing and breathing Indirect mirror laryngoscopy if possible
History[47]	Tobacco use Occupation (eg, teacher, singer) Surgical history involving the head, neck, or chest or recent intubation
Procedures/ imaging[47]	Laryngoscopy CT or MRI *not* recommended prior to laryngoscopy

Treatment

▶ *Desired Outcomes*

1. Achieve improvement or complete resolution of dysphonia as soon as possible, usually within 4 weeks for acute laryngitis, although preferably sooner.
2. Improve the patient's quality of life and restore effective verbal communication.

▶ *General Approach to Treatment*

Appropriate treatment begins with identifying the underlying cause of laryngitis. After assessing the patient through history, physical examination, and laryngoscopy, if needed, treatment can be directed accordingly.

▶ *Nonpharmacologic Therapy*

KEY CONCEPT There are several nonpharmacologic interventions that can be recommended for the prevention and supportive treatment of laryngitis. These include maintaining adequate hydration, resting the voice, using a humidifier in dry air environments, and avoiding smoking or secondhand smoke exposure. Patients should also be encouraged not to strain their voice even by whispering. Throat clearing/coughing, alcohol, caffeine, and anticholinergic medications, such as antihistamines, antipsychotics, or tricyclic antidepressants, can worsen dysphonia.[46]

In chronic reflux laryngitis, common nonpharmacologic recommendations include avoidance of certain foods (eg, coffee, alcohol, chocolate, fatty food, acidic food), smoking cessation, and weight loss.[47]

Other nonpharmacologic therapies, such as voice therapy or surgery, are less commonly used and depend on the underlying etiology. For example, voice therapy is effective for the treatment of muscle tension dysphonia, and surgery can be used in cases of malignancy or benign vocal fold lesions.[46]

▶ *Pharmacologic Therapy*

Antibiotics should *not* typically be prescribed for the treatment of acute laryngitis. While erythromycin has shown subjective improvement in the treatment of patients with laryngitis, no studies have demonstrated objective improvement with the

Patient Care Process: Laryngitis

Collect information:

- Duration of dysphonia
- Any concomitant signs and symptoms
- Medication list
- Past medical history (eg, other conditions, voice misuse, exposure to weather conditions)
- Social history (eg, smoking history/exposure to secondhand smoke, occupation)
- Perform physical examination
- Perform laryngoscopy if there are any alarming symptoms or concomitant neurologic symptoms

Assess the information:

- Determine whether the laryngitis is acute or chronic.
- Assess potential causes of laryngitis and identify any underlying conditions.
- Assess medication list to determine if any could be worsening dysphonia (eg, antihistamines, antipsychotics, tricyclic antidepressants).

Develop a care plan:

- Select nonpharmacologic therapy (eg, maintaining adequate hydration, resting the voice).
- Determine medications that could worsen dysphonia.
- Select appropriate pharmacologic treatment for any underlying conditions (eg, proton pump inhibitor for laryngitis associated with GERD).
- For persistent dysphonia, refer to otolaryngology or a voice clinic with laryngologists and SLPs.

Implement the care plan:

- Discontinue medications that could worsen dysphonia, if possible.
- Institute appropriate treatments.
- Educate the patient regarding nonpharmacologic treatment for laryngitis.
- Counsel patients regarding any new medications used to treat underlying conditions.
- Advise patient when to follow up if symptoms do not resolve.

Follow-up: monitor and evaluate

- Monitor patient for resolution of dysphonia.
- Refer patient for further investigation if symptoms with an unknown cause persist after 4 weeks.

use of antibiotics. Most cases are viral, and the use of antibiotics can potentiate adverse effects, increased costs, and antibiotic resistance.[45] Steroids also should not be routinely prescribed due to lack of evidence showing beneficial outcomes and increased adverse events. However, there may specific situations based on laryngoscopy results or other conditions that may justify their use.[46]

For laryngitis that is associated with GERD, twice-daily dosing of a proton pump inhibitor (PPI), such as omeprazole 20 or 40 mg twice daily, may be used. The use of a PPI should only be considered in patients who have concomitant esophageal GERD syndrome, and a step down of therapy should be initiated after 2 months of treatment.[47]

Botulinum toxin is sometimes used for the off-label treatment of certain types of laryngeal dystonia such as spasmodic dysphonia (SD). This is not curative for SD but is used primarily for symptom control.[46]

Outcome Evaluation

Most episodes of acute laryngitis will resolve spontaneously within 7 to 10 days regardless of treatment. If symptoms do not improve or resolve within 4 weeks, the patient should undergo laryngoscopy. Referral to otolaryngology or a voice clinic with laryngologists and speech-language pathologists (SLPs) should not be delayed in patients with persistent dysphonia.[46]

Abbreviations Introduced in This Chapter

ACE inhibitors	Angiotensin-converting enzyme inhibitors
ALS	Amyotrophic lateral sclerosis
COPD	Chronic obstructive pulmonary disease
GERD	Gastroesophageal reflux disease
HSV-1	Herpes simplex virus-1
NHANES	National Health and Nutrition Examination Survey
NSAIDs	Nonsteroidal anti-inflammatory drugs
OCS	Oral corticosteroids
OTC	Over the counter
PE	Pulmonary embolism
PPI	Proton pump inhibitors
SD	Spasmodic dysphonia
SPF	Sun protection factor
TDIT	Threshold, discrimination, identification test
UPSIT	University of Pennsylvania Smell Identification Test

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65

Allergic Rhinitis

Hanna Phan and Michael Daines

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the basic pathophysiology of allergic rhinitis (AR).
2. Define mild versus moderate–severe AR, persistent versus episodic, and differentiate between seasonal, perennial, and episodic AR.
3. Differentiate the categories of pharmacotherapy choices for treatment of AR based on mechanism, efficacy on symptom type (eg, ocular, nasal congestion), and side effect profile.
4. Identify situations in which a referral to an allergy specialist is needed.
5. Describe an approach for treatment and monitoring for treatment of mild and moderate–severe AR based on patient-specific factors.
6. Identify the differences in approach to the treatment of AR for children, pregnant women, and the elderly compared with the routine approach in adults.

INTRODUCTION

Rhinitis is inflammation of the lining of the nose and contiguous parts of the upper respiratory tract. Allergy is only one of numerous causes of rhinitis. Signs and symptoms of allergic rhinitis are noted in Table 65–1. Some patients suffer concurrently from both allergic rhinitis (AR) and one or more types of nonallergic rhinitis (NAR). This is sometimes called mixed rhinitis (MR). Because ocular symptoms (eg, itching and/or redness of eyes, tearing) frequently occur in association with AR, some sources use the term allergic rhinoconjunctivitis. This acknowledges involvement of the bulbar and palpebral conjunctivae in the allergic process.[1-4]

AR will be emphasized in this chapter, but some mention will be made of NAR (see chapter 64 for further information about nonallergic rhinitis). The most common causes of NAR are shown in Table 65–2. KEY CONCEPT AR is an allergen-induced, immunoglobulin E (IgE)-mediated inflammatory condition of the lining of the nose and upper respiratory tract. This pathophysiologic feature differentiates AR from NAR. AR has traditionally been categorized as either seasonal or perennial.[5-8] Seasonal allergic rhinitis (SAR) is attributed to inhaled allergens (**aeroallergens**) that have a seasonal variation. These allergens are usually encountered outdoors and are most often grass, tree, or weed pollens and substances from molds and fungi. Length of seasonal exposure depends on geographic location and climatic conditions. Perennial allergic rhinitis (PAR) is attributed to aeroallergens that are present in the patient's environment year-round and are usually encountered indoors.[6-8] Common perennial allergens are the house dust mite, indoor molds and fungi, insects (especially cockroaches), and companion animals (pets). Some patients are affected by AR year-round, but have seasonal exacerbations. These people are probably allergic to both seasonal and perennial aeroallergens. Other patients have only episodic manifestations. These people are probably allergic to aeroallergens that are only episodically encountered (eg, cat at a friend's house).

Because these traditional categories of seasonal and perennial AR are imperfect and help little with therapeutic management decisions, another system for categorizing AR has been suggested by guidelines.[6-10] This alternative system categorizes the manifestations by a combination of frequency and severity. There are two divisions of frequency: intermittent and persistent. Intermittent frequency is defined as AR manifestations occurring less often than 4 days per week or for fewer than 4 consecutive weeks. Persistent frequency is defined as AR manifestations occurring for 4 or more days per week *and* for 4 or more consecutive weeks. Severity is categorized as either mild or moderate–severe based on presence of the following symptoms: sleep disturbance, impairment of daily activity (including leisure and/or sports), impairment of work/school, and troublesome symptoms. Mild manifestations are those of which none of the listed symptoms are present. Moderate–severe severity includes those patients with manifestations of AR with at least one of the listed symptoms present. Additionally, AR impact on comorbidities such as asthma and sinus disease which can also be considered when evaluating a patient's AR severity. Clinicians should consider referring patients with comorbid conditions, such asthma, to an allergy specialist. See Table 65–3 for a summary of these categories of AR.

EPIDEMIOLOGY AND ETIOLOGY

Prevalence of AR is up to 40% depending on geographic location, with highest incidence in children, usually manifesting after age 2 years. AR remains the most common immunological disease, which is still relatively underrecognized and managed. It can reduce quality of life, interfering with attendance and performance at school and work, impacting overall societal as well as healthcare expenditures.[9]

Table 65–1

Clinical Presentation and Diagnosis of Allergic Rhinitis[1-4]

Typical Symptoms

- Rhinorrhea (usually clear and bilateral; primarily anterior but may be posterior [postnasal drip])
- Sneezing
- Itching (mostly nasal, but also palate, throat, eyes, ears)
- Nasal congestion (not in all patients, but when present, usually the most troublesome symptom)

Other Symptoms

- Ocular manifestations (itch, redness, tearing, **chemosis**, periorbital edema)
- Sleep disturbances often with fatigue, asthenia, malaise, and irritability
- Presenteeism (impaired performance at work or school)
- Absenteeism from work or school
- Quality-of-life impairment (including social function)
- Headache, mild facial or ear pain or fullness
- Cough (especially in those with concurrent asthma)
- Children (especially): snorting, sniffling, clearing the throat, learning or attention problems, poor appetite

Signs (Especially Common in Children)

- Pale, boggy nasal mucosa
- Rubbing the nose upward (allergic salute; may create horizontal crease just above tip of nose)
- Rubbing/scratching of eyes
- Mouth breathing
- Dark circles under the eyes (allergic shiners)
- **Dennie-Morgan** lines or folds under the eyes

Diagnosis

- Typical symptoms, confirmatory signs, especially in association with exposure to allergen triggers
- Other diagnostic testing usually optional but may be necessary to rule out nonallergic causes or if immunotherapy is considered (appropriate physical examination, specific IgE antibody testing by either skin testing or in vitro serum testing, other specialized testing)
- Several sources particularly good for differential diagnosis of nonallergic rhinitis[3,13,15]
- Vasomotor rhinitis—sneezing and itch less common than AR; anosmia more common
- Unilateral symptoms—refer for possible obstruction, anatomic abnormality, tumor, cerebrospinal fluid (CSF) leak
- Atrophic rhinitis—older adults, history of nasal surgery

Etiology of AR is multifaceted, both genetic and environmental in nature. Some studies have suggested that in addition to possible genetic predisposition, inadequate environmental exposure (eg, to animals) in early life may increase risk for AR.[11,12] The major risk factors for AR are a family history of atopy (AR, asthma, eczema, or food allergies); elevated serum IgE levels (especially before the age of 6 years); higher socioeconomic class; positive skin test results; exposure to particulate air pollution; maternal smoking; firstborn status; and emigration into a Western industrialized environment.[3,6,8,9,11,12,] Certain disorders commonly occur with AR. The most important example is asthma. While different percentages are reported, most patients with asthma have rhinitis symptoms (many of which are AR), and only somewhat fewer with AR have asthma.[3,13] In fact, there is evidence that AR can predispose to the development and/or worsening of asthma.[1,3,13] Other conditions that can occur with AR include allergic conjunctivitis, eczema, sinusitis, sleep disorders, otitis media with effusion, and the oral food allergy syndrome.[3,9]

Table 65–2

Types of Rhinitis[1-3]

Allergic (see Table 63–3 for details)

Nonallergic

- Vasomotor (also known as perennial nonallergic, idiopathic, and autonomic rhinitis) (triggered by irritants, cold air, exercise/running, or unidentified factors)
- Food/meal related (gustatory)
- Infectious
- NARES (nonallergic rhinitis with eosinophilia syndrome)
- Occupational (caused by protein allergens [IgE-mediated] or by irritants [probably non–IgE-mediated])
- Hormonally related (hypothyroidism, pregnancy, menstrual cycle related, and some drugs [see below])
- Drug-induced
  - Angiotensin-converting enzyme inhibitors (ACEIs)
  - α_1-blockers (used for treatment of BPH and HTN)
  - Phosphodiesterase-5 inhibitors (used for treatment of ED)
  - Aspirin and other NSAIDs (as an isolated side effect of AERD)
  - Oral contraceptives and hormone replacement therapy
  - Miscellaneous agents have been implicated (calcium channel blockers, some diuretics, centrally acting α_2 agonists, risperidone, gabapentin)
- Atrophic rhinitis
- Rhinitis associated with inflammatory or immunologic diseases (eg, granulomatous infections, SLE, Wegener granulomatosis, sarcoidosis, Churg–Strauss syndrome)
- Malignancy

Mixed

Combination of allergic and nonallergic manifestations

AERD, aspirin-exacerbated respiratory disease; BPH, benign prostatic hyperplasia/hypertrophy; ED, erectile dysfunction; HTN, hypertension; IgE, immunoglobulin E; NSAIDs, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.

Table 65–3

Categories of Allergic Rhinitis[7-9]

Based on Etiologic Category

- Seasonal—symptoms due to seasonal aeroallergens; present only during specific portions of the year, with length of exposure dependent on geographic location and climate conditions
- Perennial—symptoms present throughout the year due to environmental aeroallergens, such as indoor allergens (eg, dust mites)
- Episodic—symptoms present only during intermittent exposure to allergen trigger (eg, exposure to a friend's pet)

Based on ARIA 2016 Update

- Symptoms: sleep disturbance, interference with daily activities (including leisure or sport), impairment of school/work, and troublesome symptoms
- Mild versus moderate–severe
  - Mild—none of the above symptoms present
  - Moderate–severe—presence of any one of the above symptoms
- Intermittent versus persistent
  - Intermittent—symptoms are present for less than 4 days/week, or for less than 4 consecutive weeks
  - Persistent—symptoms are present for 4 or more days/week and for more than 4 consecutive weeks
  - Any one of the four possibilities of these variables can occur: mild intermittent, mild persistent, moderate–severe intermittent, and moderate–severe persistent

PATHOPHYSIOLOGY

AR is an IgE-mediated disorder of people who are allergy prone. Initial contact is required to sensitize the patient to subsequent exposures. Patients with an inherited tendency to allergic disorders produce T-helper lymphocyte type 2 (Th-2)-directed responses, including production of specific IgE antibodies, to one or more allergens. Many types of cells, mediators, and intermediate substances (including cytokines) are involved. In response to subsequent exposures to the trigger antigen(s), there is an early-phase and often a late-phase allergic response. This distinction has therapeutic implications.[1,3,5,6,8,9]

During the early phase, the trigger allergen becomes bound to IgE that is fixed to mast cells in the nasal mucosa. This occurs within minutes of subsequent exposure to the antigen. Mast cells degranulate and release preformed mediators, the most important of which is histamine. This stimulates more mast cells, as well as macrophages, eosinophils, and basophils to produce more substances, including cysteine leukotrienes and prostaglandin D_2. These mediators bind to receptors in the nose and facilitate many of the manifestations of AR. The resultant vasodilation, mucosal edema, and hypertrophy all contribute to nasal congestion. Clear, watery, and often profuse rhinorrhea is also characteristic in this early phase, a result of mucous secretion and increased vascular permeability. Sneezing and nasal itch are other prominent features of the early phase. Many patients also have ocular symptoms.[1,3,5,6,8,9]

The late phase occurs in about 50% of AR sufferers. It can begin as soon as 2 hours after the early phase and usually peaks between 6 and 12 hours. The late phase involves a second release of many of the mediators of the early phase. In addition, the late phase is characterized by an inflammatory component caused by infiltration of several cell types into the nasal mucosa. The most significant manifestation during the late phase is nasal congestion that is often severe and long lasting.[1,3,5,6,8,9]

A phenomenon known as the priming response or nasal hyperresponsiveness is also of importance. This means that prolonged and/or repeated allergen exposure makes it easier to stimulate mediator release and symptoms. A vicious cycle results in which smaller doses of allergen can create symptoms (ie, the threshold is lowered). Thus, even when pollen exposure is decreased, symptoms may continue. In some patients, the threshold is lowered to the degree that even irritant substances (eg, formaldehyde, tobacco smoke, perfumes, automobile exhaust, and other environmental pollutants) may cause symptoms, on a nonallergic basis.[1,3,5,6,8,9]

TREATMENT

General Approach and Desired Outcomes

Guideline documents have been published on AR.[6-9,14] They provide some of the basis for the sections that follow. Although guideline documents are highly regarded by many, the patients enrolled in the randomized clinical trials that are a major basis for their conclusions and recommendations are not always representative of patients in a primary practice population.[15] **KEY CONCEPT** The general approach for treatment of AR is fourfold: avoidance of allergen triggers, patient/caregiver education, pharmacotherapy, and immunotherapy.[3,6,7,8,9,10,13] Recommended approaches to AR management begin with allergen avoidance and patient/family education. If allergen avoidance is not sufficient and/or symptoms necessitate treatment, pharmacotherapy is utilized. Failure to respond to first-line over-the-counter (OTC) or prescription AR medication may warrant referral to an allergy specialist for further assessment. Based on assessment by a specialist, immunotherapy may also be an option in selected patients.

Education of the patient and the patient's support system is essential.[6] All parties need to understand the potential seriousness of AR (including complications such as asthma) and the chronic, recurrent nature of AR. All should be told about the treatment options, including their relative advantages and disadvantages. Proper understanding and use of current medication in the patient's regimen should be assured. A better educated patient and support system will result in a better relationship with healthcare providers and hopefully will optimize patient outcomes.

KEY CONCEPT The goals of treatment of AR are to minimize the frequency and severity of symptoms, prevent comorbid disorders and complications, improve the patient's quality of life, improve work attendance and productivity and/or school attendance and performance, and minimize adverse effects of therapy. Until a cure is established, these are the only realistic goals.

Patient Encounter 1, Part 1

Mrs. K, a regular customer in your community pharmacy, asks your advice about helping her 7-year-old son, LK. She states, LK has "constant" sneezing, runny nose, watery and itchy eyes, as well as "throat" itching. You determine LK has AR that could benefit from treatment.

What additional information is needed to make a recommendation in treatment?

Nonpharmacologic Therapy

Avoidance of allergen triggers is a core component of nonpharmacologic therapy of AR. Patient and caregiver education is fundamental in reducing preventable allergen exposure. Avoidance of allergen triggers, to the extent they have been identified and to the extent such avoidance is possible, underlies the treatment for all patients with AR (Table 65–4).[6-9]

▶ *Saline*

Nasal administration of saline is an alternative and often used as an adjunctive, nonpharmacological treatment of AR.[3,6,16,17] This therapy may benefit any patient with rhinitis, including those with vasomotor rhinitis.[5] Saline may be administered as drops or a spray, but the irrigation mode of administration is popularly known by several terms, including neti pot, nasal wash, nasal douche, nose bidet, and as nasal irrigation. Although less effective than intranasal corticosteroids (INCSs), it has been shown to improve sneezing and nasal congestion. It can be used either alone or as add-on therapy. The formula provided by the American Academy of Allergy, Asthma and Immunology (AAAAI) should be followed for those making their own saline nasal irrigation solution.[16] Iodized salt is not recommended as it may be irritating. Hypertonic saline seems to have no advantage over 0.9% sodium chloride. Tap water should not be used as it is not adequately filtered or treated; thus, there is risk for bacteria and protozoas (eg, amoebas) containimation. Instead, distilled, or sterile water should be used. Or, alternatively, boiled, and cooled tap water (boil for 3–5 minutes, then cooled to lukewarm).[17] Administration can be accomplished while the patient is in the shower or leaning over a sink. The head is bent forward and downward, then

Table 65–4

Allergen Avoidance Measures[6,8-10]

Allergen avoidance underlies all other treatments of AR

There are several limitations to allergen avoidance:
- Allergen(s) must be identified.
- Literature support for a clinically significant improvement in symptoms from allergen avoidance is meager.
- Quality of life may be negatively impacted by forced removal of a pet from the household.

Outdoor plant pollen and mold/fungi parts:
- Limit outdoor exposure, especially during high pollen conditions (warm sunny days with wind and low humidity) and during mold/fungi spore release (shortly after rains).
- Wear a face mask during activities that disturb soil and decaying vegetation.
- Keep windows and doors closed.
- Use central air conditioning, maintain clean equipment, and change appropriate air filters regularly. Avoid use of an evaporative cooler (eg, swamp cooler).

Indoor allergens (house dust mite, mold/fungi, cockroaches, and pets):
- Use central air conditioning, maintain clean equipment, and change appropriate air filters regularly. Avoid use of an evaporative cooler (eg, swamp cooler).
- Maintain humidity below 50% and maintain clean equipment.
- Clean frequently to prevent mold growth (dilute bleach with detergent).
- Avoid exposed food and garbage to deter insects.
- Clean kitchen frequently.
- Use roach traps that facilitate their removal.
- Vacuum frequently and use a high-efficiency particulate air (HEPA) filter.
- Minimize carpeting, fabric covered furniture, and fabric wall/window coverings.
- Cover bedding (pillows, mattresses, box springs) with allergen-proof, zippered cases.
- Launder bedding frequently, in hot water (> 130°F or 54°C) to kill mite ova.
- Consider **acaricide** (eg, benzyl benzoate) treatment of carpets to kill mites and ova.
- Put items that cannot be laundered (eg, soft toys) in a plastic bag and freeze.
- Keep pets out of bedroom and bathe cats weekly, if possible.

Irritants:
- Avoid, as possible, all exposure to smoke, chlorine fumes, formaldehyde fumes, and other substances identified as irritant triggers (eg, perfumes, newspaper ink).

Table 65–5

Intranasal and Oral Medications for AR[6-8,13,14,18,19]

Corticosteroids
Intranasal[a] (budesonide [OTC], beclomethasone, ciclesonide, flunisolide, fluticasone [propionate and furoate] [OTC], mometasone, triamcinolone [OTC])
Oral (rarely used, eg, prednisone)

Antihistamines
Intranasal[a] (azelastine, olopatadine)
Oral[b]
- First generation/sedating (cautious use in selected patients) (most OTC depending on strength: diphenhydramine, chlorpheniramine, clemastine, and others)
- Second generation/low- or nonsedating[a]: loratadine (OTC), cetirizine (OTC), fexofenadine (OTC), levocetirizine (OTC), desloratadine

Combination antihistamine/corticosteroid
Intranasal (azelastine and fluticasone propionate)

Mast cell stabilizer/cromone
Intranasal (cromolyn [OTC])

LTRA
Oral (montelukast)

Antimuscarinic
Intranasal (ipratropium)

Decongestant
Intranasal (short-term use) (tetrahydrozoline, phenylephrine [OTC], naphazoline [OTC], oxymetazoline [OTC])
Oral[b] (phenylephrine [OTC]; pseudoephedrine [BTC[c]])

[a] First-line choices.

[b] Some products combine an antihistamine with a decongestant, sometimes with other ingredients.

[c] Behind the counter (OTC plus other requirements necessary; see the Decongestants section of text).

Note: All products are prescription unless indicated as OTC.

tilted to the side opposite the treated nostril. Then, with a bulb syringe or similar device, slowly introduce about 4 oz (118 mL) of the warm saline solution into one nostril. Soon, the solution will run out of the opposite nostril. The position of the head should be adjusted as necessary to avoid the solution running into the ears or down the throat. Devices for nasal irrigation should be also cleaned appropriately and regularly to minimize possible microbial growth.[17]

Nasal irrigation is one delivery method, although the optimal method (spray, drops, nebulizer, or irrigation) is not known. Optimal frequency of administration is also not known. Nasal irrigation is usually given twice daily, but use of smaller volumes as spray products may be given up to four times daily. Side effects are usually limited to minor local nasal irritation, but nausea has been reported.

Pharmacologic Therapy

KEY CONCEPT Routine first-line agents for the treatment of AR are intranasal corticosteroids (INCSs) and oral (or possibly intranasal) antihistamines. Secondary agents, each of which may have a first-line role in selected patients, include oral (and rarely intranasal) decongestants, an intranasal mast cell stabilizer (ie, cromolyn), an oral leukotriene receptor antagonist (LTRA) (ie, montelukast), an intranasal antimuscarinic (ie, ipratropium), and intranasal saline irrigation. See Table 65–5 for intranasal and oral medications for the treatment of AR. Treatment selection, among common medications for AR, can vary based on best available evidence (ie, guidelines, clinical trials, etc) for a given medication in addition to the severity of AR of a given patient.[3,6-9,12] See Figure 65–1. In all cases, therapy must be individualized, in cooperation with the patient. Considerations include frequency and severity of specific symptoms, realistic avoidance measures, patient age, patient preferences for route of administration, tolerance of side effects, adherence issues, comorbid disorders, and concurrent therapy. Some clinicians may elect to use an action plan for AR with their patients, similar to that used for asthma.[6] Some patients may benefit from having an AR action plan, depending on their AR severity and complexity of therapy.

▶ *First-Line Agents*

Corticosteroids Corticosteroids are usually administered by the intranasal route for the treatment of AR. Occasionally, a short

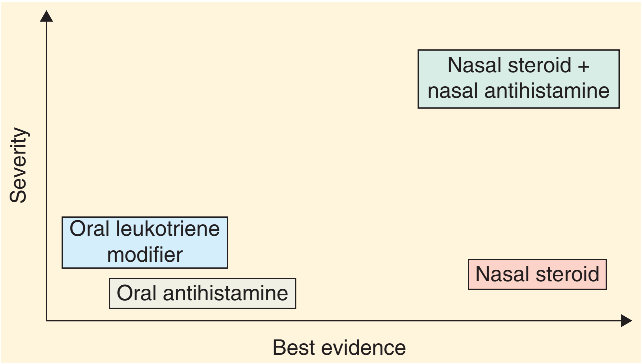

FIGURE 65–1. Evidence-based treatment options for AR based on current guidelines.[7-10]

course of oral therapy (eg, prednisone burst and taper) is necessary. Oral corticosteroids may be used to overcome severe nasal congestion, particularly due to rhinitis medicamentosa (see the section on Decongestants). Parenteral administration of corticosteroids for AR is discouraged due to side effects.[5,8,13]

INCSs provide very good relief for sneezing, itching, and rhinorrhea, and even nasal congestion and ocular symptoms. Nasal congestion is often the most bothersome symptom of AR, and the most difficult to control. This is probably because it results from inflammation that predominates in the late phase of the allergic response. **KEY CONCEPT** INCSs are the most effective therapy for AR, especially for nasal congestion. Their anti-inflammatory mechanism of action probably contributes to this superiority.[3,5,13] The majority of contemporary literature suggests that INCSs are superior to intranasal antihistamines, to oral antihistamines even when combined with a leukotriene antagonist, and to a leukotriene antagonist alone.[3,6,8-10] In recent guidelines by the American Academy of Allergy, Asthma, and Immunology (AAAAI) and American College of Allergy, Asthma, and Immunology (ACAAI), and British Society for Allergy and Clinical Immunology (BSACI), INCSs are recommended as monotherapy versus in combination with an oral antihistamine for initial treatment of nasal symptoms of seasonal allergic rhinitis in patients ages 12 years and older.[6-9,14] Additionally, in patients ages 15 years and older with moderate-to-severe SAR, INCSs are recommended over an LTRA such as montelukast, for initial treatment.[8,14]

There are currently eight INCS products available in the United States, including two different salt forms of fluticasone. Most (budesonide, ciclesonide, fluticasone furoate, mometasone, and triamcinolone) are used once daily. However, fluticasone propionate may be given either once or twice daily, beclomethasone is usually given twice daily, and flunisolide is given two or three times daily. There is no good evidence that any single product is superior in efficacy. INCSs are best given regularly, as the onset of action usually takes up to 12 hours and the maximum effects may be delayed up to 14 days.[3,6-9,13,14,18] In some people the onset is within 3 to 4 hours, so these agents may even be used on an as-needed basis.[6,19] When nasal congestion is severe, intranasal administration may not be effective due to limited exposure to the nasal mucosa. Short-term use of intranasal decongestants may facilitate better exposure. See Table 65–6 for INCS products.

The correct technique for administration of intranasal medication is important for optimum efficacy. Consult the individual product labeling for specific instructions. Also see Table 65–7 for

Table 65–6

Intranasal Corticosteroids

Generic (Brand) Name	mcg/dose	Adult Dosages (Each Nostril)	Pediatric Dosages (Each Nostril)[a]
Beclomethasone dipropionate (Beconase AQ)	42	1–2 sprays twice daily	6 years and older: 1–2 sprays twice daily, once symptoms are controlled decrease dose to 1 spray twice daily 12 years and older: 1–2 sprays twice daily
Beclomethasone dipropionate (Qnasl [HFA MDP])	40 80	— 2 sprays once daily	4–11 years: 1 spray once daily 12 years and older: 2 sprays once daily
Budesonide[a] (Rhinocort Aqua)	32	1–4 sprays once daily	6–11 years or older: 1–2 sprays once daily 12 years and older: see adult dosing
Ciclesonide (Omnaris)	50	2 sprays once daily	2–11 years: 1–2 sprays once daily (perennial AR)
Ciclesonide (Zetonna [HFA MDP])	37	1 spray once daily	6 years and older: 2 sprays once daily (seasonal AR) 12 years and older: 2 sprays once daily (perennial AR) 12 years and older: 1 spray once daily (seasonal AR)
Flunisolide	25	2 sprays two or three times daily	6–14 years or older: 1 spray three times daily or 2 sprays twice daily 15 years and older: 2 sprays two or three times daily
Fluticasone furoate[a] (Flonase Sensimist)	27.5	2 sprays once daily	2–11 years or older: 1–2 sprays once daily 12 years and older: 2 sprays once daily
Fluticasone propionate[a] (Flonase)	50	1–2 sprays once daily or 1 spray twice daily	4–11 years or older: 1 spray once daily
Mometasone[a] (Nasonex)	50	2 sprays once daily	2–11 years or older: 1 spray once daily 12 years and older: 2 sprays once daily
Triamcinolone acetonide[a] (Nasacort AQ)[b]	55	2 sprays once daily	2–5 years: 1 spray once daily 6–12 years: 1–2 sprays once daily

[a]Available OTC.

mcg, micrograms; HFA, hydrofluoroalkane (propellant); MDP, metered-dose pump.

From Ref. 19, includes any off-label dosing.

Table 65–7

Administration Instructions for Intranasal Sprays[20,21]

1. Clear the nose of mucus and debris.
2. Consult product labeling for preadministration instructions (eg, shaking the container, priming the spray pump).
3. Do not tilt head backward. This increases drug lost down the esophagus. This decreases efficacy and increases the potential for systemic absorption and thus systemic side effects.
4. For non-pump nasal sprays, keep head upright. For nasal pump sprays, bend the head forward (flex the chin onto the chest) so that the nose is the lowest portion of the head.
5. Use the contralateral hand to insert the spray nozzle into one nostril (ie, the left hand for right nostril).
6. Use the other hand to occlude the opposite nostril (the one not being medicated).
7. Aim the spray or drops toward the outer (lateral) inside surface of each nostril and away from the nasal septum.
8. Breath in slowly but deeply through the medicated nostril.
9. Repeat this procedure to apply medication to the other nostril.
10. Consult the product labeling for instructions on cleaning the device.
11. See the text for information about preparation and use of saline irrigation.

general instructions for the optimal administration of intranasal sprays. The technique described maximizes exposure of the drug to the nasal mucosa to optimize efficacy and minimizes both exposure to the nasal septum and loss of medication down the esophagus.[20,21]

Most patients tolerate INCSs very well. Local side effects include nasal burning, irritation, and dryness, which may occur in 2% to 10% of patients.[3,19,22] Also, 2% to 8% of patients may experience mild epistaxis.[3,22] This may be partly due to administration technique. Perforation of the nasal septum is very rare. This can be minimized by proper administration technique (see Table 65–7), specifically, directing the spray laterally and away from the (medial) nasal septum.[20-22]

The older INCSs (beclomethasone, flunisolide, and budesonide) have significant absorption, whereas, among the newer products, including fluticasone, ciclesonide, and mometasone have bioavailability of less than 1% to 2%.[22] The decreased absorption minimizes systemic side effects. However, there is still some concern for hypothalamic–pituitary–adrenal (HPA) axis suppression (eg, growth suppression), osteoporosis, and ocular effects (eg, glaucoma, cataracts), especially in cases with multiple sources of steroid exposure. There is no confirmation that INCSs *cause* posterior subcapsular cataracts, increased intraocular pressure, or decreased bone density; however, those with risk factors for these conditions should be monitored carefully for their development.[3,22,23] The consensus about INCSs, when used alone, and systemic side effects, even those related to HPA axis suppression, is that most products are safe. Clinicians should examine total corticosteroid exposure (ie, from all sources, nasal, inhaled, oral, etc) in assessing potential risk for adverse effects from systemic exposure.[22,23] Ultimately, patient preference for a specific INCS may be determined more by cost, availability, and formulation differences that affect odor and aftertaste.

Antihistamines Antihistamines used for AR treatment are administered by either the oral or the intranasal route. These agents interact with the histamine type 1 (H_1) receptor. They are technically inverse agonists, not competitive antagonists; however, there may be little clinical significance to the difference. These drugs bind H_1 receptors, keeping them in the inactive state. This downregulation of H_1 receptor activity results in a decrease in end-organ effects.[24]

Activation of H_1 receptors in the nose, upper airway mucosa, and the eye produce the common manifestations of AR (sneezing, itching, rhinorrhea, nasal congestion, and ocular symptoms). The antihistamines are very effective for the sneezing, itching, and rhinorrhea. There is some improvement of nasal congestion, but less so than for the other symptoms. There is also benefit for the ocular symptoms (eg, itching, redness, tearing). Intranasal administration is more effective than oral administration for the nasal congestion but less effective for the ocular symptoms. The onset of action by oral administration is usually within 1 to 2 hours and for intranasal administration within 15 minutes.[3,5,13] Antihistamines probably provide better relief when used continuously during symptomatic periods, but they are also effectively used only when needed for mild and/or intermittent or episodic AR.

The oral agents are divided into first- and second-generation drugs. The first-generation agents are distributed among six chemical classes, including the more sedating ethanolamine class (eg, diphenhydramine) and the least sedating alkylamine class (eg, chlorpheniramine). Most sources now discourage the routine use of the first-generation agents for AR. This is due to their central nervous system (CNS) and antimuscarinic side effects. The CNS effects are primarily sedation and impairment of cognitive function and performance of tasks. Decision making and driving or work/school performance can be impaired even when the patient is unaware of any overt effects.[5,6] The major antimuscarinic effects include blurred vision, dry mouth, urinary retention, and constipation. The only possible advantage of the antimuscarinic properties is an additional effect to decrease rhinorrhea. Another disadvantage of the first-generation antihistamines is that most are administered three to four times daily due to shorter half-life. Patients who take other sedative substances may have an additive effect from the antihistamine. Those taking any other medications with antimuscarinic properties may experience additive effects from the antihistamine. The elderly are, in general, more sensitive to both types of adverse effects.[3,5,13]

Currently available oral second-generation H_1 antihistamines are cetirizine, loratadine, and acrivastine. All except acrivastine are available as a single agent, and some are marketed in combination with the decongestant pseudoephedrine. As these agents are active metabolites of preceding agents, fexofenadine (preceding agent was terfenadine, removed from marked due to cardiac toxicity), levocetirizine, and desloratadine are informally labeled as "third-generation" antihistamines, but sometimes classified as "second-generation" antihistamines. The second-generation antihistamines have less antimuscarinic activity than the first-generation agents. Based on current literature, no single H_1 antihistamine (first- or second-generation) is clearly superior in efficacy; however, very few head-to-head comparative studies have been conducted. Individual variation is likely, and patients may need to try more than one product to realize optimal benefit. The oral second-generation antihistamines are effective for the sneezing, itching, and rhinorrhea of AR but less effective for the nasal congestion. They also improve ocular symptoms. Intranasal antihistamines are somewhat better for nasal congestion.[5,10]

Fexofenadine has virtually no sedative effects, even at doses higher than recommended. Loratadine and desloratadine are not sedative at recommended doses but can be at higher doses. Cetirizine, levocetirizine, and acrivastine have some sedative effects, even at recommended doses. All the oral second-generation agents require some dosage reduction with impaired renal function, but specific recommendations vary with creatinine clearance.[19] Most of the oral second-generation antihistamines can be administered once daily (except for the lower dosage forms of fexofenadine and the acrivastine combination product).

There are only two intranasal antihistamine products available in the US market as of December 2020, azelastine and olopatadine. These are considered second-generation agents, although they also have anti-inflammatory effects.[25] Both are available only by prescription. The most common side effect of these products is a bitter taste. This is more common with the original formulation of azelastine (Astelin) and less common with olopatadine. A specific formulation of azelastine (Astepro) has less bitter taste.[26] There is also an available combination product with azelastine and fluticasone propionate. There is enough systemic absorption to cause sedation in some patients using intranasal antihistamines, with possible greater incidence with azelastine compared to olopatadine. See Table 65–8 for the single-agent second-generation antihistamine products.

KEY CONCEPT Second-generation antihistamines are often effective alone, specifically for mild or intermittent AR. They are preferred over first-generation antihistamines because of fewer side effects. Although effective for most symptoms of AR, they are less

Patient Encounter 1, Part 2

Additional history from Mrs. K and LK reveals the following information.

LK's symptoms began about 2 month ago after they moved into a new home in the countryside. Both Mr. and Mrs. K have seasonal allergies and are treated with oral antihistamines. LK's symptoms have become problematic in that he had to miss school today due to his inability to stop itching his eyes and the constant runny nose. Mrs. K reports that symptoms are daily and caused LK to not sleep well for the past 2 months. Mrs. K states that LK was not recently sick (ie, no fever, aches), and he is not congested. His nasal secretions are clear. Mrs. K tried using something over-the-counter, she could not remember the name but remembered the pink color of the oral liquid. She reports that it made LK "super hyper" and has not since been given medication for his symptoms.

How would you classify LK's presumed allergic rhinitis? Why?

What OTC-specific recommendations would you make for initial management of LK's presumed AR?

Table 65–8

Single-Agent Second-Generation Antihistamine Products (Oral and Intranasal)

Oral Dosage Forms

Generic (Brand) Name	Formulation	Usual Adult Dosage	Usual Pediatric Dosage
Cetirizine[a,b] (Zyrtec, generic)	5, 10 mg tabs/chew tabs; capsule 5 mg/5 mL syrup	5–10 mg once daily	6–11 mo; 2.5 mg once daily 12–23 mo; 2.5 mg once or twice daily 2–5 yo; 2.5–5 mg once daily or 2.5 mg twice daily
Desloratadine[b] (Clarinex)	5 mg tabs; 2.5 mg/5 mL syrup 2.5, 5 mg orally disintegrating tabs	5 mg once daily	6–11 mo; 1 mg once daily 1–5 yo; 1.25 mg once daily 6–11 yo; 2.5 mg once daily
Fexofenadine[a,b] (Allegra, generic)	60, 180 mg tabs, 6 mg/mL suspension 30 mg orally disintegrating tabs	60 mg twice daily or 180 mg once daily	2–11 yo; 30 mg twice daily
Levocetirizine[a] (Xyzal)	5 mg tabs 2.5 mg/5 mL solution	5 mg once daily	6 mo–5 yo; 1.25 mg once daily 6–11 yo; 2.5 mg once daily
Loratadine[a,b] (Claritin; Alavert, generic)	10 mg tabs and cap; 5 mg/5 mL syrup and susp; 10 mg disintegrating tabs; 5 mg chewable tab	10 mg once daily	2–5 yo; 5 mg once daily

Intranasal Sprays

Generic (Brand) Name	mcg/spray	Usual Adult Dosage (Each Nostril)	Usual Pediatric Dosage (Each Nostril)
Azelastine (Astelin, Astepro)[c]	137	1–2 sprays twice daily	5–11 yo; 1 spray twice daily
Olopatadine (Patanase)	665	2 sprays twice daily	6–11 yo: 1 spray twice daily

[a] Available OTC.

[b] Available in combination with pseudoephedrine (consult labeling for pediatric dosage).

[c] Available in combination with fluticasone propionate (consult labeling for dosage)

Note: Acrivastine is available only with pseudoephedrine and so is not included in this table.

mo, months old; yo, years old.

Data from Lexi-Comp OnlineTM , Pediatric & Neonatal Lexi-Drugs OnlineTM , Hudson, Ohio: Lexi-Comp, Inc.; December 31, 2020, includes any off-label dosing.

effective than INCSs for nasal congestion. Intranasal administration is more effective than oral administration for nasal congestion. Most patients can use oral second-generation products. Others may prefer the intranasal route of administration, but they require a prescription. If nasal congestion is not relieved, addition of a decongestant is reasonable, either alone or as a combination product (see Decongestant section). Perhaps even the combination of an oral with an intranasal antihistamine is reasonable for some patients, depending on their preferences. Other pharmacologic agents can be combined with oral and/or intranasal antihistamines, as necessary for optimal control of symptoms. The intranasal combination product of azelastine and fluticasone may be appropriate for some patients. In recent guidelines, for patients age 12 years and older for initial management of moderate-to-severe SAR, use of both INCS and intranasal antihistamine may be considered.[6-10,13,14]

▶ *Adjunctive or Secondary Choice Agents*

Decongestants Decongestant drugs are useful only for nasal congestion. This results from their α_1-adrenergic agonist activity, which causes vasoconstriction in the nasal mucosa. They provide no benefit for the sneezing, itching, rhinorrhea, or the ocular manifestations. Decongestants can be given alone, either by the oral or by the intranasal route.[3,10,13] Also, numerous combination products are available, consisting of a decongestant with an antihistamine (and sometimes other ingredients). There are some special considerations for use of decongestants in pediatric and pregnant patients (see the Special Populations section).

Oral decongestant products are currently limited to pseudoephedrine and phenylephrine. Pseudoephedrine has been changed from truly OTC to a more controlled "behind-the-counter" (BTC) status because it is an ingredient in the illicit manufacture of methamphetamine. Some manufacturers changed the ingredients of their products by replacing pseudoephedrine with phenylephrine to maintain shelf presence in the OTC area. However, much controversy surrounds the efficacy of oral phenylephrine. Most contemporary literature suggests that the currently recommended adult dose is minimally effective as a nasal decongestant, even compared to placebo in SAR.[3,27]

The side effects of orally administered decongestants most often affect cardiovascular function or the CNS. The side effects are primarily due to sympathetic stimulation and are usually dose-related. Some elevation of blood pressure may occur, but in normotensive and well-controlled hypertensive patients, the elevation is usually small, especially when used briefly or intermittently. In patients with known cardiovascular disease, such as hypertension, use of intranasal agents is recommended to minimize systemic exposure and side effects. Insomnia, nervousness, irritability, and anxiety are relatively common CNS side effects. Some patients may have decreased appetite, tremors, headache, and even hallucinations. Men with benign prostatic hyperplasia (BPH) and other patients with disorders causing bladder outlet obstruction may have increased urinary retention due to α_1 stimulation of the urethral sphincter.[28]

The intranasal agents currently available in the United States include the OTC products phenylephrine, oxymetazoline, and naphazoline. Intranasal application of decongestants provides rapid and effective relief of nasal congestion. This therapy may provide relief for nasal congestion, even for those patients already on INCSs. However, the continuous use of intranasal decongestants often causes a paradoxical rebound phenomenon of persistent nasal congestion, called rhinitis medicamentosa.[29] Although some patients do not develop rhinitis medicamentosa, even after several weeks of continuous use of intranasal decongestants, the usual recommendation is to use them for no more than 3 consecutive days.[28,29] Intranasal decongestants can cause local side effects, including stinging, burning, dryness, and even sneezing. These are usually mild and well-tolerated. Due to very limited absorption, the intranasal route rarely causes systemic side effects.[3,28] Administration technique should be optimized as described in Table 65–7. Should rhinitis medicamentosa occur, the best management is first to discontinue the decongestant, possibly with a taper to minimize worsening the situation. However, the response to withdrawal is often delayed for days. Therefore, it may be necessary to start INCSs and/or begin a short course of oral corticosteroid.[29] KEY CONCEPT Whenever possible, intranasal decongestants in AR should be limited to short-term use to overcome severe nasal congestion and to facilitate improved efficacy of other intranasal agents. The intranasal administration of decongestants should usually not exceed 3 consecutive days. Despite the usual good tolerance of recommended doses of oral decongestants, caution is warranted when they are used in patients with cardiac disease (dysrhythmias, angina pectoris, heart failure), hypertension, cerebrovascular disease, bladder outlet obstruction (including BPH), glaucoma (especially closed angle), hyperthyroidism, and possibly diabetes.[3,28] The choice between the two routes of administration is often based on several considerations, including cost, convenience, patient preference, speed of onset (within 30 minutes orally, within 5–10 minutes intranasally), and side effects.

Mast Cell Stabilizer Cromolyn is available as an OTC intranasal product. The mechanism of action in AR is mast cell stabilization. The drug binds to mast cells and prevents release of the mediators of AR that would otherwise result from allergen exposure. The drug is moderately effective, but less so than both INCSs and oral or intranasal antihistamines. It does have effects on both early and late phases of AR. Its effects begin within 4 to 7 days of use but may not be maximal for up to 2 weeks. However, it can be used effectively on an as-needed basis for episodic exposures to allergen. Cromolyn is very well-tolerated. The most common side effects are mild local stinging and/or burning, sneezing, unpleasant taste, and possibly nosebleed. A disadvantage is the frequency of administration. At least initially, it should be used four times daily. Some patients may need only two or three daily doses when used continuously after the first few weeks at four times daily. It is most useful for patients with mild or intermittent symptoms, especially in the pediatric population and in pregnant women.[3,10,13,30]

Leukotriene Receptor Antagonist Leukotrienes are involved in the pathophysiology of AR and, in particular, contribute to the nasal congestion in the late phase. There is some difference of opinion about benefits of LTRAs. LTRAs are recommended by some guidelines in the case of PAR (not SAR) over oral antihistamines.[8] Most sources indicate good benefit for nasal congestion and rhinorrhea, some benefit for ocular symptoms but less for nasal itch and sneezing compared to INCSs and antihistamines.[31] Montelukast is the only LTRA approved for treatment of AR. It is marketed as oral granules and as both chewable and regular tablets and is administered once daily. The combination of montelukast with an oral antihistamine may have improved efficacy over either agent alone, according to some sources; however, even the combination is probably not better than INCSs.[3,6,8,14] The onset of action of montelukast is delayed for a day or more. The drug is usually considered to be very well-tolerated. However, there are postmarketing reports of neuropsychiatric events,

Patient Encounter 1, Part 3

Mrs. K and LK come back to speak with you. It has been over 6 months since you last spoke with them about LK's allergies. LK is getting nosebleeds occasionally and stopped wanting to use any nasal product and only uses the OTC antihistamine you originally recommended. About 6 months ago, LK was diagnosed with asthma and was started on fluticasone 44 mcg HFA MDI 2 puff twice a day and as-needed albuterol. LK is due to see his pediatrician for a follow-up visit this week, and he still has nasal symptoms (rhinorrhea, some congestion) and eye itching. LK's allergies are now beginning to affect his breathing with some additional use of his albuterol over the last couple of weeks (ie, used once each week at night, with relief of symptoms).

What suggestions would you offer for control of LK's symptoms, now? What should be monitored?

including sleep disturbances, depression, and suicidal ideation, as well as headache, gastrointestinal (GI) disturbances, skin rash, and Churg–Strauss syndrome.[19] A boxed warning was added by the Food and Drug Administration (FDA) for montelukast, strengthening existing warning about behavioral and mood-related changes. Use of this medication for allergic rhinitis should be reserved for those who are not treated effectively with or cannot tolerate first-line agents (eg, INCS, oral or inhaled antihistamines). Clinicians should consider benefits and risks of its use in a given patient.[32]

Antimuscarinic Agent Ipratropium is currently the only antimuscarinic agent indicated for treatment of AR. Systemic absorption is minimal. It is available by prescription as an intranasal spray. Its use is limited to those patients whose rhinorrhea has not been controlled by other therapy (antihistamines and/or INCSs).[3,13] There are two strengths available: 0.03% and 0.06%. The 0.03% product is approved for AR in children as young as 6 years of age. This agent may be particularly helpful for patients who have vasomotor (idiopathic, autonomic) rhinitis or those who may have a mixed etiology.[5] Local side effects are usually limited to nasal and oral dryness, throat irritation, and mild epistaxis.[3,10,13,19]

Biologic Agents Biologic agents such as omalizumab are currently not FDA approved for AR nor are they recommended for routine use in treatment of AR. Omalizumab is a monoclonal antibody that binds to IgE. The product is approved for moderate-to-severe persistent asthma with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids in patients ages 6 years and older. Omalizumab is not approved for treatment of AR as of September 2020. It is administered by subcutaneous injection. Dosage is determined by the patient's circulating IgE levels. The cost is high compared with that of other modes of therapy. Investigational use has demonstrated possible efficacy in AR, although relative efficacy is unknown. Its use is best limited to those with concurrent asthma and AR until further data are known.[33] Dupilumab, an anti-IL-4 receptor α-antagonist, is approved as an add-on maintenance treatment for inadequately controlled chronic rhinosinusitis with nasal polyps as well as moderate-to-severe persistent atopic dermatitis where topical prescription therapies are not adequately effective or not tolerated and as add-on maintenance treatment for moderate-to-severe asthma that is eosinophilic or oral corticosteroid dependent. It is not approved for AR as of September 2020; however, there are data describing efficacy and safety of its use in adults with PAR and comorbid asthma.[34,35] Data regarding safety and efficacy of biologic agents, such as omalizumab and dupilumab, for routine use in the treatment of AR are currently lacking.

Immunotherapy Immunotherapy could be considered a type of pharmacotherapy. Allergen-specific immunotherapy (SIT) involves repetitive dosing of allergen(s). This approach to treatment can be considered for patients with moderate–severe AR, especially those who have limited response to usual therapy (eg, intranasal steroid, antihistamine) and limiting environmental exposure.[36-39] Immunotherapy is almost always initiated by an allergist or otolaryngologist, after referral for specific allergen testing to determine individualized therapy. This type of therapy is intended for patients with IgE-mediated AR by history and confirmed with specific allergen testing. Historically, immunotherapy was considered for patients in three categories.[3] The first were those with severe, complicated, or worsening rhinitis. This was partly for additional diagnostic testing to rule out nonallergic causes of rhinitis. The second were those patients with AR who did not tolerate or responded poorly to appropriate pharmacotherapy. The third were those patients who had a single, or one major allergen identified, for which there was an immunotherapy product available for treatment. In addition, some patients requested immunotherapy based on superior and durable effectiveness.

Currently, the role of any other healthcare provider is limited to referral of appropriate candidates to allergy specialists.

Currently, SIT can be done via subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT). The major advantage of SLIT over SCIT is ease of administration. Possible adverse effects of SLIT include oral or ear pruritis, throat irritation, tongue pruritis, and mouth edema, with decrease in occurrence and severity of such events in subsequent years of treatment. Potential adverse effects of SCIT include local injection reactions, systemic reactions, and rare, allergic, anaphylaxis reactions. The first dose of immunotherapy is given in the prescriber's office, for purposes of safety. Subsequent doses are self-administered by the patient. SCIT is always done under medical supervision, requiring regular clinic visits and observation after SCIT administration.[39,40] Potential risk factors for SLIT-associated anaphylaxis include previous systemic reaction to SCIT, severe or uncontrolled asthma, acute infection, interruption of dose regimen, and oral lesions.[36] Both SCIT and SLIT can induce long-term symptom remission and have been found to be effective for SAR as well as perennial mite allergy. Comparisons between SCIT and SLIT as well as use

Patient Encounter 2, Part 1

Mr. J is a 35-year-old man. He works full time as an assistant coach for the local college basketball team. He reports that he has had allergies since starting his position and moving to town about 1 year ago. He moved from New York City to Ann Arbor, Michigan, and since his move, he reports daily sneezing, itchy, watery eyes. He is currently on loratadine 10 mg daily and fluticasone nasal spray daily. He reports his treatment worked initially but has not worked as well in the last few months.

What additional information do you need to better evaluate Mr. J?

of some available agents in pediatric populations are currently lacking.[41]

As of September 2020, four products have been FDA approved for administration as SLIT. There are currently two products for grass pollen: Oralair and Grastek. Oralair contains a mixture of pollens from Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass and is approved for adults and children ages 5 to 65 years.[42] Grastek, which contains only Timothy grass pollen, is approved for adults and children ages 5 to 65 years.[43] Ragwitek is a SLIT for short ragweed pollen, approved for adults ages 18 to 65 years.[44] Odactra, the SLIT for house dust mites, is approved for adults ages 18 to 65 years.[45]

Complementary and Alternative Medicine Therapy Complementary and alternative therapy (CAM) for AR has been reviewed.[46] For example, capsaicin (Capsicum annuum), once regarded as CAM, in the form of a nasal spray, is being investigated as a possible agent in treatment of AR. Previous data behind this compound were inconclusive, citing the need for future studies.[47] Consistent evidence for efficacy has not been established, and there are some safety concerns. In general, data regarding efficacy and safety of CAM products for routine treatment of AR are currently limited.

Special Populations

▶ *Children*

KEY CONCEPT Generally, the treatment of AR in children is the same as it is for adults. There are, however, limitations in terms of FDA-approved products for different age groups. Also, depending on the age of the patient, there may be administration issues with some products. Most children affected by AR are more than 2 years old, because usually, several years of antigen exposure is required to establish sensitization. Children who have rhinitis before the age of 2 should be evaluated for other etiologies.[48]

There has been concern about use of combination cough and cold products (many contain an antihistamine and a decongestant) in children due to side effects. Most negative outcomes have resulted from inadvertent overdosage, often by giving the same drug from more than one product concurrently. These products are discouraged in children less than 4 years old.[48]

First-generation H_1 antihistamines are discouraged for children as they are for adults, due to the possible detrimental effects on school performance and learning. They may also cause paradoxical CNS stimulation in the very young age (< 2 years old). Second-generation (less sedating) H_1 antihistamines (primarily for mild or intermittent symptoms) or INCSs (for moderate–severe or persistent manifestations) are first-line modes of therapy. Antihistamines may need to be used even for more severe and/or persistent symptoms in those children who have difficulty with use of intranasal products. If necessary, these two classes can be combined.[48] See Table 65–8 for dosages of second-generation antihistamines by age groups for which they are indicated. Special care should be given to avoid administration of the same medication from different (especially combination) products. The side effects of second-generation antihistamines in children are similar to those for adults.

See Table 65–6 for dosages of INCSs by age groups. The consensus about INCSs and systemic side effects, especially delay in growth, is that most products are safe. Three INCSs, mometasone, fluticasone furoate, and triamcinolone, are FDA approved for children as young as 2 years of age. The local side effects of INCSs are the same in children as for adults.[22,48]

Other therapy options may be worth consideration for some pediatric patients. Montelukast provides an oral alternative, especially for those who are too young to cooperate with intranasal administration of corticosteroids. It may be used in combination with an oral antihistamine for additional efficacy. Another option for mild or intermittent symptoms is intranasal cromolyn, primarily due to its excellent safety.[3,6-10,14,48] This OTC product is labeled for use in children 2 years of age and older. Intranasal ipratropium may be considered for patients 5 years of age or older and may benefit unresponsive rhinorrhea.[48]

▶ *Pregnant Women*

Women who have AR may suffer an exacerbation of symptoms during pregnancy. However, only minor changes in the routine approach to therapy are necessary because of the pregnancy. Nasal saline irrigations are safe, effective, and improve the response to most other modes of therapy. They can be the foundation of AR therapy for pregnant patients.[28,49] Physical exercise increases vasoconstriction of the nasal mucosa, decreasing congestion and rhinorrhea. External adhesive strips can be used to help keep the nares open, especially during sleep. Second-generation antihistamines are generally considered safe, based on an increasing number of studies and experience; however, clinicians should review specific pregnancy data for specific agents. Data are somewhat lacking regarding fetal harm regarding various INCSs.[49] Data on cromolyn demonstrate no perinatal mortality or prematurity in nearly 300 infants when it was used in asthmatic mothers, thus may be a relatively safe option to consider.[49] The disadvantages are frequent administration and less efficacy than antihistamines and INCSs. Montelukast has also not demonstrated increased risk of adverse perinatal outcomes, but some recommend it primarily in those with concurrent asthma or who have demonstrated a good response prior to pregnancy.[49] Ipratropium may be useful for troublesome rhinorrhea.[9] Oral decongestants are best avoided, especially in the first trimester. If nasal congestion is severe enough to warrant a decongestant, the intranasal route of administration is preferable, due to decreased systemic exposure. If use is absolutely needed, clinicians should recommend that the maximum duration of use to maximum of 2 to 3 days.[49]

Patient Encounter 2, Part 2

Mr. J returns months later after having taken your advice. He is now noticing an increase in symptoms since taking up golfing as a hobby. He was prescribed a combination nasal corticosteroid and antihistamine by his primary care physician, but it does not seem to be helping much with his symptoms. He does saline nasal rinses several times a week with limited relief. He has missed work several times in the last few months due to unbearable congestion and sinus headaches, in addition to his nasal and ocular itching. One of his friends tells him about "allergy treatments" that helped his "bad allergies" that were once a "shot" but heard there now noninjectable options. Mr. J asks you, "would this be something I can do? Would it help me with my allergies?"

What is your explanation to Mr. J about his inquiry, and what is your recommendation at this time?

▶ *Breast-Feeding Women*

There is available information about the relative safety of AR medication use in breast-feeding women.[49] Budesonide is probably the safest INCS, and loratadine is probably the safest antihistamine if treatment is needed. Intranasal cromolyn is also considered relatively safe. Nasal saline irrigation could also be considered as a safe initial choice in treatment in breast-feeding women.

▶ *Elderly*

AR in elderly patients is treated generally as it is in younger adults; however, consideration of increased risk for certain side effects (eg, antimuscarinic) should weigh into therapy choices.[50] Therefore, first-line agents are primarily INCSs and second-generation oral or possibly intranasal antihistamines. Older patients may also have a component of atrophy of nasal tissues that can result in more nasal congestion. Most will benefit from regular nasal saline irrigation. The elderly patients are more sensitive to the sedative and antimuscarinic effects of (especially first-generation) antihistamines and to the cardiovascular and CNS stimulant effects of decongestants. These drugs should be used cautiously, if at all. An increase in cholinergic activity may result in more rhinorrhea, which may respond well to ipratropium.

Ocular Symptoms

Several products are available for instillation directly into the eyes for those patients with predominant or unresponsive ocular manifestations. They may be appropriate for occasional moderate–severe flares or episodic AR when other modes of therapy are not optimally effective. The combination (antihistamine and mast cell stabilizing) agents may be the most effective, and they have the advantages of rapid onset of action and (usually) only twice-daily administration.[3] Ketotifen is in this category and because it is available OTC, it can be an appropriate initial agent. See Table 65–9 for these products.

Patient Encounter 2, Part 3

It is now several years later, and Mr. J accompanies his wife, Mrs. J, to the clinic—they are expecting their first child. Mrs. J states, my allergies are definitely a problem, but not nearly as bad as my husband's. Mrs. J states, "I have not taken anything before for my allergies but for some reason my symptoms are really bad this season. I was not sure what to do since I am about 16 weeks along in my pregnancy, so I have not started anything yet." She reports sneezing, nasal and ocular itching, and rhinorrhea, nearly every day. She has no other comorbidities or known medication allergies.

What do you recommend and why?

Summary of Treatment

Once an agent appropriate for initial therapy is chosen, ongoing management requires repeated checks to ascertain response and freedom from intolerable or adherence limiting side effects. Either "step-up" or "step-down" therapy may be appropriate, depending on individual response. Duration of therapy can depend on type and severity of AR. For example, those with SAR may only need treatment during certain times of year, for example, spring or summer, versus those with PAR may require chronic treatment, year-round. If a given patient is well-controlled for a sustained period (eg, weeks to months) and/or allergen exposure decreases, stepping down therapy may be considered. In stepping down therapy, symptoms frequency and severity should be monitored for possible need to step up therapy. See Table 65–10 for a summary of the approach to treatment of AR. Table 65–11 attempts to rank the relative effectiveness of the classes of agents for treatment of AR by specific symptoms.

Table 65–9

Intraocular Medications

Category	Generic (Brand) Name	Formulation	Frequency	Age
Decongestant/vasoconstrictor	Naphazoline[a] (Naphcon, Privine, others)	0.012% + 0.025%	Four times daily	Adult
Decongestant/vasoconstrictor + antihistamine	Naphazoline + pheniramine[a] (Visine A)	0.025%/0.3%	Four times daily	6 yo or more
Antihistamine	Emedastine (Emadine)	0.05%	Four times daily	3 yo or more
	Alcaftadine (Lastacaft)	0.25%	Once daily	2 yo or more
Mast cell stabilizer	Cromolyn (generic)	4%	Every 4–6 hours	4 yo or more
	Lodoxamide (Alomide)	0.1%	Four times daily	2 yo or more
	Nedocromil (Alocril)	2%	Twice daily	3 yo or more
	Pemirolast (Alamast)	0.1%	Four times daily	3 yo or more
Antihistamine + mast cell stabilizer	Azelastine (Optivar)	0.05%	Twice daily	3 yo or more
	Epinastine (Elestat)	0.05%	Twice daily	2 yo or more
	Ketotifen[a] (Zaditor, Alaway, Claritin,	0.025%	Every 8–12 hours	3 yo or more
	Zyrtec, generic)	0.1%/0.2%	Twice daily/once daily	3 yo or more
	Olopatadine (Patanol/Pataday)	1.5%	Twice daily	2 yo or more
	Bepotastine (Bepreve)			
NSAIDs	Ketorolac (Acular)	0.5%	Four times daily	3 yo or more
Corticosteroid	Loteprednol (Alrex)	0.2%	Four times daily	Adult

[a] Available OTC.

Also, see Chapter 62, Glaucoma, for more details.

NSAID, nonsteroidal anti-inflammatory drug; yo, years old.

Data from Lexi-Comp OnlineTM, Pediatric & Neonatal Lexi-Drugs OnlineTM, Hudson, Ohio: Lexi-Comp, Inc.; December 31, 2020, includes any off-label dosing.

Table 65–10

Routine Approach to Therapy of AR[3,6-10,14]

All patients should practice avoidance of identified allergens

Mild Intermittent

First line:
Oral antihistamine (OTC, initially; preferably second generation)
Adjunctive/secondary (may use more than one; no specific order intended):

- Add nasal saline (eg, as irrigation)
- Consider intranasal cromolyn, especially preexposure for episodic AR
- Consider OTC INCS for refractory symptoms
- Consider intraocular medications, as needed for ocular symptoms (see Table 63–9)
- Consider OTC oral decongestant for nasal congestion
- Consider OTC intranasal decongestant for refractory nasal congestion (not more than 3 days)
- Consider prescription therapy for inadequate response (see below)

Possibly consider referral for immunotherapy

Persistent or Moderate–Severe

First line:
Intranasal corticosteroid
Add oral antihistamine (preferably second generation) for possible additional benefit if necessary

Adjunctive/secondary (may use more than one):

- Add nasal saline (eg, as irrigation)
- Consider intranasal antihistamine
- Consider combination intranasal antihistamine with corticosteroid
- Consider intraocular medications, as needed for ocular symptoms (see Table 63–9)
- Consider OTC oral decongestant for nasal congestion
- Consider short-term intranasal decongestant for refractory nasal congestion
- Consider montelukast
- Consider intranasal ipratropium for inadequately controlled rhinorrhea

Consider referral for immunotherapy

Episodic (no order of preference intended)
Oral antihistamine (OTC, initially; preferably second generation)
Consider addition of or replacement with intranasal cromolyn (OTC) or intranasal antihistamine or intranasal corticosteroid

Special Situations (children, pregnant women, elderly, ocular symptoms)
See Special Populations section of text

Table 65–11

Relative Efficacy (Semiquantitative) by Classes of Agents for Specific Symptoms of Allergic Rhinitis[6-9,13,14]

Drug Class	Nasal Congestion	Sneezing	Rhinorrhea	Nasal Itch	Ocular Symptoms
Intranasal corticosteroids[a]	+++	+++	+++	+++	+
Oral antihistamines[a]	+	++	++	++	++
Intranasal antihistamines	++	++	++	++	+
Oral decongestants[a]	++	0	0	0	0
Intranasal decongestants[a,b]	+++	0	0	0	0
Oral leukotriene antagonist	++	+	++	+	++
Intranasal mast cell stabilizer[a]	++	++	++	++	++
Intranasal antimuscarinic	0	0	++	0	0

[a] Some products in these classes are available OTC.

[b] Intranasal decongestants are best used for severe, unresponsive nasal congestion, or to facilitate mucosal contact of other intranasal medications, but in either case, they should usually be limited to no more than 3 days.

Note: There are different opinions about some of the rankings, partly due to inadequate study. Individual variation may create different relative efficacy in some patients. +++, greatest relative efficacy; 0, no relative efficacy.

Patient Care Process

Collect Information:

- Collect information from the history of present illness (HPI), past medical history (PMHx), and physical assessment. HPI includes location, onset, quality, quantity, setting, associated symptoms, and modifying factors (see Clinical Presentation and Diagnosis of Allergic Rhinitis). PMHx should include conditions associated with AR and its complications (see Epidemiology section). Physical assessment includes observation of patient and examination of nasal mucosa (see Clinical Presentation and Diagnosis of Allergic Rhinitis and Table 65–1).
- Identify therapies attempted and their efficacy.
- Determine additional considerations in treatment (eg, pregnancy, lactation, child or elderly; see Selected Populations section).

Assess the Information:

- Rule out nonallergic type of rhinitis (see Table 65–2).
- Determine extent and severity of patient's assessing frequency and severity of AR symptoms (see Clinical Presentation and Diagnosis of Allergic Rhinitis and Table 65–3).
- Determine the patient's understanding of AR.
- Assess response to past and current AR treatment. If clinical response is inadequate, assess adherence and technique. See Table 65–6. If nonadherence and poor technique do not explain suboptimal response, consider alternative treatments or specialist referral. See Table 65–10.

Develop a Care Plan:

- Advise allergen avoidance. See Table 65–4.
- Review optimal administration technique and adherence.
- Base therapy recommendations on symptoms and response to current and past treatment.

Implement the Care Plan:

- For mild AR where OTC agents can be used, provide patient with recommended therapy including drug name, dose, and dosing frequency. Educate on appropriate administration, expected outcomes, and possible side effects.
- For moderate-to-severe AR where physician management is likely needed, communicate recommendations to primary care provider and assist with follow-up if needed by monitoring patient symptoms control and treatment of side effects.

Follow up: Monitor and Evaluate:

- Follow up weekly at first, especially during worse times/seasons for change in symptoms and possible side effects.
- When optimal control is approached, increase duration between follow-up visits (eg, monthly, every 2–3 months, or less frequently).

OUTCOME EVALUATION

- Confirm the patient's understanding of the disorder (see Clinical Presentation and Diagnosis of Allergic Rhinitis).
- Confirm the patient's understanding about allergen avoidance measures (see Table 65–4).
- Assess the patient's symptom response, tolerance, and adherence.
- Assess the patient's administration technique with intranasal products.
- Recommend second-generation oral antihistamine therapy for most patients with mild or intermittent symptoms (see Clinical Presentation and Diagnosis of Allergic Rhinitis and Tables 65–8 and 65–10).
- Recommend INCS therapy for moderate–severe or persistent symptoms. Suggest additional therapy for those with incomplete control (see Clinical Presentation and Diagnosis of Allergic Rhinitis and Tables 65–6 and 65–9).
- Consider step-up therapy for exacerbations or incomplete response.
- Consider step-down therapy if symptoms are minimal or stable for several months.
- Consider referral to rule out nonallergic causes of rhinitis in nonresponding patients or those with an atypical presentation (see Clinical Presentation and Diagnosis of Allergic Rhinitis).
- Consider referral to an allergy specialist for patients who request immunotherapy.
- Consider referral to an allergy specialist for patients with comorbid conditions, especially asthma.

Abbreviations Introduced in This Chapter

AAAAI	American Academy of Allergy, Asthma, and Immunology
ACAAI	American College of Allergy, Asthma, and Immunology
ACEI	Angiotensin-converting enzyme inhibitor
AERD	Aspirin-exacerbated respiratory disease
AR	Allergic rhinitis
ARIA	Allergic rhinitis and its impact on asthma
BPH	Benign prostatic hyperplasia/hypertrophy
BTC	Behind-the-counter
CHPA	Consumer Health Protection Agency
H_1	Histamine type 1 (receptor)
HEPA	High-efficiency particulate air (filter)
HFA	Hydrofluoroalkane ("green" propellant for metered-dose INCSs)
HPA	Hypothalamic–pituitary–adrenal (axis)
HPI	History of present illness
HTN	(Essential or primary) hypertension
IAR	Intermittent allergic rhinitis (ARIA system)
IgE	Immunoglobulin E
INCS(s)	Intranasal corticosteroid(s)
LTRA	Leukotriene receptor antagonist

MDP	metered-dose pump
NARES	Nonallergic rhinitis with eosinophilia [on nasal smear] syndrome
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over-the-counter
PAR	Perennial allergic rhinitis (AAAAI/ACAAI system)
PDE-5	Phosphodiesterase (isoenzyme)-5
PER	Persistent allergic rhinitis (ARIA system)
PMHx	Past medical history
QT	Interval between the Q and T waves in an ECG
SAR	Seasonal allergic rhinitis (AAAAI/ACAAI system)
SCIT	Subcutaneous immunotherapy
SIT	Allergen-specific immunotherapy
SLIT	Sublingual immunotherapy

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66

Acne Vulgaris

Laura A. Perry and Jenna M. Mills

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the pathophysiology of acne.
2. Assess the signs and symptoms of acne in a presenting patient.
3. List the goals of treatment for patients with acne.
4. Select appropriate nonpharmacologic and pharmacologic treatment regimens for patients presenting with acne.
5. Identify adverse effects that may result from pharmacologic agents used in the treatment of acne.
6. Develop a monitoring plan that will assess the safety and efficacy of the overall disease state management of acne.
7. Create educational information for patients about acne, including appropriate self-management, available drug treatment options, and anticipated therapeutic responses.

INTRODUCTION

Acne vulgaris is an inflammatory skin disorder of the pilosebaceous units of the skin. Although most commonly seen on the face, acne can also present on the chest, back, neck, and shoulders.[1] Acne is not just a self-limiting disorder of teenagers. The clinical course of acne can be prolonged or recur, resulting in long-term physical complications, such as extensive scarring and psychological distress.[2]

EPIDEMIOLOGY AND ETIOLOGY

With an estimated 40 to 50 million people affected, acne vulgaris is the number one skin disease in the United States. Acne affects approximately 85% of adolescents and adults aged 12 to 25 years, with severity of acne correlating with pubertal maturity.[3] Additionally, acne may persist beyond puberty and has been found to affect 64% and 43% of individuals into the 20s and 30s, respectively. Acne is more likely to occur in males during adolescence and females during adulthood. Individuals with a positive family history of acne have been shown to develop more severe cases of acne at an earlier age. Prevalence of acne among ethnic groups is similar.[2,3]

The link between diet and acne has continued to be controversial, with emerging evidence suggesting a link to foods with high glycemic indexes as well as dairy products (ie, skim milk)—partially due to the hormones in the milk; however, no specific dietary changes are recommended in the management of acne.[2,4,5,] Local irritation from occlusive clothing or athletic equipment, oil-based cosmetics or beauty products, prolonged sweating or environments of high humidity, and a variety of medications may also worsen acne.[6]

PATHOPHYSIOLOGY

KEY CONCEPT The development of acne lesions results from four pathogenic factors: excess **sebum** production, **keratinization**, bacterial growth, and inflammation.[1]

The **pilosebaceous unit** of the skin consists of a hair follicle and the surrounding sebaceous glands. Sebum is released by the sebaceous glands and naturally maintains hair and skin hydration. Increased androgen levels, especially during puberty, can cause an increased size of the **sebaceous gland** and production of abnormally high levels of sebum within those glands. Keratinization, the sloughing of epithelial cells in the hair follicle, is also a natural process. In acne, however, *hyper*keratinization occurs resulting in an increased adhesiveness of the sloughed cells.

An initial acne lesion invisible to the naked eye, called a microcomedo, forms as a result of the increased cell division and cohesiveness. Subclinical microcomedo formation is a precursor for noninflammatory acne lesions called comedos. A **closed comedo** or "whitehead" appears when accumulation of epithelial cells and sebum partially obstruct the follicular opening. If the follicular opening is dilated, the keratin buildup can darken and form an **open comedo** or "blackhead."

Propionibacterium acnes, an anaerobic organism, is also found in the normal flora of the skin. This bacteria proliferates in the mixture of sebum and keratinocytes and can result in an inflammatory response producing more severe acne lesions such as **papules**, **pustules**, and **nodules**. Inflammatory lesions may result in scarring if treated inadequately.

TREATMENT

Desired Outcomes and Goals

Although traditionally thought of as a self-limiting disorder, acne can have patterns of recurrence. Because acne cannot be cured, proper treatment must involve both short-term and long-term strategies. **KEY CONCEPT** Goals of therapy are to (a) Reduce the number and severity of existing lesions, (b) Prevent the development of new lesions and recurrence, (c) Prevent long-term disfigurement and permanent scarring, and (d) Encourage treatment adherence.[4,6]

Clinical Presentation and Diagnosis of Acne

Acne lesions are most often seen on the face but can also present on the chest, back, neck, and shoulders and are described as either noninflammatory or inflammatory (Figure 66–1). Severe inflammatory lesions may lead to scarring and hyperpigmentation.

Noninflammatory Lesions

Closed comedo or "whitehead": A partially plugged follicle containing sebum, keratinocytes, and bacteria that remains beneath the surface of the skin. Closed comedos usually appear as small white bumps about 1 to 2 mm in diameter.

Open comedo or "blackhead": A partially plugged, dilated follicle containing sebum, keratinocytes, and bacteria approximately 2 to 5 mm in diameter that protrudes from the surface of the skin and appears black or brown in color. Although dark in color, blackheads do not indicate the presence of dirt, but rather, an accumulation of melanin.

Inflammatory Lesions

Papules: Solid, elevated lesion less than 0.5 cm in diameter.

Pustules: Vesicles filled with purulent fluid less than 0.5 cm in diameter.

Nodules: Warm, tender, firm lesions greater than 0.5 cm in both width and depth.

Cysts: Nodules that harden into larger, pus-filled lesions.

Scars

Inflammatory acne can result in permanent scarring that ranges from small, depressed pits to large, elevated blemishes.

Hyperpigmentation

Inflammatory acne may result in hyperpigmentation of the skin that can last for weeks to months.

Diagnosis

The diagnosis of acne vulgaris is clinical. Lesion cultures may be warranted when treatment regimens fail to rule out Gram-negative folliculitis and other skin infections. Endocrinological laboratory evaluation is only recommended for patients who have acne and additional signs of androgen excess.[4]

Assessment

No standard acne grading scale has been identified. While several grading scales exist,[4,7] most clinicians describe acne as mild (non-inflammatory lesions), moderate (many inflammatory lesions), or severe (numerous severe inflammatory lesions and evidence of scarring).

Acne can cause psychological symptoms of stress, anxiety, frustration, embarrassment, and even depression.[1,2,4] Evaluating both physical and psychological aspects of acne is imperative.

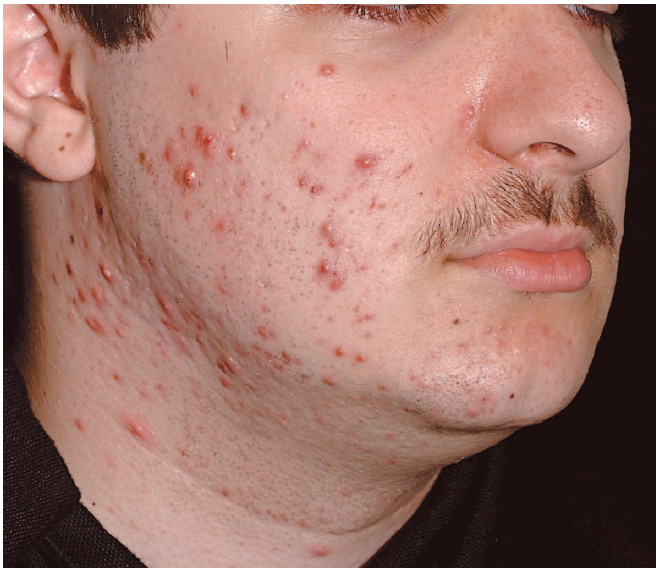


FIGURE 66–1. 20-year-old male. In this case of papulopustular acne, some inflammatory papules become nodular and thus represent early stages of nodulocystic acne. (From Wolff K, Johnson RA. Disorders of sebaceous and apocrine glands. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 8th ed. New York, NY: McGraw-Hill; c2017 [cited 2020 Sept 20]. Available from https://accessmedicine-mhmedical-com.ezproxy.findlay.edu/content.aspx?bookid=2043&sectionid=154896913.)

General Approach to Treatment

KEY CONCEPT Acne treatment regimens should be based on acne severity and type of acne lesion. Other factors such as response to previous treatment, patient preference, cost, and adherence should also be considered. Topical therapy is considered first-line for mild acne with oral therapies added to topical therapy in

Patient Encounter, Part 1: Assessment

OH, a 26-year-old female, presents with facial acne. She has experienced acne since she was a teenager, which she describes as "small white bumps that appeared sporadically and weren't anything that a little makeup couldn't cover up." Her facial acne has since worsened, as the lesions have increased in number and now manifest as "red, irritated, and yellow fluid–filled bumps accompanied by larger and firmer bumps that cannot be popped." Visual examination reveals numerous noninflammatory lesions, a few papules and pustules around her nose and on her chin, and two nodules on her forehead above her right eyebrow. She states, "I thought acne was a teenager issue…it should be going away as I progress into adulthood, not getting worse!" OH washes her face twice daily with a cleansing oil and applies a deep moisturizing cream to her entire face before bed. She is a personal trainer and very physically active, especially during the summer months when she spends "as much time as possible" outdoors partaking in activities.

What reported symptoms support the diagnosis of acne?

How would you classify the patient's acne?

What factors could be contributing to the patient's acne?

moderate-to-severe acne. Using multiple topical agents that target different aspects of acne pathogenesis is more effective, reduces adverse effects, and minimizes treatment resistance.[4,7] Topical therapies should be applied to the entire area affected by acne to prevent new lesions from developing.[8]

Optimal management includes aggressive induction treatment and maintenance therapy to prevent recurrence. Improvement of symptoms following induction therapy occurs gradually, sometimes taking 6 to 8 weeks for results to be physically apparent. Patients need to be educated on continual treatment compliance during this time and should not get discouraged if acne lesions appear to worsen before getting better. Maintenance therapy should begin after 12 weeks of induction therapy and is continued for 3 to 4 months in most clinical trials. Due to frequent acne recurrences, clinical experience indicates that a longer duration of maintenance therapy may be beneficial for most patients.[4,7,8]

Nonpharmacologic Therapy

There is significant variance in the clinical benefit of many nonpharmacologic interventions for acne vulgaris. Patients should be counseled to avoid aggressive skin washing and to use a mild, noncomedogenic facial soap twice daily. Excessive washing or use of harsh or abrasive cleansers can disrupt the skin barrier and promote comedones and bacterial colonization. Manipulating or squeezing lesions should also be avoided to minimize scarring. The use of an oil-free, noncomedogenic moisturizer daily may improve the tolerability of topical drug therapy.[6,8,9]

Pharmacologic Therapy

▶ *Topical Agents*

Retinoids Topical retinoids are the foundation of first-line therapy for induction and maintenance regimens in all forms of acne. Although success is seen with monotherapy in comedonal acne, using topical retinoids in combination with benzoyl peroxide, topical antibacterial agents, or oral antibacterial agents is preferred for inflammatory acne lesions.[4,7]

Retinoids normalize epithelial cell turnover, which in turn promotes clearing of obstructed follicles and prevents microcomedo formation. Retinoids also exhibit anti-inflammatory properties through the inhibition of neutrophil and monocyte chemotaxis.[10]

Available topical retinoids include tretinoin, adapalene, tazarotene, and trifarotene. Adapalene, available by prescription and over the counter, is considered the drug of first choice because it has similar efficacy and a lower incidence of adverse effects.[4,6,7,10] Microsphere gel (Retin-A Micro) or a polyolprepolymer-2 gel or cream (Avita) gradually release the active ingredient over time and may also cause less initial skin discomfort. Topical retinoid products with a foam vehicle have a more favorable tolerability profile than comparable gel formulations.[10] Table 66–1 describes available products and adverse effects of topical retinoids.

Topical retinoids should be applied once daily at bedtime, beginning with a low-potency formulation. Increased strengths are then initiated according to treatment results and tolerance.[8] Patients should be advised that a worsening of acne symptoms generally occurs in the first few weeks of therapy, with lesion improvement occurring in 3 to 4 months.[8,11] The safety and efficacy of topical retinoids in children younger than 12 years of age and in pregnant women is not well established.[9]

Benzoyl Peroxide Benzoyl peroxide is easy to use and is recommended as an alternative to, or in combination with, topical retinoids, topical antibacterial agents, or oral antibacterial agents in the treatment of acne of all severities.[47] Benzoyl peroxide has a comedolytic effect that increases the rate of epithelial cell turnover and helps to unclog blocked pores. It also has antibacterial activity against *P. acnes*, which appears to be the main reason for its effectiveness.[12,13]

Benzoyl peroxide is available with or without a prescription and remains the most commonly purchased over-the-counter topical treatment for acne.[6,14] Some data suggests that lower strengths offer similar efficacy to higher strengths. Beginning benzoyl peroxide treatment regimen with the lowest strength and titrating to higher effective strengths over several weeks, if needed, will reduce the incidence of localized adverse effects. Newer formulations of benzoyl peroxide are combined with moisturizers to help decrease skin redness and irritation.[9,12,14]

A typical regimen for benzoyl peroxide is to apply the product to clean, dry skin no more than two times a day. The strength and dosage form selected may vary from patient to patient depending on acne severity and the sensitivity of the patient's skin. Gel preparations are the most potent dosage form. Patients with dry or overly sensitive skin should try a cream, lotion, or facial wash first.[4,8] If severe irritation or an allergic reaction develops, benzoyl peroxide should be discontinued. Patients should avoid contact with hair and dyed fabric, which may be bleached by benzoyl peroxide products.[6] Table 66–1 describes available products and adverse effects.

Antibacterials Topical antibacterials directly suppress *P. acnes* and are first-line agents used in combination with benzoyl peroxide for the treatment of mild-to-moderate inflammatory acne. To reduce the likelihood of bacterial resistance, topical antibiotics should be combined with benzoyl peroxide and never be used as monotherapy or as long-term maintenance therapy.[4,7]

Clindamycin is currently the preferred topical antibiotic for acne therapy due to increased bacterial resistance to erythromycin preparations.[4] Topical minocycline was recently approved, but long-term safety and efficacy studies are needed to determine place in therapy.[15] Applied once or twice daily for 3 months, these agents are available in various formulations and combinations with benzoyl peroxide and topical retinoids.[4,7] Table 66–1 describes the strengths, formulations and adverse effects of the available antimicrobial agents.

Azelaic Acid With antibacterial and anti-inflammatory properties, and the ability to stabilize keratinization, azelaic acid is an effective alternative in the treatment of mild-to-moderate acne in patients who cannot tolerate benzoyl peroxide or topical retinoids.[4,7,11] It can also even out skin tone and may prove effective in patients who are prone to postinflammatory hyperpigmentation resulting from acne.[4,11,16] Azelaic acid 20% cream should be applied twice daily, with improvement of symptoms seen within 4 weeks.[11]

Dapsone Dapsone gel, a sulfone drug, has antimicrobial and anti-inflammatory properties.[17] Dapsone gel may be used as an alternative agent for inflammatory acne as monotherapy or in combination with topical or oral agents. Topical dapsone gel has been shown to be more effective in adult females than in males or adolescents.[4]

Dapsone 5% is a gritty gel that should be applied in a thin layer to the affected areas twice daily.[17,18] When administered concomitantly with benzoyl peroxide, topical dapsone may become oxidized, causing orange-brown coloration of the skin which can be brushed or washed off. If no improvement is seen after 12 weeks, treatment should be reevaluated.[4,18]

Clascoterone Clascoterone cream, an androgen receptor inhibitor, decreases sebum production and inflammation that in turn

Table 66–1

Topical Agents Used in the Treatment of Acne

Drug	Brand	Dosage Form	Adverse Reactions	Comments
Retinoids				
Tretinoin	Altreno Atralin Avita Retin-A Retin-A Micro Retin-A Micro Pump	0.05% lotion 0.05% gel 0.025% cream, gel 0.025%, 0.05%, 0.1% cream; 0.01%, 0.025% gel 0.04%, 0.1% gel 0.04%, 0.06%, 0.08% gel	Erythema, dryness, scaling, stinging/burning, pruritus, initially may worsen acne Possibly teratogenic Photosensitivity	Local adverse reactions most likely occur in first 2–4 weeks of use and will usually lessen with continued use Should not be used in pregnancy; potential teratogenicity Minimize exposure to sunlight and sun lamps. Sunscreen use and protective clothing recommended
Tazarotene	Arazlo Fabior Tazorac	0.045% lotion 0.1% foam 0.1% cream, gel	Erythema, dryness, scaling, stinging/burning, pruritus, initially may worsen acne Teratogenic Photosensitivity	Local adverse reactions most likely occur in first 2 to 4 weeks of use and will usually lessen with continued use Should not be used in pregnancy; potential teratogenicity Minimize exposure to sunlight and sun lamps. Sunscreen use and protective clothing recommended
Adapalene	Differin Differin Gel (over the counter) Epiduo and Epiduo Forte	0.1% cream 0.1%, 0.3% gel 0.1% lotion 0.1% gel 0.1–2.5% and 0.3–2.5% benzoyl peroxide combination gel	Erythema, dryness, scaling, stinging/burning, pruritus, initially may worsen acne Photosensitivity	Local adverse reactions most likely occur in first 2–4 weeks of use and will usually lessen with continued use Less irritation compared to other retinoids Should not be used in pregnancy; potential teratogenicity Minimize exposure to sunlight and sun lamps. Sunscreen use and protective clothing recommended
Trifarotene	Aklief	0.005% cream	Erythema, scaling, dryness, stinging/burning, pruritus Photosensitivity	Local adverse reactions most likely occur and worsen within the first 4 weeks of treatment; often decreases with continued use Should not be used in pregnancy; potential teratogenicity Minimize exposure to sunlight and sun lamps. Sunscreen use and protective clothing recommended
Other Topical Agents				
Benzoyl Peroxide	2.5%–10%, Various over-the-counter and prescription products	Cream, foam, foaming cloths, gel, liquid wash, lotion, pad	Excessive drying, peeling, erythema, allergic contact sensitization/dermatitis Bleaching of hair and colored fabric Body odor on clothes/bedding Photosensitivity	Local reactions are dose dependent. Gradually increase dose as tolerance develops Minimize exposure to sunlight and sun lamps. Sunscreen use and protective clothing recommended Preferred topical agent in pregnancy; limited data
Azelaic Acid	Azelex	20% cream	Erythema, skin irritation	Alternative to benzoyl peroxide Possible alternative in pregnancy; limited data
Clindamycin	Cleocin-T Clindagel ClindaMax Evoclin Acanya, BenzaClin, Neuac, Onexton Veltin, Ziana	1% solution, lotion, gel, swab 1% gel 1% gel, lotion 1% foam 1.2%/2.5%, 1%/5%, 1.2%/5%, 1.2%/3.75% benzoyl peroxide combination gel 1.2%/0.025% tretinoin combination gel	Burning, itching, dryness, erythema, peeling Diarrhea, colitis (pseudomembranous colitis)	Rare cases of colitis have been observed with topical use. Discontinue immediately and seek medical attention if diarrhea occurs Should be combined with benzoyl peroxide May be considered with benzoyl peroxide during pregnancy

(Continued)

Table 66–1

Topical Agents Used in the Treatment of Acne (*Continued*)

Drug	Brand	Dosage Form	Adverse Reactions	Comments
Erythromycin	ERYGEL Ery Benzamycin	2% gel 2% pad 3%/5% benzoyl peroxide combination gel	Burning, peeling, dryness, pruritus, erythema	Should be combined with benzoyl peroxide Combination with benzoyl peroxide has not been evaluated in animal reproduction studies
Dapsone	Aczone	5%, 7.5% gel	dryness, erythema, oiliness, and peeling	Does not have a risk of phototoxicity Not a preferred agent in pregnancy; limited data
Minocycline	Amzeeq	4% foam	Redness, hyperpigmentation, headache Photosensitivity Potential risk of systemic side effects (see oral minocycline)	Avoid use in children 8 years and younger Avoid during pregnancy Avoid or minimize exposure to natural or artificial sunlight. Skin protection and loose-fitting clothing recommended
Clascoterone	Winlevi	1% cream	Redness, exfoliation of skin, xeroderma, atrophic striae	Approved for children ≥ 12 years of age Avoid during pregnancy; limited data

Data from 1) Lexicomp [Internet]. Hudson (OH): Wolters Kluwer Clinical Drug Information, Inc.1978-2020 [cited 2020 May 31]. Available from: http://online.lexi.com/lco/action/home/switch

2) IBM Micromedex [Internet]. IBM Corporation.2020 [cited 2020 May 31]. Available from: https://www.micromedexsolutions.com/home/dispatch

reduces follicular plugging.[19] This novel mechanism is the first antiandrogen therapy that can be used in both males and females. Clascoterone has demonstrated efficacy and a favorable safety profile in males and nonpregnant females with moderate-severe facial acne.[20] Long-term safety and efficacy data and comparator studies are needed to determine the benefit of clascoterone over other first-line topical agents.

Keratolytics Sulfur, resorcinol, and salicylic acid have limited evidence available to support efficacy but can be used as second-line therapies in the treatment of mild-to-moderate acne.[4,6]

Although these agents may cause less skin irritation than benzoyl peroxide or the topical retinoids, several disadvantages exist. Sulfur preparations produce an unpleasant odor when applied to the skin, whereas resorcinol may cause brown scaling. And although rare, the possibility of salicylism exists with continual salicylic acid use.[6,11,14]

▶ *Oral Agents*

Antibacterials Oral antibiotics are indicated for use in patients with moderate-to-severe acne and forms of inflammatory acne that are resistant to topical therapy. When used, oral antibiotics should be combined with a topical retinoid and/or benzoyl peroxide.[2,4,7] Because of the ability to decrease *P. acnes* colonization, oral antibiotics can prevent acne lesions from developing. The use of oral antibiotics should be limited to short periods of time, ideally 3 to 4 months, or less.[4] Assessment of response to oral antibiotics after 6 to 8 weeks of therapy is recommended. After inflammatory lesions have stopped emerging, oral antibiotics should be discontinued and replaced with topical retinoid or benzoyl peroxide containing maintenance regimens.[4,9] As with topical antibiotics, oral antibiotics should never be used as monotherapy or as long-term maintenance therapy. Additionally, the use of topical antibiotics in combination with oral antibiotics should be avoided due to increased risk of bacterial resistance.[24,7]

Tetracycline, doxycycline, and minocycline are the most commonly prescribed oral antibiotics for acne. Doxycycline and minocycline are more effective than tetracycline, but neither is superior to each other.[4] Sarecycline, a recently approved tetracycline, displays a more narrow spectrum of activity designed to target skin bacterium with the potential for fewer gastrointestinal adverse effects. Long-term safety and efficacy data are needed to clarify the benefit of using sarecycline over minocycline or doxycycline as a first-line agent.[21] Erythromycin, azithromycin, and trimethoprim (± sulfamethoxazole) are appropriate second-line agents for use when patients cannot tolerate or have developed resistance to tetracycline or its derivatives. Although effectiveness is similar to the tetracyclines, erythromycin use is often limited due to potential adverse outcomes and increased bacterial resistance.[4,22] (See Table 66–2 for antibiotic dosing guidelines and adverse effects.)

Isotretinoin Isotretinoin works on the four pathogenic factors that contribute to acne development and can produce acne remission rates of up to several years. Oral isotretinoin is Food and Drug Administration (FDA) approved for patients with severe recalcitrant nodular acne unresponsive to other topical and oral treatment regimens.[4,7] Additional evidence suggests that oral isotretinoin may be useful in treatment-resistant moderate acne or acne that is producing physical scarring or psychosocial distress.[2,4,7] Some expert clinicians suggest that oral isotretinoin therapy may be used as first-line therapy in patients with severe nodular acne due to clinical effectiveness, prevention of scarring, and quick improvements in patient quality of life.[7,8]

Adverse effects with the use of isotretinoin are frequent and generally dose-related. Table 66–2 lists common isotretinoin adverse effects and management strategies for those symptoms.

Because isotretinoin is teratogenic and is contraindicated in pregnancy, the FDA mandates an online registry program called iPLEDGE to ensure that females do not become pregnant while taking isotretinoin. Wholesalers, pharmacies, doctors, and patients must be registered in the iPLEDGE computer-based system in

Table 66–2

Oral Agents Used in the Treatment of Acne

Drug	Dosage Form (mg)	Dosing Regimen	Adverse Reactions	Comments
Oral Antibiotics				
Tetracycline	250, 500 capsule	250–500 mg twice daily	GI upset, diarrhea, headache, blurry vision, vaginal candidiasis, tooth discoloration in children Vaginal candidiasis Photosensitivity Administer 1–2 hours prior to or 4 hours after dairy products, multivitamins, iron, or antacids	Avoid use in children < 8 years Avoid use in pregnancy; possible teratogenicity Minimize exposure to sunlight and sun lamps. Sunscreen use and protective clothing recommended Take 1 hour before or 2 hours after dairy products, antacids, vitamins, or iron supplements
Doxycycline	50, 75, 100 Tablets and capsules	100 mg twice daily on day 1, then 100 mg once daily	GI upset, diarrhea, headache, blurry vision, tooth discoloration in children Vaginal candidiasis Photosensitivity Administer 1 to 2 hours prior to or 4 hours after dairy products, multivitamins, iron, or antacids	Avoid use in children < 8 years Avoid use in pregnancy; possible teratogenicity Minimize exposure to sunlight and sun lamps. Sunscreen use and protective clothing recommended Take 1 hour before or 2 hours after dairy products, antacids, vitamins, or iron supplements
Minocycline	50, 75, 100 immediate-release tablets 45, 55, 65, 80, 90, 105, 115, 135 extended-release tablets 50, 75, 100 immediate-release capsules	Immediate release: 50–100 mg twice daily Extended release: 1 mg/kg daily for 12 weeks.	GI upset, diarrhea, headache, blurry vision, lupus-like syndrome, hepatitis, exfoliative dermatitis, tooth discoloration in children Vaginal candidiasis Photosensitivity Administer 1–2 hours prior to or 4 hours after dairy products, multivitamins, iron or antacids	Avoid use in children < 8 years Avoid use in pregnancy; possible teratogenicity Minimize exposure to sunlight and sun lamps. Sunscreen use and protective clothing recommended Take 1 hour before or 2 hours after dairy products, antacids, vitamins, or iron supplements
Sarecycline	60, 100, 150 tablet	Weight-based; 33–54 kg: 60 mg once daily 55–84 kg: 100 mg once daily 85–136 kg: 150 mg once daily	GI upset, diarrhea, tooth discoloration in children Photosensitivity Administer 1 to 2 hours prior to or 4 hours after dairy products, multivitamins, iron or antacids	Avoid use in children < 8 years Avoid use in pregnancy; possible teratogenicity Minimize exposure to sunlight and sun lamps. Sunscreen use and protective clothing recommended Take 1 hour before or 2 hours after dairy products, antacids, vitamins, or iron supplements
Erythromycin	250, 500 tablets	250–500 mg twice daily	GI upset, diarrhea, rash, hearing loss, hypersensitivity reactions Vaginal candidiasis	Highest incidence of GI intolerance and increasing bacterial resistance Possible drug interactions: CYP3A4 substrate and p-glycoprotein inhibitor Alternative to tetracyclines Oral antibiotic option for pregnant women and children < 8 years
Azithromycin	500 tablet	Dosing regimens used in clinical trials have varied greatly, using pulse dose regimens (eg 500 mg once daily for 4 consecutive days per month for 3 consecutive months)	GI upset, diarrhea, rash, headache, drowsiness	Alternative if other antibiotics cannot be used Oral antibiotic option for pregnant women and children < 8 years

(*Continued*)

Table 66–2

Oral Agents Used in the Treatment of Acne (*Continued*)

Drug	Dosage Form (mg)	Dosing Regimen	Adverse Reactions	Comments
Trimethoprim	100-mg tablet	100 mg three times daily or 300 mg twice daily	GI upset, diarrhea, allergic rash, Stevens-Johnson syndrome Photosensitivity	Alternative if other antibiotics cannot be used Not preferred in pregnancy; may affect folic acid metabolism Minimize exposure to sunlight and sun lamps. Sunscreen use and protective clothing recommended
Sulfamethoxazole + trimethoprim	400/80, 800/160 tablet	400-800/80–160 mg One to two times daily	GI upset, diarrhea, allergic rash, urticaria, Stevens-Johnson syndrome Photosensitivity	Alternative if other antibiotics cannot be used Not preferred in pregnancy; may affect folic acid metabolism and possible teratogenicity Minimize exposure to sunlight and sun lamps. Sunscreen use and protective clothing recommended
Hormonal Agents				
Oral Contraceptives	Norgestimate/ethinyl estradiol (Tri-Estarylla, Tri-Previfem, Tri-Sprintec) Norethindrone acetate/ethinyl estradiol (Estrostep Fe, Tilia Fe, Tri-Legest Fe)	One tablet daily	Nausea, headache, weight gain, breast tenderness, break through bleeding, venous thromboembolism	Not for treatment of acne in men Use only in females ≥ 15 years of age Contraindicated in pregnant women
Spironolactone	25,50, 100 tablet	50–200 mg daily	Menstrual irregularities, breast tenderness, nausea, dizziness, headache, transient diuretic effect, hyperkalemia	Not recommended for treatment of acne in men Monitor serum creatinine and potassium Not recommended in pregnancy; limited data
Oral Retinoid				
Isotretinoin	10, 20, 30, 40 tablets	0.5–1 mg/kg/day in two divided doses with food	Cheilitis, dryness of the nose, eyes, and mouth, peeling, pruritus, and drying of the face and skin, alopecia, acne flare up at start of therapy Teratogenicity Depression/suicidality Musculoskeletal pain Increased serum cholesterol, triglycerides, creatine phosphokinase, and blood glucose Photosensitivity	Nasal sprays, lip moisturizers, and hard candy may help to reduce drying of mucous membranes Apply oil-free moisturizers to face to relieve drying of skin Contraindicated in pregnancy (US Boxed Warning) Monitor patient closely for changes in mood May use nonsteroidal anti-inflammatory drugs to relieve pain Monitor lipid panel, liver function tests, and blood glucose Minimize exposure to sunlight and sun lamps. Sunscreen use and protective clothing recommended

Data from 1) Lexicomp [Internet]. Hudson (OH): Wolters Kluwer Clinical Drug Information, Inc.; 1978–2020 [cited 2020 May 31]. Available from: http://online.lexi.com/lco/action/home/switch

2) IBM Micromedex [Internet]. IBM Corporation.2020 [cited 2020 May 31]. Available from: https://www.micromedexsolutions.com/home/dispatch

order to control the distribution, prescribing, and dispensing of isotretinoin. Two negative pregnancy tests prior to initiating therapy and one negative pregnancy test each month thereafter must be obtained and confirmed in the system before a prescription can be dispensed to female patients of childbearing potential. These patients must also commit to using two effective forms of birth control 1 month prior, during, and at least 1 month after discontinuation of isotretinoin therapy. Contact the program at their website: *https://www.ipledgeprogram.com/* for further details.

The initial dose for treatment of severe acne is typically 0.5 mg/kg daily in two divided doses, then increasing to 1 mg/kg daily, as tolerated, with goal cumulative doses of 120 to 150 mg/kg. Increasing the total daily dose to 1 mg/kg daily resulted in a significantly lower relapse and retreatment rate.[4,9,7] For patients with treatment-resistant moderate acne, low-dose isotretinoin (0.25–0.4 mg/kg/day) has comparable efficacy to conventional dosing with decreased adverse effects and improved tolerability. Intermittent dosing of isotretinoin is not recommended due to the lack of efficacy and increased relapse rates.[4] Treatment with oral isotretinoin should be continued for 4 to 6 months but may be extended for patients with an insufficient response.[4,7]

Hormonal Agents Oral contraceptives and antiandrogens are valuable second-line treatment options for moderate-to-severe inflammatory acne in female patients.[4,7] Hormonal agents primarily work by decreasing androgen production resulting in reduced sebum formation. Because sebum production occurs early in the pathogenesis of acne, it takes several months to see the full effect of hormonal agents.[4]

Although many contraceptives are effective,[23] agents containing ethinyl estradiol/norgestimate, ethinyl estradiol/norethindrone acetate/ferrous fumarate, and ethinyl estradiol/drospirenone have been FDA approved for the treatment of acne.[4] While not FDA approved, spironolactone, at higher doses, is effective for acne through antiandrogenic properties.[4,7] (See Table 66–2 for hormonal agent dosing guidelines and adverse effects).

Other Agents Although use is infrequent, several other agents are available as second- or third-line treatment options for acne when first-line therapies fail:[2,4,7]

- Corticosteroids
- Chemical peels
- Surgical extraction
- Phototherapy/photodynamic therapy
- Laser treatments

Figure 66–2 shows useful algorithms for the effective treatment of the various stages of acne.

Patient Encounter, Part 2: Plan

OH has never seen a dermatologist and has not previously tried any medication for her acne. She has friends who are being treated for acne and knows their treatment regimens consist of multiple products and repeated applications daily. She expresses, "I am ultimately looking for the simplest option available because I don't anticipate I will keep up with multiple products every day. With how much time I spend at the gym and outside, that just isn't realistic for me." She asks if Differin Gel would be a good option to "make her acne go away," since a client recommended it to her after seeing it is available over the counter. The patient appears to be in good physical health and has no known drug allergies.

Describe your treatment goals for this patient.

What nonpharmacologic treatment options and lifestyle modifications would you suggest to this patient?

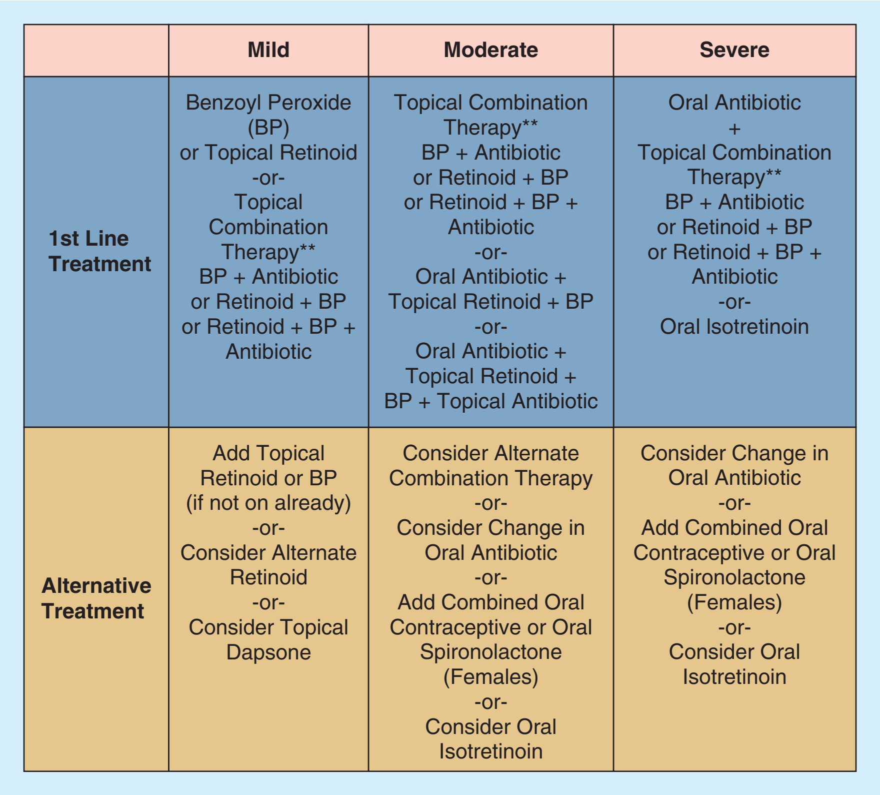
Consider a pharmacologic treatment plan for this patient:

Do you recommend Differin Gel for this patient? Why or why not?

What pharmacologic treatment options are available for this patient?

List 1–2 pros and 1–2 cons for each potential treatment option. Please take patient-specific considerations into account.

Given the information presented, develop a patient-specific therapeutic plan.



	Mild	Moderate	Severe
1st Line Treatment	Benzoyl Peroxide (BP) or Topical Retinoid -or- Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic	Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic -or- Oral Antibiotic + Topical Retinoid + BP -or- Oral Antibiotic + Topical Retinoid + BP + Topical Antibiotic	Oral Antibiotic + Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic -or- Oral Isotretinoin
Alternative Treatment	Add Topical Retinoid or BP (if not on already) -or- Consider Alternate Retinoid -or- Consider Topical Dapsone	Consider Alternate Combination Therapy -or- Consider Change in Oral Antibiotic -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin	Consider Change in Oral Antibiotic -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin

FIGURE 66–2. Algorithms for acne treatment. (From Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74:945–973.)

Patient Care Process: Acne

Collect Information:

- Perform dermatologic exam and note the number and type of acne lesions: open and closed comedos, papules, pustules, nodules, cysts.
- Obtain age of onset and family history of acne, including severity.
- Determine patient's current skin care routine, including use of cosmetics, facial washes, moisturizers, and other possible exacerbating factors.
- Review patient preferences and beliefs, health goals, and socioeconomic factors.
- Conduct a medication history (nonprescription, prescription, and herbal medications). Identify previous acne treatment regimens.
- Note allergies to medications or other substances.

Assess the Information:

- Assess patient symptoms and acne lesions to determine acne severity: mild, moderate, or severe.
- Determine if any medications or behaviors may be exacerbating acne.
- If patient is already receiving pharmacotherapy, assess whether active and/or previously tried therapies were effective, safe, and used as directed.

Develop a Care Plan:

- If acne not well controlled, determine appropriate pharmacotherapy options for the patient's acne severity (Figure 66–2).
- Determine whether patient has prescription medication coverage to identify possible recommendations included in the plan formulary.
- Select nondrug and drug therapy likely to be effective and safe and determine drug, dose, route, and frequency of administration/application. Use combination products as appropriate to improve adherence and reduce adverse effects (Tables 66–1 and 66–2).
- Choose appropriate changes to lifestyle.

Implement the Care Plan:

- Provide patient education on acne:
  - What is acne and how does it develop?
  - Physical and psychological complications that can result from acne.
- Educate patient on proper use, adverse effects, and expectations of acne drug therapy.
  - Inform the patient of recommended changes, deletions, and additions to acne drug regimen.
  - Review drug, dose, route/proper administration technique, and duration of therapy. Topical acne therapy should be applied to entire acne prone area and existing lesions.
  - Review possible side effects of drug therapy.
  - Inform patient of possible initial worsening of acne and/or delay of therapeutic effectiveness of acne drug therapy.
- Emphasize medication compliance and adherence to lifestyle modifications for treating existing acne lesions and preventing recurrence.
- Address any patient concerns.

Follow-up: Monitor and Evaluate:

- Follow-up every 1 to 2 months to assess effectiveness and safety of nondrug and drug therapy (Tables 66–1 and 66–2).
- If acne lesions do not respond after 3 months of drug therapy, consider an alternative acne regimen (Figure 66–2).
- If the patient experiences resolution of acne symptoms, transition to maintenance drug therapy.

OUTCOME EVALUATION

Depending on severity, complete resolution of acne lesions may take weeks to months. Monitor patients every 4 to 8 weeks during pharmacologic therapy to assess for efficacy.[4,9]

- Decreased number of lesions
- Decreased severity of lesions
- Relief of pain/irritation
- Presence of scarring or pigmentation
- Psychological effects
- Medication adherence

If no improvement is reported after 6 weeks of drug therapy or if symptoms have worsened, patients should be reevaluated and a change to an alternative drug regimen may be necessary (Figure 66–2).

Educate patients on potential adverse effects of drug therapy (Tables 66–1 and 66–2). Consider changing therapy if a patient experiences effects that are not tolerated or are a compromise to their health.

Patient Encounter, Part 3: Monitoring and Follow-Up

After implementing a therapeutic plan, OH asks, "what's the next step? Should I follow up after a certain amount of time, or am I good to go?"

Formulate a monitoring plan to assess the efficacy and safety of OH's therapeutic plan. Include timeframes and specific monitoring parameters.

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67

Dermatitis

Lori Ernsthausen and Jenna M. Mills

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the pathophysiology of dermatitis.
2. Assess the signs and symptoms of dermatitis in a presenting patient.
3. List the goals of treatment for patients with dermatitis.
4. Select appropriate nonpharmacologic and pharmacologic treatment regimens for patients presenting with dermatitis.
5. Identify adverse effects that may result from pharmacologic agents used in the treatment of dermatitis.
6. Develop a monitoring plan that will assess the safety and efficacy of the overall disease state management of dermatitis.
7. Create educational information for patients about dermatitis, including appropriate self-management, available drug treatment options, and anticipated therapeutic responses.

INTRODUCTION

Several thousand skin disorders are currently documented, and many patients seek the assistance of a health care provider when a complication with their skin develops. Others will utilize self-care to effectively treat their symptoms.

This chapter discusses contact dermatitis (irritant and allergic), atopic dermatitis, and diaper dermatitis; other common skin and soft tissue infections, and superficial fungal infections are discussed in Chapters 76 and 85, respectively. Providing patients with appropriate therapy options, as well as patient education on treatment and prevention, will assist the successful management of many common skin disorders.

CONTACT DERMATITIS

Contact dermatitis is a condition in which exposure to an offending substance produces inflammation, erythema, and pruritus of the skin.[1,2] More specifically, contact dermatitis can be divided into either irritant or allergic forms.[3] **KEY CONCEPT** Irritant contact dermatitis (ICD) results from first-time exposure to irritating substances, such as soaps, plants, cleaning solutions, or solvents. Allergic contact dermatitis (ACD) is a delayed hypersensitivity reaction that occurs after an initial exposure to an allergen results in sensitization. With additional exposure, activation of the immune system results in dermatitis. Allergens that commonly cause ACD include poison ivy, latex, and certain types of metal (Figures 67–1 and 67–2). Table 67–1 lists agents commonly responsible for irritant and ACD. Although generally occurring on the exposed skin, such as the hands and face, contact dermatitis can appear anywhere on the body.[4,5]

Epidemiology and Etiology

Contact dermatitis is the most common occupational related skin disease.[6] Although most often seen in adults, contact dermatitis can affect all age-groups, with females at slightly greater risk than males due to increased risk of exposure.[5]

Pathophysiology

ICD is not the result of an immunologic process but rather occurs from direct injury to the skin. An irritating agent comes into contact with the skin, damages the protective layers of the epidermis, and can cause erythema, the formation of vesicles, and pruritus.[1,6] Symptoms occur within minutes to hours of exposure and begin to heal soon after the removal of the offending substance.

ACD is a type IV hypersensitivity reaction.[4] Upon initial exposure, a substance penetrates the skin, is processed by antigen-presenting cells, and activates allergen-specific T cells. Subsequent exposures to that substance will elicit a response by circulating memory T cells, resulting in an allergic reaction.[1,4,6] Symptoms of ACD are similar to those of the irritant type but may take several hours to several days to develop following reexposure.[4]

Treatment

▶ *Desired Outcomes and Goals*

KEY CONCEPT Identifying the causative substance and eliminating its exposure is the initial treatment goal for contact dermatitis. Although physical symptoms can develop almost immediately after contact, removal of the offending agent will improve existing symptoms and prevent further complications.[2] Removing the offending agent includes washing the skin and any clothing or objects that may have come into contact with the agent to prevent reexposure. *The second treatment goal is symptom relief.* Since inflammation and pruritus, as well as lesion formation, are likely to result from contact dermatitis, appropriate selection of nonpharmacologic and pharmacologic agents for these symptoms is necessary.[3]

Clinical Presentation and Diagnosis of Contact Dermatitis

Contact dermatitis is generally confined to the area of contact, but, in a highly sensitive person, a widespread or even generalized eruption may occur. Contact dermatitis is divided into two forms—irritant and allergic. Both forms may include but are not limited to:

- Erythema
- Pruritus
- Vesicles
- Papules
- Crusts
- Burning
- Pain

Irritant Form

The irritant form usually presents within hours of exposure and the rash is often localized. Irritant contact dermatitis may also result in fissuring and scaling.

Allergic Form

The allergic form can take several days to present and the condition may extend beyond the borders of the region exposed. Allergic contact dermatitis may cause intense itching and include oozing pustules and skin erosion.

Diagnosis

Contact dermatitis may be suspected based on clinical presentation, especially if the causative agent is known; however, patch testing may be necessary to confirm the diagnosis.[7]

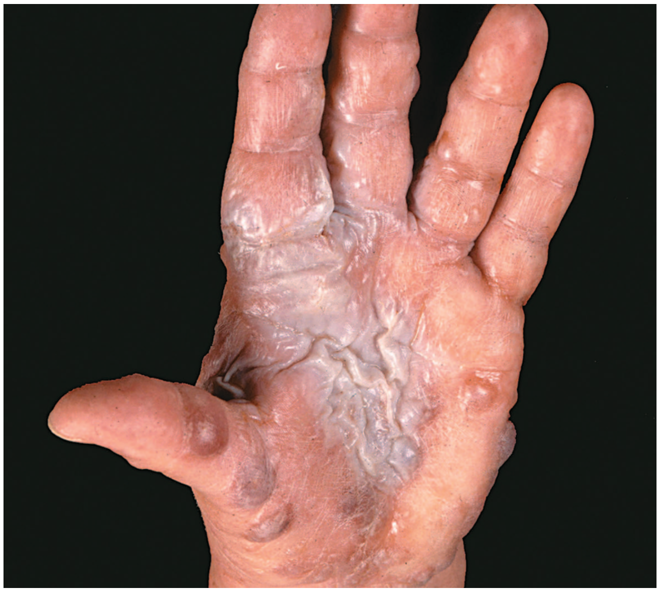

FIGURE 67–1. Acute irritant contact dermatitis on the hand due to an industrial solvent. There is massive blistering on the palm. (From Wolff K, Johnson RA, Saavedra AP, Roh EK. Eczema/dermatitis. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 8th ed. New York, NY: McGraw-Hill; 2017:5.)

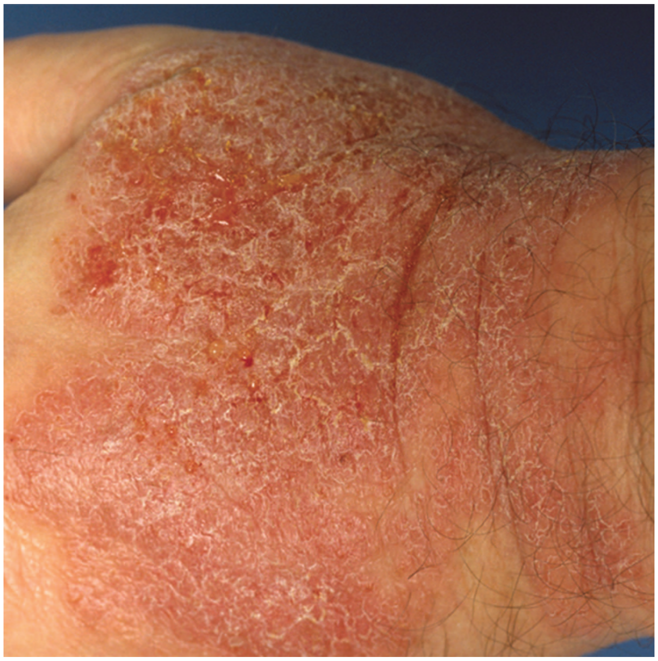

FIGURE 67–2. Allergic contact dermatitis of the hand: chromates. Confluent papules, vesicles, erosions, and crusts on the dorsum of the left hand in a construction worker who was allergic to chromates. (From Wolff K, Johnson RA, Saavedra AP, Roh EK. Eczema/dermatitis. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 8th ed. New York, NY: McGraw-Hill; 2017:13–14.)

▶ *Nonpharmacologic Therapy*

In many cases, contact dermatitis may not require medical treatment. Nondrug therapy for contact dermatitis is aimed at relieving pruritus and maintaining skin hydration.[4] Effective agents used for this include the following[1,7]:

- Colloidal oatmeal baths
- Cool or tepid soapless showers
- Cool, moist compresses applied to the area for 20 to 30 minutes as often as needed
- Emollients applied to the area after bathing

Preventative measures to prevent additional exposure should be considered including gloves, protective clothing, barrier creams, and skin conditioning products.

Table 67–1

Common Agents Causing Contact Dermatitis

Irritant Contact Dermatitis
Soaps
Detergents
Cosmetics
Solvents
Acid, mild or strong
Alkali, mild or strong

Allergic Contact Dermatitis
Plant resins, poison ivy, poison oak, sumac
Metals (nickel or gold in jewelry)
Latex and rubber
Cigarette smoke
Local anesthetics (lidocaine, benzocaine)

▸ *Pharmacologic Therapy*

Topical Steroids Erythema, inflammation, pain, and itching caused by ACD can be effectively treated with topically applied corticosteroids. The use of topical corticosteroids for the management of ICD is controversial, as patients with ACD generally respond better to therapy than those with ICD.[8] With such a wide range of products and potencies, appropriate steroid selection is based on severity and location of lesions (see Table 67–2 for a list of topical steroids and potencies.) Higher potency preparations are used in areas where penetration is poor, such as the elbows and knees. Lower potency products should be reserved for areas of higher penetration, such as the face, axillae, and groin.

Table 67–2

Topical Steroids and Potencies

Potency Rating	Topical Dosage Forms
Group 1: Super-high potency	Betamethasone dipropionate 0.05% gel, lotion, ointment (Diprolene ointment)
	Clobetasol propionate 0.05% lotion/spray/shampoo (Clobex lotion/spray/shampoo, OLUX foam)
	Clobetasol propionate 0.05% cream and ointment (Cormax, Temovate)
	Fluocinonide 0.1% cream (Vanos)
	Halobetasol propionate 0.05% cream, lotion, ointment (Ultravate)
	Flurandrenolide tape 4 mcg/cm^2 (Cordran)
Group 2: High potency	Amcinonide 0.1% ointment (Cyclocort ointment)
	Betamethasone dipropionate 0.05% cream/gel (Diprolene cream, gel, and Diprosone cream)
	Clobetasol propionate 0.025% cream (Impoyz)
	Desoximetasone 0.25% cream, ointment (Topicort)
	Desoximetasone 0.25% spray (Topicort)
	Diflorasone diacetate 0.05% (ApexiCon, Florone, Psorcon)
	Fluocinonide 0.05% cream, gel, ointment, solution (Lidex)
	Halcinonide 0.1% cream (Halog)
	Halobetasol propionate 0.01% lotion (Bryhali)
Group 3: Upper mid-strength	Amcinonide 0.1% cream, lotion (Cyclocort, Amcort)
	Betamethasone dipropionate 0.1% cream, hydrophilic emollient (Diprosone)
	Betamethasone dipropionate 0.12% foam (Luxiq)
	Betamethasone valerate 0.1% ointment (Valisone ointment)
	Desoximetasone 0.05% cream (Topicort LP)
	Diflorasone diacetate 0.05% cream (Florone cream)
	Fluocinonide 0.05% cream aqueous emollient (Lidex-E)
	Fluticasone propionate 0.005% ointment (Cutivate ointment)
	Mometasone furoate 0.1% ointment (Elocon ointment)
	Triamcinolone acetonide 0.5% cream and ointment (Aristocort)
Group 4: Medium potency	Betamethasone dipropionate 0.05% spray (Sernivo)
	Clocortolone pivalate 0.1% cream (Cloderm)
	Fluocinolone acetonide 0.025% ointment (Synalar ointment)
	Flurandrenolide 0.05% ointment (Cordran)
	Hydrocortisone valerate 0.2% ointment (Westcort ointment)
	Mometasone furoate 0.1% cream, lotion, ointment, solution (Elocon)
	Triamcinolone acetonide 0.05%–0.1% ointment, cream, aerosol spray, dental paste (Kenalog, Trianex, Oralone)
Group 5: Lower mid-potency	Betamethasone dipropionate 0.05% lotion (Diprosone lotion)
	Betamethasone valerate 0.1% cream and lotion (Betnovate/Valisone cream and lotion)
	Desonide 0.05% ointment, lotion (DesOwen, Desonate, Tridesilon)
	Fluocinolone acetonide 0.025%, 0.03% cream (Synalar cream)
	Flurandrenolide 0.05% cream and lotion (Cordran)
	Fluticasone propionate 0.05% cream and lotion (Cutivate cream and lotion)
	Hydrocortisone butyrate 0.1% cream (Locoid)
	Hydrocortisone valerate 0.2% cream (Westcort cream)
	Prednicarbate 0.1% cream (Dermatop)
	Triamcinolone acetonide 0.1% cream and lotion (Kenalog cream and lotion)
Group 6: Low potency	Alclometasone dipropionate 0.05% cream and ointment (Aclovate)
	Betamethasone valerate 0.05% lotion (Beta-Val, Valisone)
	Desonide 0.05% cream, ointment, gel (DesOwen, Desonate, Tridesilon)
	Desonide 0.05% foam (Verdeso)
	Fluocinonide acetonide 0.01% cream and solution (Synalar)
	Fluocinonide acetonide 0.01% FS oil (Derma-Smoothe)
	Fluocinolone acetonide 0.01% shampoo (Capex shampoo)
	Triamcinolone acetonide 0.25% cream and lotion (Kenalog, Aristocort)
Class 7: Least Potent	Hydrocortisone 0.5%, 1%, 2%, 2.5% cream, lotion, spray, and ointment (various brands)

Data from Lexicomp [Internet]. Comparison of Representative Topical Corticosteroid Preparations (Classified According to US System). Hudson, OH: Wolters Kluwer Clinical Drug Information, Inc. 1978-2020 [cited 2020 Oct 17]. Available from: http://online.lexi.com.ezproxy.findlay.edu:2048/lco/action/doc/retrieve/docid/patch_f/3674386?cesid=6ESWxn7qMvl&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dtopical%252520corticosteroid%26t%3Dname%26va%3Dtopical%252520corticosteroid.

Low-potency steroids are also recommended for the treatment of infants and children.[9,10,11] The use of topical corticosteroids for prolonged periods of time should be avoided.

Adverse effects from topical steroids are usually related to the potency of the steroid, frequency of application, duration of therapy, and the site of application. Skin atrophy, hypopigmentation, striae, and steroid-induced acne are all possible side effects associated with long-term use.[12] Ointments, because of their occlusive properties, should be avoided on weeping lesions.[1,11]

Topical steroids are typically applied two to four times daily. As improvement begins, maintenance therapy should be limited to the lowest strength steroid that continues to control the condition. Once symptoms are completely resolved, use should be discontinued and should not exceed 1 to 2 weeks.[11]

Antihistamines Whether due to their antihistaminic activity or their sedative side effects, pruritus caused by contact dermatitis can be relieved with the use of sedating oral antihistamines, such as diphenhydramine or hydroxyzine. Topical antihistamines are available, but their use is limited due to their high-sensitizing potential.[1,13] In addition to sedation, many oral antihistamines can cause hypotension, dizziness, blurred vision, and confusion.

Astringents The drying effect of astringents will decrease oozing from lesions and relieve itching.[4,11] Due to their ability to cause blood vessel constriction, astringents can also decrease inflammation. Aluminum acetate (Burow's solution), aluminum sulfate/calcium acetate solution (Domeboro), calamine lotion, colloidal oatmeal baths/soaks, and witch hazel are safe and effective.[1] Aluminum acetate or aluminum sulfate/calcium acetate may be applied as a compress for 30 minutes at least four times daily as needed. Colloidal oatmeal baths or soaks may be applied for 15 to 20 minutes at least twice daily.

Adverse effects reported with these agents are minimal and include drying and tightening of the skin.

T-Cell Selective Inhibitors Topical T-cell selective inhibitors, such as tacrolimus and pimecrolimus, are approved for the treatment of atopic dermatitis but may also be effective in the treatment of ACD.[10,11]

Outcome Evaluation

With adequate treatment, most cases of contact dermatitis should improve within 7 days. Complete resolution of symptoms may take up to 3 weeks.[1] If patients experience severe symptoms associated with fever or difficulty breathing, they should be instructed to seek medical attention immediately. Furthermore, patients should return to their health care provider if any of the following occur:

- Rash has not improved (increased in size or spread to other locations) after several days of treatment.
- Patient is experiencing adverse effects from the treatment regimen.

Patient Care Process: Contact Dermatitis

Collect Information:

- Assess symptoms.
- Obtain a thorough patient history. Can the agent/exposure be identified? Has there been prior exposure to that agent? If so, what treatment regimens were used to alleviate symptoms?
- Obtain patient's allergy status.

Assess the Information:

- Determine whether the patient has ICD or ACD.
- Discuss testing needed to suggest or confirm the etiologic agent (patch testing).

Develop a Care Plan:

- Develop a treatment plan for ICD or ACD. In most cases, nondrug and nonprescription treatment options are most appropriate. If case is severe or if the patient has ACD, the plan may also include prescription therapy.

Implement the Care Plan:

- Provide patient education on ICD or ACD and treatment:
  - Possible adverse effects of drug therapy
  - Symptoms that warrant physician referral?
  - Importance of treatment compliance.
  - Educate on the recognition of agents that may cause contact dermatitis.

Follow-up: Monitor and Evaluate:

- Symptoms should improve within 2 to 3 days. If no improvement, the patient should be advised to follow up with the provider.

Patient Encounter 1

A 55-year-old woman presents to your pharmacy with complaints of intense itching and shows you a red, raised rash with papules on her arms. The patient tells you that she spent the weekend gardening around her home and yard. She tells you that she wore work gloves but had on a short-sleeved shirt. She doesn't recall seeing any poison ivy, but she indicates the rash is similar to a past exposure to poison oak several years ago. The patient states she tried some kind of soap that said it would help treat poison ivy but hasn't tried anything else to manage her symptoms, which are worsening. From the information he has presented, you conclude that she did likely come in contact with an agent while camping and that exposure caused an allergic contact dermatitis to develop.

What information supports the possibility of exposure to an allergic agent?

Describe the symptoms that support this diagnosis.

Determine what the patient has tried to relieve his symptoms.

Describe the differences between allergic and irritant contact dermatitis.

What are your treatment goals for this patient?

What nonpharmacologic and pharmacologic treatment options are available for this diagnosis?

Given the information presented, develop a treatment regimen for this patient that includes the following:

a. A statement of the problem

b. A patient-specific therapeutic plan

c. Monitoring parameters to assess efficacy and safety

ATOPIC DERMATITIS

Introduction

Atopic dermatitis, commonly referred to as eczema, is a chronic inflammatory skin disorder characterized by dry and itchy skin.[14] Atopic dermatitis has been considered to signify the first step of the "**atopic march**", which describes the development of allergic diseases, and be followed by the development of other allergic disorders, such as allergic rhinitis and asthma[14,15,16]; this progression does not happen in all individuals, however, as the association of atopic dermatitis with other atopic conditions is multifactorial and complex.[14,15] The simultaneous occurrence of atopic dermatitis, allergic rhinitis, and asthma is referred to as the atopic triad.[17] While an estimated 70% of individuals with atopic dermatitis during childhood experience remission before adolescence,[16] atopic dermatitis may persist into adulthood and lead to quality-of-life impairments, such as sleep disruption and low self-esteem.[18]

Epidemiology and Etiology

Affecting up to 25% of children and 2% to 3% of adults,[15] the incidence of atopic dermatitis has increased by two- to threefold in the past several decades in industrialized countries.[16] The lifetime prevalence of atopic dermatitis is approximately 10%.[19] Onset of atopic dermatitis most commonly occurs between 3 and 6 months of age[15]; approximately 60% and 90% of individuals experience symptoms by 1 and 5 years of age, respectively.[15] Prevalence of atopic dermatitis among males and females is similar.[14,15,20] Black race and urban living have been found to be associated with a higher prevalence of atopic dermatitis.[20] Studies regarding the effect of socioeconomic status on risk of atopic dermatitis are conflicting.[15] While atopic dermatitis is commonly associated with food allergies, no specific dietary changes are recommended for prevention.[15]

Family history of **atopy** and filaggrin gene mutations are two risk factors strongly associated with the development of atopic dermatitis.[15] Individuals with atopy may be genetically predisposed to predominantly demonstrate T-helper type 2 (Th_2) cells, which may ultimately lead to increased immunoglobulin E (IgE) production, blood eosinophilia, and increased mast cell development as a result of the cytokines produced.[14] The filaggrin gene ultimately plays a key role in maintaining epidermal hydration and barrier function[14,15]; abnormalities in the epidermal barrier may lead to increased absorption of allergens.[14] Triggers that may exacerbate atopic dermatitis are individualized; common triggers include environmental allergens (such as dust mites and pollen), infections, soaps and detergents, fragrances, clothing that is abrasive or occlusive, sweat, hot temperatures (increases sweating), cold temperatures (increases skin dryness), and psychosocial stress.[14,21,22]

Pathophysiology

KEY CONCEPT Epidermal barrier dysfunction and increased Th2 cell activity, leading to increased IgE production, are characteristic pathophysiologic features of atopic dermatitis.[14]

Under normal circumstances, corneocytes and lipids tightly bind together to form a barrier, which prevents water from leaving the skin and allergens and microbes from entering the skin.[22] However, filaggrin mutations, decreased skin barrier proteins, lipids, and ceramides, increased peptidase activity, and lack of protease inhibitors may compromise the skin barrier.[14,17,22,23] Allergens may penetrate an abnormal skin barrier and subsequently come into contact with **dendritic cells**.[14] A predominantly Th2 cell response in the skin ensues, resulting in the release of proinflammatory cytokines, such as interleukin (IL)-4, IL-5, and IL-13.[14,18,23] IgE production increases in response and results in itchy, inflamed skin.[14,23] Atopic dermatitis has been considered to be a biphasic T-cell-mediated disease, with Th2 cell response driving acute disease, and T-helper type 1 (Th1) cell response driving chronic disease.[18,23]

Clinical Presentation and Diagnosis of Atopic Dermatitis

KEY CONCEPT Atopic dermatitis is commonly described as the "itch that rashes" since pruritus is the hallmark symptom.[17,18,21,22] Sleep can be disrupted by itchy atopic skin. Rubbing or scratching atopic skin can lead to further skin irritation and inflammation, leading to additional pruritus.[14]

Atopic dermatitis may manifest as periods of exacerbations (flare-ups) followed by periods of remission[14,17] and result in erythema, edema, xerosis, crusty or scaly skin, and **lichenification**.[15] The clinical presentation of atopic dermatitis can vary based on age and lesion chronicity (see **Figure 67–3**).[15]

Age[21,23] (Figure 67-4):

Infants: Face (cheeks, chin, forehead), scalp, neck, trunk, and extensor surfaces of extremities commonly affected

Childhood: Flexural surfaces of extremities, neck, wrists, and ankles commonly affected

Adolescence/Adulthood: Flexural surfaces of extremities, hands, and feet commonly affected

Lesion Chronicity[17]:

Acute: Skin is erythematous and pruritic with papules (small, solid, elevated lesions) or vesicles (filled with fluid or air). **Excoriation** and secretions are common.

Subacute: presence of erythematous and excoriated papules and scaly plaques (large, flat, slightly elevated lesions)

Chronic: presence of thickened plaques

Skin Infections:

Secondary skin infections may present as yellow crusting over eczematous lesions, pustules (lesions filled with purulent fluid), or vesicles filled with purulent fluid, exudate, or pus.[17]

Diagnosis:

The diagnosis of atopic dermatitis is clinical.[15] No specific confirmatory laboratory test has been established.[17] Occasionally, skin biopsy, serum IgE, potassium hydroxide preparation, patch testing, or genetic testing may be performed to rule out other skin conditions.[15]

Assessment:

No standard atopic dermatitis disease severity grading scale has been identified.[16] While three validated grading scales exist,[15,17,24,25] atopic dermatitis is generally described as mild, moderate, or severe. In addition, scales assessing quality of life, disease impact, and other psychological outcomes have been developed.[15]

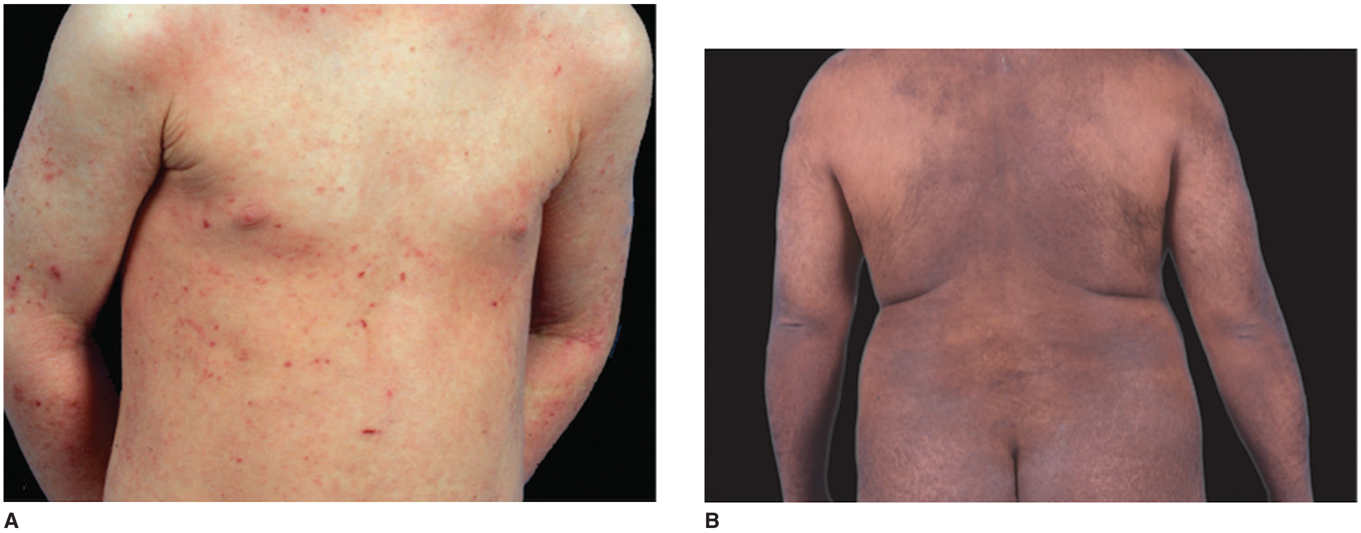

FIGURE 67–3. A: Childhood atopic dermatitis. Generalized eruption consisting of confluent, inflammatory papules that are erosive, excoriated, and crusted. **B:** Adult atopic dermatitis. Generalized eruption of follicular papules that are more heavily pigmented than normal skin in a 53-year-old woman of African extraction. There is extensive lichenification. (From Wolff K, Johnson RA, Saavedra AP, Roh EK. Eczema/dermatitis. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 8th ed. New York, NY: McGraw-Hill; 2017:28.)

Individuals with atopic dermatitis are more susceptible to secondary skin infections due to the presence of a weakened skin barrier, reduced antimicrobial peptides in atopic skin, resulting in a decreased antimicrobial barrier, and pathogenic colonization.[14,22] *Staphylococcus aureus* colonizes approximately 90% of individuals with atopic dermatitis.[23] Infection by *Streptococcus pyogenes*, molluscum contagiosum, and herpes simplex virus should also be considered.[22]

Treatment

▸ *Desired Outcomes and Goals*

The successful management of atopic dermatitis includes (a) controlling pruritus, (b) healing skin lesions, (c) maintaining skin integrity, (d) identifying and removing triggers, and (e) preventing flare-ups. Ultimately, the desired goal of treatment is to

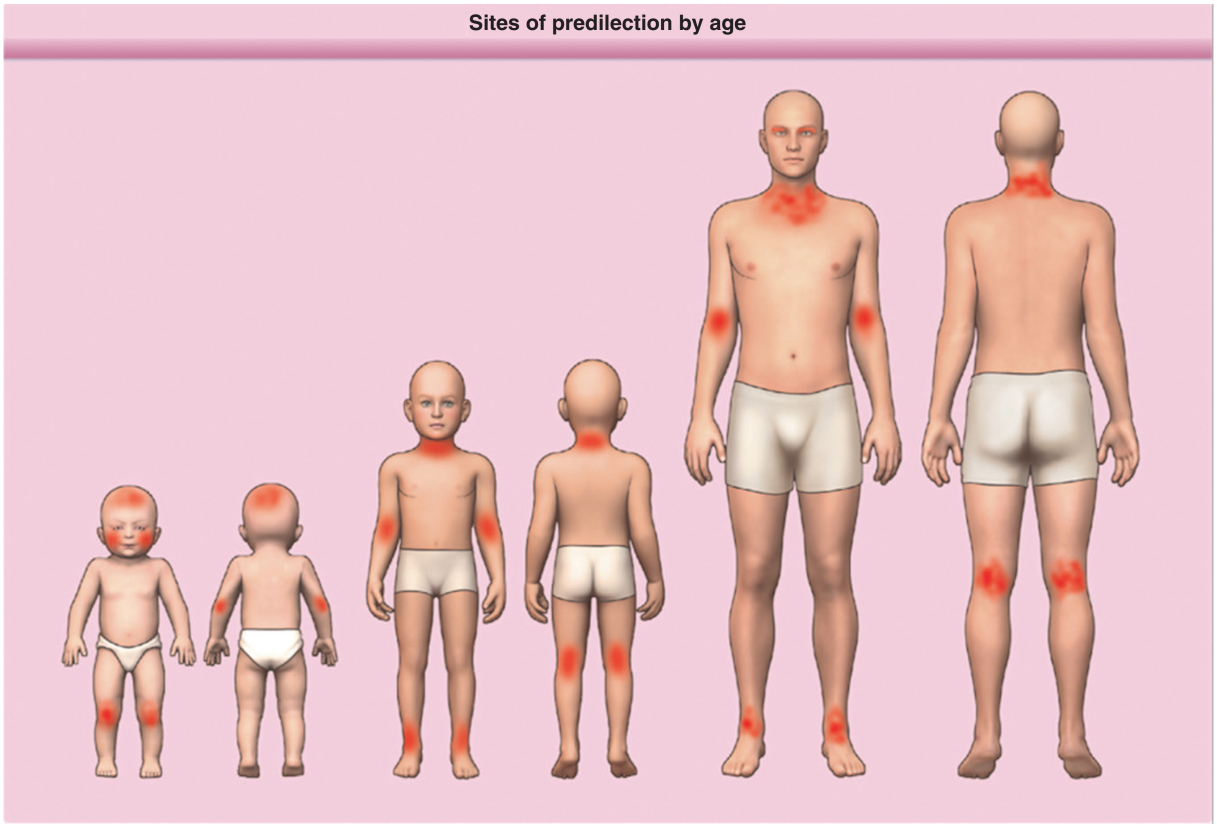

FIGURE 67–4. Atopic dermatitis progression and distribution: infancy, older childhood, and adulthood. (From Kang S, Amagai M, Bruckner AL, et al. Atopic dermatitis. Fitzpatrick's Dermatology, 9th ed. New York, NY: McGraw-Hill; 2019:4.)

prevent future exacerbations and limit the impact on the patient's quality of life. KEY CONCEPT Management of atopic dermatitis generally includes both prescription and nonprescription therapies.

▶ *Nonpharmacologic Treatment*

Nonpharmacologic treatment involves skin care maintenance to repair skin damage and maintain a functional skin barrier. In addition, by identifying and minimizing triggers or allergens, symptoms may be avoided or lessened. Application of moisturizer, especially after bathing, is important to keep skin hydrated. Reapplication may be advised; however, an optimal frequency or amount has not been defined. The use of mild soaps without fragrance may be used to cleanse skin without exacerbating symptoms and it is suggested that bathing daily, followed by the application of emollients, keeps skin hydrated and removes scales or crusts from the skin along with any irritants or allergens.[26,27] Other nonpharmacologic treatments may include light therapy and wet wrap therapy in which a topical agent is applied, followed by a wet dressing and a second dry, outside layer which can be left in place for several hours. Caution should be used with higher potency steroids in wet wrap therapy due to increased absorption and risk for hypothalamic–pituitary–adrenal axis suppression.[27]

▶ *Pharmacologic Treatment*

Prescription medication is typically indicated during exacerbations and continued until the rash resolves. After the rash has cleared, prescription medication may be discontinued or applied less frequently until another flare-up occurs. Topical steroids and/or topical calcineurin inhibitors are both used to manage itching and improve redness, papules, and plaques. Dupilumab, a newer agent, is an injectable product that may be used in patients who are not responding or responding inadequately to topical therapy.

Topical Corticosteroids KEY CONCEPT Topical corticosteroids are considered first-line treatment and are the most used medications to treat atopic dermatitis. They provide relief of inflammation, pruritus, and prevent relapse.[27] Topical corticosteroids are generally considered safe but may result in adverse effects with high doses or prolonged use. Most are prescribed for once or twice a day application during flare-ups with less frequent administration, such as once or twice weekly, once symptoms improve and treatment approach switches from treatment to management. High-potency topical corticosteroids may be used to initially gain control of the skin lesions; however, long-term use should focus on the lowest potency product to minimize adverse effects.[27] Risks for long-term use of topical corticosteroids is discussed in the "Dermatitis" section of this chapter. See Table 67–2 for a list of steroid classes and potencies.

Patient Care Process: Atopic Dermatitis

Collect Information:

- Assess the patient's symptoms, including intensity of itching and quality-of-life impairments (eg, disrupted sleep).
- Note the skin's appearance and rash location(s).
- Obtain family history of atopic conditions.
- Evaluate the patient's skin care regimen, including current use of moisturizers and any products that may exacerbate atopic dermatitis.
- Review what medications the patient has tried for atopic dermatitis in the past.
- Review the patient's health-related goals and preferences.
- Gather a medication list, including prescription and nonprescription drugs and dietary supplements.
- Obtain medication allergies and reaction.
- Review patient's comorbid medical conditions.

Assess Information:

- Assess the patient's symptoms and skin's appearance to determine disease severity (mild, moderate, or severe).
- Determine if the atopic dermatitis is flaring up or in remission.
- Assess for the presence of a secondary skin infection.
- Determine if any products, behaviors, or the environmental influences may be exacerbating the patient's atopic dermatitis.
- Assess if previous therapies were used as directed.
- Determine goals of therapy.

Develop a Care Plan:

- Develop a treatment plan that is likely to be effective based on disease severity, safe, and cost-effective.
- For nondrug and drug therapies, determine frequency of application. If pharmacotherapy is warranted, determine drug, dose, and duration of therapy.
- Eliminate potential triggers and institute appropriate lifestyle measures.

Implement the Care Plan:

- Provide patient education on atopic dermatitis and treatment:
  - Clinical presentation and potential complications of atopic dermatitis.
  - Triggers that can exacerbate atopic dermatitis.
  - Signs of secondary skin infection and when to seek medical attention.
  - Review changes to atopic dermatitis drug regimen.
  - Review drug, dose, frequency of application, and duration of therapy.
  - Inform the patient of appropriate application technique.
  - Review side effects of therapy.
  - Emphasize compliance to therapy, lifestyle measures, and avoidance of triggers.

Follow-Up: Monitor and Evaluate:

- Follow-up in 2 weeks to assess the effectiveness and safety of nonpharmacologic and pharmacologic therapy (eg, relief of itching, resolution of rash, presence of adverse effects).
- Refer for medical evaluation if signs of a skin infection are observed during therapy, such as oozing, draining, pus, or formation of yellow crusts.
- If the rash has improved, continue routine application of a moisturizer.

Topical Calcineurin Inhibitors Second-line pharmacologic agents for the treatment of atopic dermatitis include the topical calcineurin inhibitors, tacrolimus, and pimecrolimus. These products are approved for short term or intermittent use in patients aged 2 years or older in whom topical corticosteroids are not providing adequate relief of symptoms and improvement of skin lesions or who cannot tolerate topical corticosteroids.[28,29] Topical calcineurin inhibitors block T-cell activation and proliferation, which prevents the production of additional proinflammatory mediators that play a role in atopic dermatitis.[27] Because topical calcineurin inhibitors do not cause skin thinning and atrophy like topical corticosteroids, they may be used on more sensitive areas of the skin and for longer term use. Topical tacrolimus has been shown to be more potent than topical pimecrolimus, though both are effective at the treatment of atopic dermatitis. Both tacrolimus and pimecrolimus have a black box warning related to an increased risk of cancer (including skin cancers and lymphoma). Patients should be advised to limit exposure to sunlight and avoid use on malignant or premalignant skin conditions.[28,29]

Biologic Therapy Dupilumab (Dupixent) is an injectable humanized monoclonal antibody targeting IL-4. It is administered subcutaneously with an initial dose of 600 mg followed by 300 mg once every other week for maintenance therapy. The adverse effects that patients taking dupilumab are at highest risk for include hypersensitivity reactions and local injection site reactions. Dupilumab is approved for use in patients 6 years of age or older in whom topical prescription therapies have failed to control symptoms or in patients in whom the use of topical therapies is not advised. Patients started on dupilumab, who are currently using topical therapies, are generally titrated off as symptoms improve.[30]

Patient Encounter 2

A 22-year-old Black, female patient presents to the outpatient clinic with a worsening rash of small red raised lesions and papules with intense itching on her forearms and hands. She shares that this rash is similar to exacerbations she has had in the past and that typically the application of moisturizer to the area several times a day helps to manage the itch until the rash goes away. The patient has a past medical history of seasonal allergies and asthma. She's concerned that a new laundry detergent she used may be causing the rash to worsen and is wondering if there is anything else she might try to relieve the itching?

What reported symptoms support the diagnosis of atopic dermatitis?

What additional information would assist you in your assessment of the patient?

What factors could be contributing to the patient's atopic dermatitis?

Describe your treatment goals for this patient.

What nonpharmacologic treatment options would you suggest for this patient?

Consider a pharmacologic treatment plan for this patient.

Given the information presented, develop a patient-specific therapeutic plan.

Formulate a monitoring plan to assess the efficacy and safety of the patient's therapy.

Outcome Evaluation

Treatment with prescription skin medications should improve rash and itching within 2 weeks. Once rash has improved, continue application of moisturizers daily to the face and body. The presence of oozing, drainage, pus, or yellow crusts may indicate a skin infection. Patients should alert their medical provider if these symptoms develop.

DIAPER DERMATITIS

Epidemiology and Etiology

Diaper dermatitis, more commonly known as diaper rash, is a form of ICD that affects the buttocks, upper thighs, lower abdomen, and genitalia of an estimated 7% to 35% of all infants.[31,32] Onset of occurrence is usually between 3 weeks and 2 years of age, with the most cases reported between 9 and 12 months of age.[32] The use of diapers for incontinence in adults also increases the risk of developing diaper dermatitis.[32]

Pathophysiology

KEY CONCEPT Although many factors contribute to diaper rash, it is most likely the result of prolonged contact of the skin with urine and feces in the diaper. If a diaper is not changed soon after urination or defecation, the excessive hydration, friction of the diaper, and enzymes in the feces lead to breakdown in the protective layer of the skin making the area more susceptible to irritation and infection.[33,34,35,36] Although most mild cases of diaper rash present as erythema, moderate-to-severe cases can result in the formation of papules, vesicles, and even ulceration. If these cases are not effectively treated, the likelihood of secondary fungal or bacterial infections developing is greatly increased.[33]

Treatment

▶ *Desired Outcomes and Goals*

KEY CONCEPT The primary goal in the treatment of diaper rash is prevention and is most often accomplished through frequent diaper changes. **KEY CONCEPT** When a diaper rash is already present, repairing the damaged skin, relieving discomfort, and preventing secondary infections from occurring are important factors to consider when developing an effective treatment regimen.[34]

▶ *Nonpharmacologic Therapy*

Most mild cases of diaper rash can be resolved with the use of nonpharmacologic therapies. Keeping the diaper area clean and dry by changing diapers as soon as practically possible (at least every 2 hours or more frequently) is highly effective for treatment and prevention.[34,35,36] Other nondrug options include[34,36,37,38]:

- Gently wash the area with lukewarm water and mild soap and allow to completely dry before applying a new diaper
- Use water and a cotton cloth or commercial "baby wipes" without coloring, fragrances or other additives
- Keeping diapers loose and well ventilated. If financially feasible, use super-absorbent disposable diapers
- Avoiding plastic pants over diapers
- Allowing infants to take naps on an open diaper or absorbent pad to promote drying and healing

▶ *Pharmacologic Therapy*

Protectants Protectants form an occlusive barrier between the skin and moisture from the diaper. Cream and ointment preparations are effective in providing a sufficient barrier in mild, irritant,

Clinical Presentation and Diagnosis of Diaper Dermatitis

Typical Symptoms

- Erythema is the most common symptom presented with a diaper rash. The rash may begin as light-to-medium pink with poorly defined edges but may become dark red and raised lesions with distinct edges.
- Rashes generally appear in the folds of the skin around the diaper area, thighs, genitals, and buttocks.
- Other typical symptoms include irritation and pruritus.

Atypical Symptoms

Patients presenting with the following symptoms may indicate the need for more aggressive antibiotic or antifungal therapy and should be referred to a physician for further evaluation:

- Rashes not responding to typical creams and concurrent nonpharmacologic treatment
- Rashes extending beyond the diaper region (upper abdomen, back)
- Formation of papules, bullae, ulceration
- Excessive oozing
- Presence of genital discharge
- Concurrent fever
- Rashes appearing when diapers have not been used or rashes that fail to improve upon discontinuing diaper usage for extended periods of time (several days or more)
- Bleeding or open skin

Diagnosis

- The diagnosis of diaper dermatitis is clinical. The presence of *Candida albicans* can be determined by KOH testing or culture but is generally not necessary.

and noninfected diaper rashes. For more severe cases, a paste is the topical agent of choice. Pastes are thicker and often contain additional ingredients (petrolatum, moisturizers) to decrease discomfort and promote healing.[34] Zinc oxide is one of the most used topical protectants. In addition to forming an effective barrier against moisture, it has astringent and antiseptic properties that provide added symptom relief.[34]

Protectants are generally applied to the affected area after every diaper change and can be discontinued when the rash resolves. Other available protectants that can be used alone or in combination for the safe and effective treatment of diaper rash include white petrolatum, Vitamins A and D, lanolin, and topical cornstarch. Many agents contain a combination of occlusive and protective agents such as Triple Paste and Calmoseptine.

Topical Steroids Because of the increased permeability of their skin, infants are at risk for excessive absorption and toxicity from the use of topical steroids. Although effective in decreasing inflammation and relieving pruritus, steroid use in infants for the treatment of diaper dermatitis should be limited to only low-potency preparations.[37]

A thin layer of hydrocortisone cream (0.25% to 1%) applied twice a day for no more than 2 weeks is an appropriate regimen. The use of higher potency steroids, use in patients younger than 2 years old, or use extending beyond 2 weeks should be at the discretion of a physician only.

Antifungals Diaper rashes lasting longer than 48 to 72 hours are at increased risk for the development of fungal infections. These complications are most frequently caused by *C. albicans* and will require treatment with a topical antifungal[31,36] (Figure 67–5).

Adverse events with the use of topical antifungals are generally limited to local irritation at the site of application.

Nystatin, clotrimazole, and miconazole creams or ointments applied two to four times daily with diaper changes have all shown to be effective in the treatment of candidal diaper rash.[36,39] Although some of these products are available over the counter, parents and caregivers should be advised to initiate treatment with antifungal agents only after physician recommendation.

Antibacterials If conventional treatment fails, unresolved diaper rash can also lead to secondary bacterial infections. *S. aureus* and *Streptococcus* are the most likely pathogens responsible for these infections and require treatment with prescription topical (if mild and localized) or systemic (if more severe) antibiotics.[33,35,36,40] While topical protectants may be used as an adjunct in treatment, suspected bacterial infections should always be referred to a physician for accurate diagnosis and the selection of an appropriate antibacterial regimen.[33] Figure 67–6 shows a useful algorithm for the effective treatment of diaper dermatitis.

▶ *Outcome Evaluation*

Most diaper rashes can be effectively treated in less than 1 week. If symptoms do not resolve or begin to worsen, advise caregivers to seek medical attention to determine the presence of secondary fungal or bacterial infections. In addition, provide educational information on proper diaper hygiene techniques in order to prevent the development of future diaper rashes.

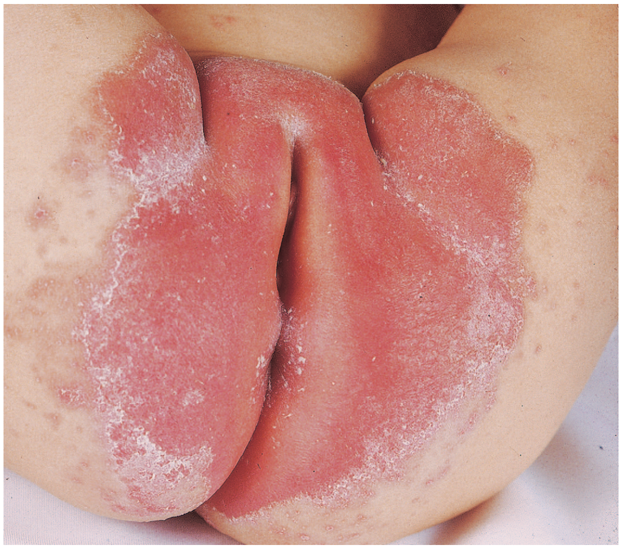

FIGURE 67–5. Candidiasis: diaper dermatitis. Confluent erosions, marginal scaling, and "satellite pustules" in the area covered by a diaper in an infant. (From Wolff K, Johnson RA, Saavedra AP, Roh EK. Fungal infections of the skin, hair, and nails. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 8th ed. New York, NY: McGraw-Hill; 2017:7.)

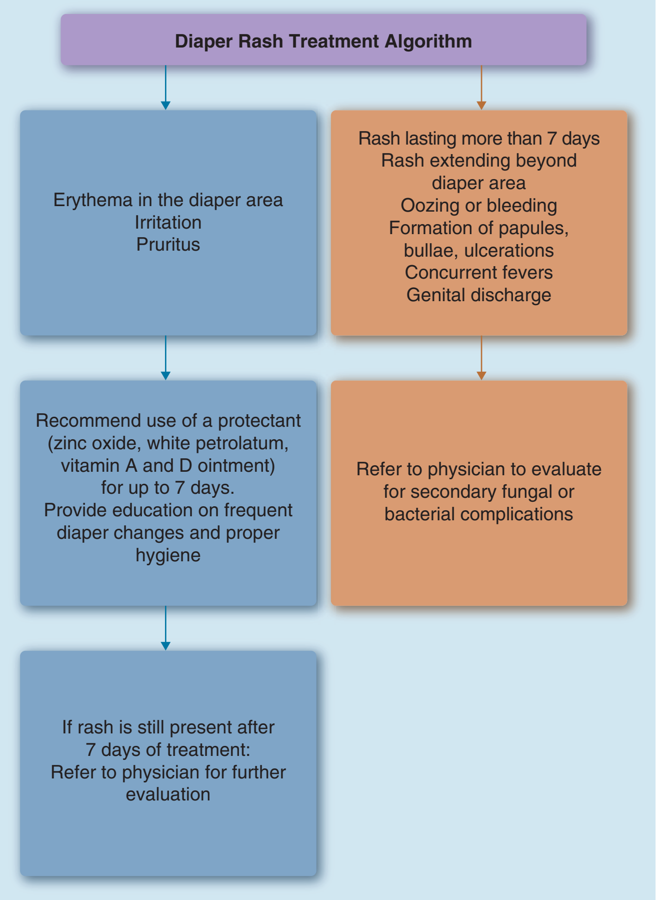
Diaper Rash Treatment Algorithm
Erythema in the diaper area Irritation Pruritus
Rash lasting more than 7 days Rash extending beyond diaper area Oozing or bleeding Formation of papules, bullae, ulcerations Concurrent fevers Genital discharge
Recommend use of a protectant (zinc oxide, white petrolatum, vitamin A and D ointment) for up to 7 days. Provide education on frequent diaper changes and proper hygiene
Refer to physician to evaluate for secondary fungal or bacterial complications
If rash is still present after 7 days of treatment: Refer to physician for further evaluation

FIGURE 67–6. Diaper dermatitis treatment algorithm. (From Krinsky DL, Ferreri SP, Hemstreet B, et al. Diaper dermatitis and prickly heat. Handbook of Nonprescription Drugs, 19th ed. Washington, DC: American Pharmacists Association; 2017:10–11.)

Patient Encounter 3

A woman presents to the front counter of a community pharmacy with a tube of diaper rash ointment. She asks if this is the best product to purchase for her 11-month-old daughter, who she suspects has developed diaper rash. The woman states her daughter woke up fussy and in a wet and dirty diaper this morning, and upon changing the diaper, found the skin to be light pink. She explains using baby wipes with each diaper changing but is concerned about how sensitive the diaper area appears to be compared to normal.

What reported symptoms support the diagnosis of diaper dermatitis?

What additional information would assist in your assessment of the patient?

What factors could be contributing to the patient's diaper dermatitis?

Describe your treatment goals for this patient.

What nonpharmacologic treatment options would you suggest to this patient?

Consider a pharmacologic treatment plan for this patient:

a. Do you recommend a protectant for this patient? Why or why not?

b. What other pharmacologic treatment options for available for the treatment of diaper dermatitis?

Given the information presented, develop a patient-specific therapeutic plan.

Formulate a monitoring plan to assess the efficacy and safety of the patient's therapy.

Patient Care Process: Diaper Dermatitis

Collect Information:

- Gather information related to rash symptoms, characteristics, location, and onset.
- Inquire about the patient's history, including similar rashes in the past, and any previous treatment.
- Obtain patient allergy status.

Assess the Information:

- Determine the level of severity—is there a possibility of a secondary fungal or bacterial infection?
- Identify any signs and symptoms that require immediate physician referral.
- Determine what treatment options, if any, have been tried and if they were successful.
- Discuss labs that may be necessary if a secondary infection is suspected (cultures, biopsies).

Develop a Care Plan:

- Discuss available barrier treatment options with the caregiver.
- Identify appropriate preventative and treatment measures.

Implement the Care Plan:

- Provide caregiver education that includes proper usage instructions and potential side effects.
- Educate the caregiver on the importance of frequent diaper changes and proper hygiene.
- Emphasize importance of treatment compliance and the use of preventative measures.

Follow-up: Monitor and Evaluate:

- Discuss symptoms to report to a physician (blistering, oozing, bleeding, changes in rash, or no improvement in symptoms within 2 to 3 days).

List of Abbreviations

ACD	Allergic contact dermatitis
ICD	Irritant contact dermatitis

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Psoriasis

Amy K. Kennedy

LEARNING OBJECTIVES

Upon completion of this chapter, the reader will be able to:

1. Discuss the etiology of, and risk factors for, psoriasis.
2. Describe the pathophysiology and clinical presentations of psoriasis.
3. Delineate treatment goals for patients diagnosed with psoriasis.
4. Develop an appropriate treatment and care plan for patients diagnosed with psoriasis.
5. Recommend nonpharmacological and pharmacological treatments for psoriasis.
6. Recommend appropriate monitoring parameters for patients diagnosed with psoriasis.
7. Provide education for patients and caregivers as part of the psoriasis care plan.

INTRODUCTION

KEY CONCEPT Psoriasis is a chronic inflammatory condition that exhibits a cyclical pattern of relapse and remission. There is currently no cure for the disease and treatment is designed to manage signs and symptoms associated with the disease.[1] Remission may last years in some, whereas, in others, exacerbations may occur every few months. Patient factors known to exacerbate psoriasis are stress, environmental factors including seasonal changes, and certain medications.[2] Depression, alcohol-related problems, cardiovascular diseases, metabolic syndrome, irritable bowel disease (Crohn's and ulcerative colitis), and skin cancers are select comorbidities associated with the most severe forms of psoriasis.[1] Severity of the condition ranges from mild to severely disabling. Thus, management of psoriasis is lifelong, and treatment changes according to the illness severity at the time. Treatment should be individualized to meet patient needs. The disease may cause emotional distress requiring empathy and caring attitude, when making treatment decisions.

EPIDEMIOLOGY AND ETIOLOGY

Psoriasis is a common chronic inflammatory skin disorder with a prevalence of 2% to 3% worldwide. The prevalence in the United States is approximately 3.2%, while African, African American, and Asian populations have an estimated 0.4% to 0.7% prevalence of the disease.[3] While the overall incidence rate does not differ between men and women, the disease may present at any age, with new diagnoses peaking between ages 15 and 30 and again from 50 to 60 years.[3] Psoriasis can manifest as several different types including **plaque**, **flexural (aka inverse or intertriginous)**, **erythrodermic**, **pustular**, **guttate**, **nail**, and **psoriatic arthritis (PsA)**. Eighty to ninety percent of patients diagnosed with psoriasis present with plaque psoriasis. Plaque psoriasis presents with red-pink lesions of varying sizes covered with silvery-white scales.[2] Approximately 30% to 33% of patients with psoriasis have co-occurring PsA.[1,4] PsA is limited to joints, ligaments, and tendons and presents with pain, stiffness, swelling, and/or tenderness in the affected area. PsA progresses from mild symptoms to the destruction of joints, negatively impacting quality of life for patients.

Psoriatic patients have an increased risk of cardiovascular disease, especially myocardial infarction.[4,5] Risk is present in both mild and severe disease, with the highest risk in younger patients with severe psoriatic disease.[6] These findings persist even when corrected for other cardiovascular risk factors.[5,6,7]

Researchers have identified a mutation in the CARD14 gene that, when activated by an environmental trigger, leads to plaque psoriasis.[8] Up to 36 additional gene loci are suspected in the manifestation of psoriasis and the histocompatibility complex region of chromosome 6 (HLA-Cw*06) has been suspected in the disease.[9] KEY CONCEPT While genetic variations have a significant role, modifiable risk factors greatly impact the likelihood of developing or exacerbating existing psoriasis. These include stress, skin injury (including trauma), medications, infection, obesity, tobacco use, and cold, dry weather. First-degree relatives with psoriasis can increase risk of presentation, affecting males more than females. Women exposed to tobacco smoke have a higher risk of developing psoriasis than their male counterparts with the same exposure. Risk is also higher in urban versus rural settings. Additional factors exacerbating psoriasis include drugs such as lithium, NSAIDs, antimalarials, β-adrenergic blockers, and corticosteroid withdrawal.[10]

PATHOPHYSIOLOGY

Pathogenesis of psoriasis involves multiple components of the immune system. Cytokines, such as interleukins and tumor necrosis factor alpha, T cells, and keratinocytes, are central to the inflammatory process associated with psoriasis. Additionally, it has been found, when keratinocytes are disturbed, release of antimicrobial peptide LL-37 takes place, which binds with DNA and RNA. This complex leads to activation of plasmacytoid and myeloid dendritic cells that secrete interleukin IL-12 and IL-13. Production of these two interleukins eventually results in IL-17 and T helper cell type 1 differentiation.[2] The T cells then release

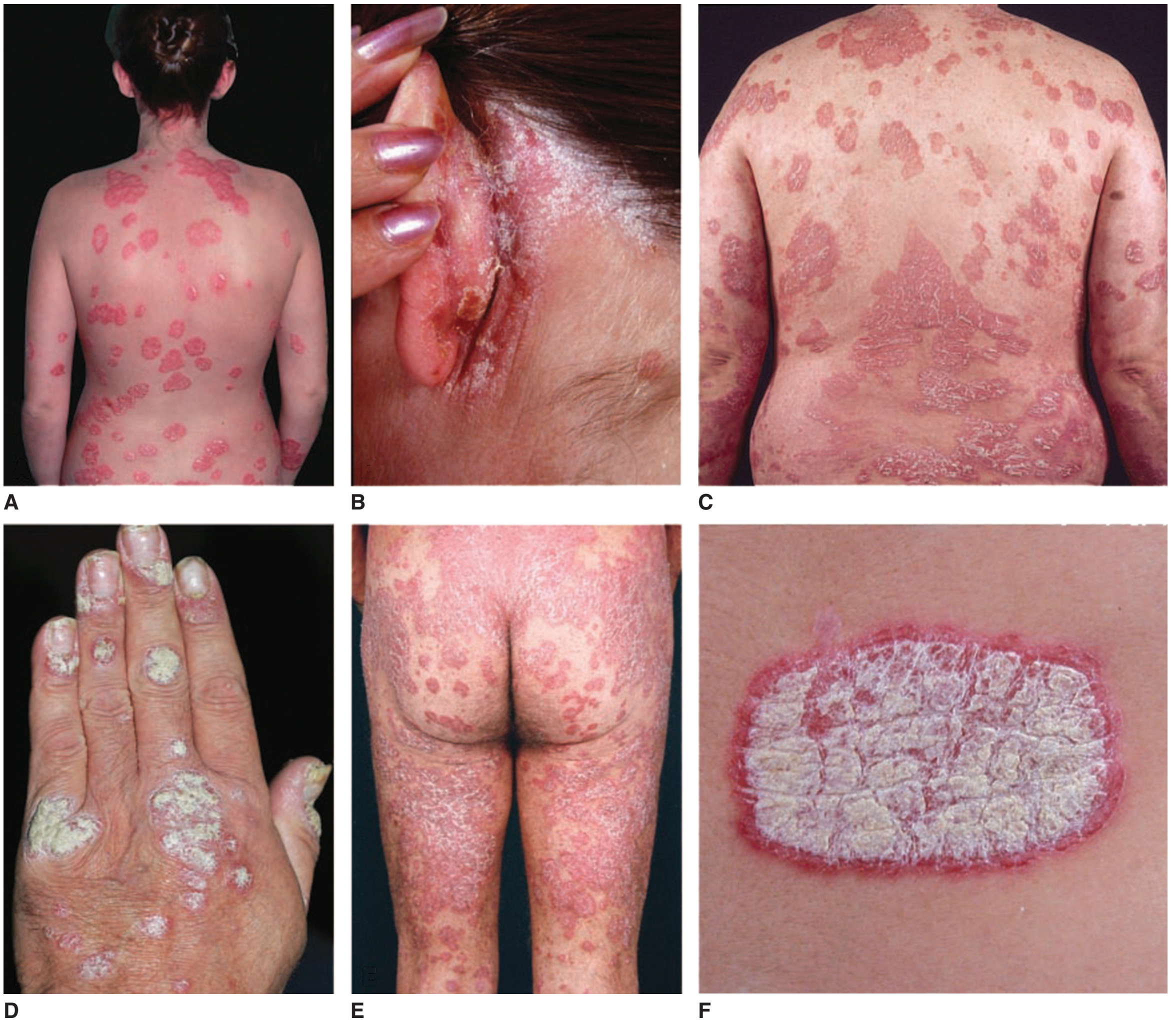

FIGURE 68–1. Chronic plaque psoriasis located at typical sites. Note marked symmetry of lesions. (From Kang S, Amagai M, Bruckner A, et al., eds. Fitzpatrick's Dermatology, 9th ed. New York, NY: McGraw-Hill; 2019. Photos used with permission from Dr. Johann Gudjonsson and Mr. Harrold Carter.)

Interleukin IL-17A, IL-17F, IL-22, and IL-23 as mediators that activate keratinocytes. This process generates a complex cascade including proinflammatory cytokines such as tumor necrosis factor (TNF alpha), interferon (IFN-alpha and IFN-gamma), and interleukin (IL-1beta, and IL-6). The entire process leads to alteration of the immune system and chronic inflammation that manifests in the skin causing vascular changes and formation of psoriatic lesions.[2] Hyperkeratosis that results from immune derangements causes the characteristic thick, scaly skin lesions. The pathologic pathway of psoriatic arthritis is the same, except the changes occurring as a result of T-cell mediators happen in the synovial fluid within joints. Osteoclast activation, osteolysis, and bone resorption produce the damage that occurs within joints.[2]

CLINICAL PRESENTATION AND DIAGNOSIS

KEY CONCEPT Diagnosis of psoriasis is usually based on recognition of characteristic plaque lesions and not on laboratory tests.

The severity of the disease is classified as mild, moderate, or severe disease based on BSA involvement. Additionally, classification may be based on assessment tools used such as the Psoriasis Area and Severity Index (PASI) which measures

Clinical Presentation and Diagnosis of Plaque Psoriasis

General characteristics	Small, discrete lesions to generalized confluent lesions over a large body surface area (BSA).
Symptoms	Severe itching (Not all patients experience)
Signs	• Raised lesions red to violet in color (commonly known as plaques). • Sharply demarcated lesion borders, except where confluent. • Lesions loosely covered with silvery-white scales, which if lifted off, show small pinpoints of bleeding (Auspitz sign). • Plaques appear on elbows, knees, scalp, umbilicus, and lumbar areas, and often extend to involve the trunk, arms, legs, face, ears, palms, soles, and nails. • Nail involvement presents as pitting, discoloration ("oil spots"), crumbling, splinter hemorrhages, growth arrest lines, or tissue buildup around the nails.

Clinical Presentation and Diagnosis of Other Types of Psoriasis

Flexural psoriasis	• Appears in intertriginous areas • Minimal scaling
Guttate psoriasis	• Sudden eruption of small, disseminated erythematosquamous papules and plaques • Often preceded by a streptococcal infection 2–3 weeks prior
Pustular psoriasis	• May be localized or generalized • May be an acute emergency requiring systemic therapy due to loss of skin integrity
Generalized pustular psoriasis	• Disseminated deep-red erythematous areas and pustules • May merge to become "lakes of pus"
Erythrodermic psoriasis	• Generalized, life-threatening condition • Erythema, desquamation, and edema • May require life support measures as well as systemic therapy

Patient Encounter, Part 1

RH is a 52-year-old man who has noticed red lesions that flake covering his back and elbows. When questioned, the patient says he has had these before, but they started spreading about 3 months ago. Since then, the lesions have become more noticeable, increasing in size. He is feeling self-conscious about what is happening and does not know what to do.

PMH: Hypertension

FH: Mother has psoriasis and rosacea. Father has hypertension. Younger brother has depression and Type 1 diabetes.

SH: RH is single with no children. He works for the city parks department and routinely forgets to wear sunscreen. He has a beer with dinner nightly and does not use tobacco.

Meds: Metoprolol ER 25 mg daily

Physical Exam

Gen: He appears distressed about the lesions.

VS: BP 134/77 mm Hg, P 78 beats/min, RR 20 breaths/min, T 37.0°C (98.6°F)

Height and Weight: Ht. 5 ft 7 in. (170 cm), Wt. 242 lb. (110 kg)

Abd: Soft, NTND; (+) Bowel sounds;

Exts: Within normal limits; no joint pains; lesions covering both elbows

Skin: Red lesions with silvery scale on elbows and back (BSA 9%)

Labs: All within normal limits, including lipids, renal function tests, and LFTs

What type of psoriasis is RH experiencing?

What risk factors does he have for psoriasis?

Table 68–1

Disease Severity Classification[4,12,14]

Mild disease	Less than 3% BSA involvement
Moderate disease	3%–10% BSA involvement OR PASI greater than or equal to 8 (higher in trials of biologics)
Severe disease	The Rule of Tens: PASI greater than or equal to 10 or DLQI greater than or equal to 10 or BSA greater than 10% (in some phototherapy trials, BSA greater than or equal to 20% is used as the lower limit) OR results in serious emotional consequences, causes intractable pruritus or occurs on the hands, feet, scalp, face, or genital area

three plaque issues: erythema, induration and scaling (overall score 0–72), Physician Global Assessment (PGA) (overall score 0–5,6), and the Dermatology Life Quality Index (DLQI) (score 0–30).[11,12]

TREATMENT

Desired Outcomes and Goals

KEY CONCEPT Given its manifestations, inflammation, involvement of multiple areas of the affected skin, and the chronic nature of psoriasis, treatment goals must be individualized. Goals of treatment must be set based on clinical presentation, disease-related comorbidities, treatment-related morbidity, mortality, quality of life, staging of disease, and remission status at any given time.[4,6,7,11,12,13,14] It is imperative to remember that no cure exists for any type of psoriatic disease. However, evidence shows that current treatment options increase remission periods and reduce severity of disease.[3,14] Treatment goals should include:

- Minimize or eliminate signs of psoriasis, such as plaques and scales
- Alleviate pruritus and minimize excoriations when present
- Extend remission cycles
- Ensure appropriate management of associated comorbidities such as psoriatic arthritis, cardiovascular disorders, Crohn's disease, or clinical depression
- Avoid or minimize adverse effects from treatments
- Provide cost-effective therapy
- Provide counseling as needed (eg, stress-reduction techniques)
- Maintain or improve the patient's quality of life

General Approach to Treatment

The management of psoriasis should target the type that the patient presents with. General treatment considerations must include disease severity, location, the extent of BSA involvement, and pertinent lifestyle modifications.[11] The psychological impact of psoriasis may not correlate with the severity of the skin presentation, and it is important to continually evaluate the psychosocial effects of psoriasis on each patient.

For psoriatic arthritis (PsA), the goal of treatment is to reduce pain, reduce swelling, slow or minimize joint damage and maintain joint function.[2,3,4,6,7,11] KEY CONCEPT Effective psoriasis treatment should include both pharmacologic and nonpharmacologic approaches.[3,14]

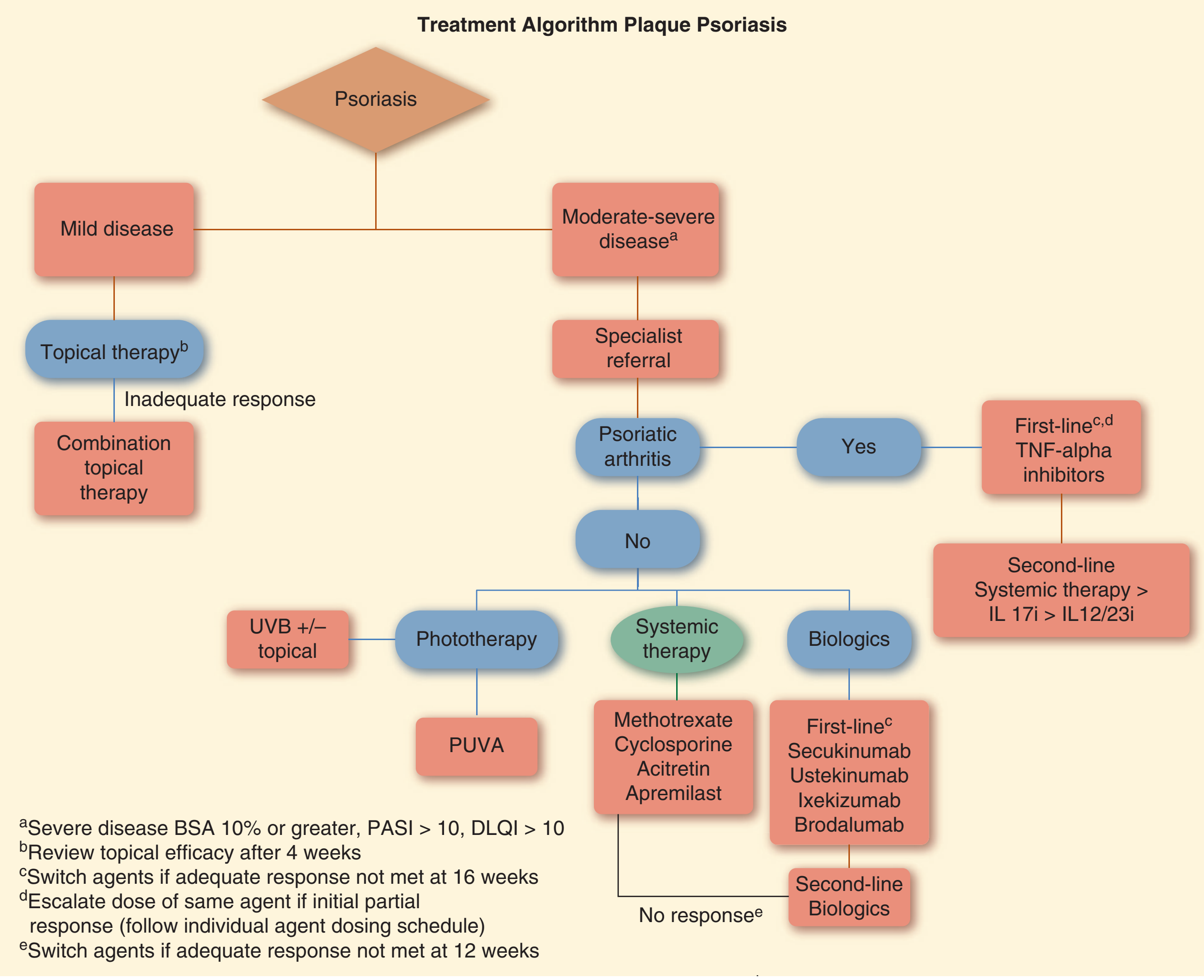
Treatment Algorithm Plaque Psoriasis
Psoriasis
Mild disease
Moderate-severe disease[a]
Topical therapy[b]
Inadequate response
Combination topical therapy
Specialist referral
Psoriatic arthritis
Yes
First-line[c,d] TNF-alpha inhibitors
Second-line Systemic therapy > IL 17i > IL12/23i
No
UVB +/– topical
Phototherapy
Systemic therapy
Biologics
PUVA
Methotrexate Cyclosporine Acitretin Apremilast
First-line[c] Secukinumab Ustekinumab Ixekizumab Brodalumab
Second-line Biologics
No response[e]
[a]Severe disease BSA 10% or greater, PASI > 10, DLQI > 10
[b]Review topical efficacy after 4 weeks
[c]Switch agents if adequate response not met at 16 weeks
[d]Escalate dose of same agent if initial partial response (follow individual agent dosing schedule)
[e]Switch agents if adequate response not met at 12 weeks

FIGURE 68–2. Treatment algorithm for plaque psoriasis.[4,6,7,14,17,19]

Nonpharmacologic Management

KEY CONCEPT Several effective nonpharmacologic options are available to patients with psoriasis. However, considering the inflammatory nature of the disease, these treatments should be used as adjunctive treatments to therapeutic agents when appropriate.[12]

Stress reduction techniques such as psychotherapy, guided imagery, and relaxation techniques have been shown to reduce the extent and severity of psoriasis.[13,14] Oatmeal baths in tepid water may help soothe the itching associated with psoriasis. Nonmedicated moisturizers (occlusive agents, humectants, and/or emollients) help the skin retain moisture and reduce the silvery-white scaling of skin lesions. Emollients can be applied multiple times during the day to prevent skin dryness. Patients with skin sensitivities should consider the use of fragrance-free products to prevent flareups.[14] Harsh soaps, detergents, and other skin irritants should be avoided as they may worsen symptoms. Skin cleansing is appropriate; however, it should be done with lipid-free cleansers and tepid water when possible. Trauma to the skin must always be avoided as damage to skin integrity can precipitate a flare. Consequently, the use of sunscreen with sun protection factor (SPF) of 30 or greater is recommended as sunburn is one of the most common skin traumas.[15] Loose-fitting clothes are desired to help reduce skin irritation.[14]

Pharmacologic Therapy

The pathogenesis of the disease involves a complex mechanism that disturbs the immune system, causes vascular changes, and results in the development of skin lesions.[2] It is paramount that therapeutic agents opposing these processes are well represented in the treatment plan. **KEY CONCEPT** These agents are anti-inflammatory, anticytokines, and biologic therapies. They are classified into topical, phototherapy, conventional systemic therapy, and biologics.[6,14,18,19] Several factors must be taken into consideration in identifying the right therapy for a patient with psoriasis. These include the affected area of the disease, cost, availability of medication, and the preferred lifestyle of the patient. A full patient history including allergies must be collected to ensure a successful therapeutic approach. Topical agents are recommended for mild-to-moderate disease due to their affordability and fewer adverse effects. Low potency corticosteroids are used first line for mild conditions. If the condition persists, it is recommended to switch to a very high potency steroid in combination with a vitamin D analogue or topical retinoids. In general, a patient BSA should be less than 3% to qualify for topical therapy alone. A general recommendation after unsuccessful treatment with topical agents is to add phototherapy. Psoralen and ultraviolet A (PUVA) was found to be more effective than UVB in the treatment of patients with moderate-to-severe psoriasis.[16] Traditional systemic agents can be used for patients with severe disease and are often combined with topical therapy to improve effectiveness. Clinical trials indicate immunosuppressants are more effective than oral retinoids. Biological agents may be the drug of choice for severe disease depending on patient comorbidities, those intolerant to, or that fail traditional systemic agents. The choice of biologic agents depends on the patient's preference and comorbidities.[6,17] Psoriasis affecting more than 3% of BSA should be the justification for initiating systemic/biologic therapy. For patients with liver disease, kidney dysfunction, and skin cancer, it is recommended to avoid methotrexate, cyclosporine, and PUVA treatment, respectively.[6,18,19]

▶ *Topical Treatment*

These agents are first-line treatment for mild-to-moderate psoriasis. They are known for their anti-inflammatory, antiproliferative, and anti-immunologic properties. They are classified as corticosteroids, vitamin D analogues, retinoids, calcineurin inhibitors, coal tar, anthralin, and salicylic acid derivatives. Topicals can also be used as adjunct therapy to phototherapy, systemic and/or biologic agents. Different dosage forms are available such as creams, lotions, gels, foams, ointments, shampoos, oil solutions, tapes, and sprays. **KEY CONCEPT** The choice of specific dosage form or vehicle is dependent on several factors including the BSA involved, location, thickness of the lesions, and the appearance of the plaques.[14] Ointments are recommended for dry and thick lesions to enhance absorption and maintain skin moisture. Creams are indicated for acute, but moist appearing, lesions that do not require ointment-based products. Solutions/shampoos and gels are recommended for scalp lesions and foams and sprays are usually used for lesions in genital areas.[14]

Vehicle selection is an important consideration as it impacts topical efficacy. Ointments and tapes provide occlusion, enhancing drug penetration to improve efficacy. Shampoos incorporating coal tar distillates or salicylic acid with corticosteroids are useful for scalp psoriasis. Coal tar and salicylic acid are rarely used as lone agents due to tolerability issues related to staining and irritation, respectively. It is important to remember that changing vehicles may significantly alter drug potency. Ultimately, the optimal vehicle may be the one the patient is willing to use. Occlusive ointments may be too greasy and cosmetically unappealing, resulting in poor adherence. Sometimes using a cream formulation during the day and an ointment at night may be the best option.[14]

KEY CONCEPT Corticosteroids are the topical first-line treatment for mild-to-moderate psoriasis. They exert anti-inflammatory and immunosuppressive effects, resulting in reduced scaling and overall plaque size. Additionally, topical corticosteroids can be combined with other topicals or systemic/biologic agents to enhance therapy. Adverse effects include skin atrophy with prolonged use (especially if used with an occlusive agent), hypopigmentation, and striae. More than 2 to 4 weeks of continuous use should be avoided to prevent these complications.[14] Nonsteroid topicals can be used as single agents or in combination (most commonly vitamin D analogues and retinoids) with the corticosteroids to reduce exposure to corticosteroids.

▶ *Phototherapy for Psoriasis*

Phototherapy and **photochemotherapy** are generally used to manage moderate-to-severe disease, when topical treatment is not sufficient, when the patient wants to avoid systemic side effects, or as adjunct therapy to a failing regimen.[19]

Patient Encounter, Part 2

The diagnosis is the patient has plaque psoriasis.
Patient expresses to you at this time his elbows are the most bothersome, but he wants something that will take care of his psoriasis all over.

What nonpharmacologic alternatives are appropriate for this patient?

What pharmacologic agents are appropriate for this patient?

Phototherapy is commonly done using narrow band UVB (NB-UVB) radiation two to three times weekly. Once skin clears or improves, sessions can be once weekly for maintenance. UVB disrupts synthesis of proteins and nucleic acids in skin, reducing epidermal keratin proliferation. Phototherapy may be administered during pregnancy and is considered a first-line therapy for those patients as long as the patient is on adequate folate supplementation (UVB can deplete folate above a certain exposure).[19]

Photochemotherapy is the administration of phototherapy together with topical or systemic agents.[14,19] UVA has a long wavelength, and therapy with UVA is always combined with **psoralens** (eg, methoxsalen or trioxsalen), which are used as photosensitizers to increase efficacy. Use of psoralens + ultraviolet A (PUVA) for psoriasis causes two types of reactions: (a) an anoxic reaction that affects cellular deoxyribonucleic acid (DNA) that inhibits proliferation of epidermal cells and induces cell death (apoptosis), and (b) an oxygen-dependent reaction that increases formation of free radicals and reactive oxygen that may damage membranes by lipid peroxidation. PUVA applies to a group of therapies utilizing psoralens to sensitize cells to UVA light.[19]

▶ *Systemic Therapy*

Systemic therapies are used for moderate-to-severe disease. To minimize drug toxicities or increase efficacy, systemic therapies are sometimes used in conjunction with topical or phototherapy.[3,4,12,18,19,20] These agents are classified into immunosuppressants, oral retinoids, T-cell activation inhibitors, cytokine modulators, tumor necrosis factor-alpha inhibitors, and interleukin 12 and 23 blockers.[1]

Cyclosporine is an immunosuppressant that inhibits helper T cells and keratinocyte activation and proliferation. Cyclosporine is efficacious in both inducing and maintaining remission for patients with moderate-to-severe plaque psoriasis and is also effective in treating pustular, erythrodermic, and nail psoriasis.[12,18]

Methotrexate is a folic acid antagonist that interferes with purine synthesis, thus inhibiting DNA synthesis and cell replication. In addition to the antimitotic effect, it suppresses T-cell effects, and, in low doses, has anti-inflammatory and antiproliferative effects by acting on lymphoid cells. Methotrexate has a more modest effect than cyclosporine but can be used continuously for years, with persistent benefits for both psoriasis and PsA.[11] Folic acid is added to the methotrexate treatment to reduce gastrointestinal symptoms and bone marrow toxicity. Due to these side effects, extensive monitoring is required. It may take up to 4 weeks to see a clinical response after a dose increase.[11,18]

Oral apremilast is one of a class of "small molecule" systemic biologics specifically approved for PsA. It inhibits phosphodiesterase

Table 68–2

Topical Medications[2,12,14]

Actions and Effects	Selected Agents	Criteria	Approach to Therapy	Efficacy Assessment (PGA) Scores	Dosage Form/ Strength	Place in Therapy
Corticosteroids						
Corticosteroids Anti-inflammatory Vasoconstriction Immunosuppression Antiproliferative	**Very High Potency** • Betamethasone • Clobetasol • Diflorasone	Mild to moderate	Monotherapy for acute episode	41%–92% with increase in potency	Ointments Creams Lotions Gels Foams Solutions Shampoos, spray and tape	First line To avoid disease flares, taper use first every other day then twice a week then stop Lower potency should be tried on the face, intertriginous areas and areas susceptible to atrophy (e.g. forearms) Safe to use in pregnancy at low doses (60 g per week) and avoid nipple and areola area
	High Potency • Amcinoride • Betamethasone dipropionate and valerate • Desoximetasone		Monotherapy for acute episode			
	Intermediate Potency • Betamethasone • Triamcinolone		Monotherapy for acute episode			
	Low Potency • Alclometasone • Desonide • Hydrocortisone		Monotherapy for acute episode			
Vitamin D Analogues						
Not well-known Vitamin D Receptor binding is proposed Keratinocytes proliferation is attenuated	Calcipotriene	Mild to moderate	Mono- or steroid-sparing adjunctive therapy First consideration with steroid when rapid lesion eradication is desired	60%–70%	Cream Scalp solution	First line with or without steroid Can be used with methotrexate to lower doses and increase time to relapse Long-term combo with corticosteroid more effective than either alone Can be used with phototherapy but must be applied subsequently to avoid inactivation May be used during pregnancy and lactation if benefits outweigh risks
	Calcitriol			60%–70%	Ointment	
Retinoids						
Not well known. Modifies gene transcription Decrease inflammation and keratinocyte proliferation due to its retinoid acid receptors binding	Tazarotene	Mild to moderate	Mono- or adjunctive therapy with steroid. More effective with high potency steroids	63%	Gel	Second line with or without steroid Should be avoided in pregnant women (obtain pregnancy test 2 weeks prior to start of therapy)

Calcineurin Inhibitors Topical calcineurin inhibitors bind to calcineurin, blocking its phosphorylation, and thus, inhibiting T-cell activation and the synthesis of several proinflammatory cytokines that play a critical role in the pathogenesis of psoriasis	Tacrolimus	Mild to Moderate	Monotherapy for more sensitive areas of the skin such as face	65%–70%	Ointment Strengths: 0.03% and 0.1%	Third line with or without steroid Not FDA approved but often used in facial or intertriginous areas Safety in pregnancy is unknown
	Pimecrolimus	Mild to Moderate	Monotherapy for more sensitive areas of the skin such as face	56%–62%	Cream Strength: 1%	
			Other Agents			
Moisturizers Unknown	Nonmedicated Moisturizers	Mild to moderate	Commonly used throughout the day In combination with other topicals to reduce adverse effects	31%	Creams and ointments	Symptom relief/appearance of lesions Safe to use during pregnancy and lactation
Salicylates Acts as a keratolytic agent and reduces lesion scaling to improve absorption of applied medications	Salicylic acid	Mild to moderate	More effective when used as an adjunctive therapy to other topical agents (allows for more effective absorption of combination agent)	unknown	Creams Foams Ointments Shampoos Strengths 1.8%–2.5% and 3%	Adjunct therapy for scalp psoriasis used with steroids to increase efficacy (breaks down keratin)
Anthralin Inhibition of T-cell proliferation and migration of neutrophils Keratolytic agent	Anthralin	Mild to moderate	Used infrequently due to irritation	Unknown	Creams and Shampoos Strengths 1%–1.2%	Adjunct therapy often used in conjunction with steroids in a paste
Coal Tar Inhibition of cell proliferation Acts as keratoplastic Agent	Coal Tar crude Coal Tar combinations	Mild to moderate	Used infrequently due to skin irritation	Unknown	Creams, Gels Shampoo Solutions Lotions Oil Strengths 0.5% to 3%	Adjunct therapy with steroids to increase efficacy May be advisable to avoid during pregnancy

Table 68–3

Topical Medications[2,12,14]

Drug Class	Dosing and Application	Administration Guidelines	Cautions and Side Effects
Corticosteroid	• Mostly once or twice daily • Every other day or weekends only application may be suitable for long term therapy • Treatment is recommended for 2 to 3 weeks • Low and intermediate potency can be used up to 3 months	• Intermediate and low potency agents are indicated for acute and mild lesions and tapering is recommended to the lowest tolerated dose when the condition improves • Low potency agents are suitable for lesions in infants due to large BSA and elderly for the sensitive and thin layer of the skin • High and very high potency agents are indicated for chronic and severe lesions • Palms and soles of the skin require high and very high potency agents to maximize absorption and penetration due to the thickness of the skin	• Skin irritation • Dryness • Withdrawal effects
Vitamin D Analogues	Mostly once or twice daily for a maximum of 2 months for effective result	• Recommended to be used with topical steroids to speed up the healing process • Considered less toxic than topical steroids • Combination therapy with steroids has shown to be more effective than the single agent • Onset of action is slow • Avoid calcipotriene use with salicylic acid due to instability of calcipotriene	• Pruritus • Skin irritation on facial area and skin folds • Skin irritation is less with Calcitriol • Skin rashes • Burning • Changes in systemic vitamin D levels
Retinoids	Preferred as once daily at bedtime	• Best used to achieve better efficacy results with high potent steroids or UVB phototherapy • Monotherapy duration of use 8 to 12 weeks	• Skin irritation (erythema, burning) • Pruritus • Dryness • Photosensitivity • Adverse effects reduced by using cream, lower concentration or in combination
Calcineurin Inhibitors	Mostly once or twice daily depending on the product until effective result is observed	• Comparison data to other agents or in combination is lacking • Use with salicylic acid for 8 weeks showed efficacy improvement in facial lesions	• Skin irritation • Pruritus • Photosensitivity • Flushing in combination with alcohol • Black box warning-skin cancer and lymphoma (no evidence with topical use)
Other Agents • Salicylic Acid • Coal Tar • Anthralin	As directed	• Decreases the scaling of the skin lesions to allow application of other agents • Infrequent use of tars and anthralins due to irritation and staining	• Skin irritation • Potential salicylic acid toxicity manifesting as nausea and ringing in ears (can occur when treating large surface areas and in renal or hepatic impairment)

4 (PDE4) which controls part of the inflammatory actions within cells via cAMP to decrease nitric oxide synthase, TNF-alpha and interleukin [IL] 23, and increase IL-10.

Acitretin is an oral retinoid that is likely safer, but less effective, than methotrexate or cyclosporine since potentially serious adverse effects can be minimized by appropriate patient selection, careful dosing, and monitoring. Acitretin, given concurrently with phototherapy, acitretin + ultraviolet B (ReUVB) or oral retinoid + PUVA (RePUVA), has a synergistic treatment effect.[21,22] Acitretin monotherapy is usually given for 14 days before instituting UVB or PUVA.[15] ReUVB and RePUVA are well-established treatment regimens for psoriasis.[4,6,7,18,19] Pregnancy and blood donation must be avoided during treatment and for 3 years after discontinuation of therapy.[6,7,12] Acitretin can transform spontaneously or be converted by ethanol (transesterification) into etretinate, which may take up to 3 years to completely clear the body. Due to this, acitretin patients should abstain from alcoholic beverages during therapy and for at least 2 months after discontinuation.

Biologics Biologics and their biosimilars are currently recommended for consideration as first-line therapies alongside traditional systemic agents for moderate-to-severe disease.[6,18] These agents inhibit various molecular signaling steps of the immunological signaling cascade that are key determinants of the pathogenesis of psoriasis. The following agents are available for the treatment of chronic plaque psoriasis:[23,24,25]

1. Inhibitors of tumor necrosis factor, which include biologic agents such as etanercept, adalimumab, infliximab, certolizumab, and golimumab.
2. Inhibitors of interleukin, which include ustekinumab, ixekizumab, brodalumab, risankizumab, tildrakizumab, guselkumab, and secukinumab.

Their safety profile, in comparison with other systemic agents, and relatively good patient acceptability are all positive factors for use.[6] However, given immunosuppression is an adverse effect of many of these agents, clinicians should ensure appropriate vaccinations are administered and tuberculosis skin testing performed prior to initiation of therapy. Additionally, clinicians should monitor for signs/symptoms of infection throughout therapy. Primary response success with biologics is defined as 50% or greater reduction in baseline disease severity. Treatment efficacy should be assessed at 12 to 16 weeks except for infliximab which should be assessed after 8 to 10 weeks of use. Therapy should be switched if the primary response is not achieved or if the psoriasis initially responds but then loses its response. Consider a dose escalation, increase in frequency or addition of other modalities if a partial response is achieved.

All TNFα inhibitors improve the signs and symptoms of PsA, improve functional status and quality of life and inhibit progression of joint damage. Due to this, they are the preferred biologic treatment for psoriasis with concomitant PsA. Many other biologics may be used when PsA is present, but certolizumab (TNF-alpha inhibitor), guselkumab (interleukin inhibitor), and abatacept (T-cell inhibitor) can only be used for PsA and not severe psoriasis.[6,24,25]

OUTCOME EVALUATION

- Monitor for clearance of skin lesions. Depending on the agent(s) used and site of lesions, it may take 2 to 6 weeks or longer to see a response. Complete clearance may not be achieved for all patients. A BSA of 3% or less or a BSA improvement of 50% or more from baseline is considered an acceptable response.
- Beginning 3 months after the start of new therapies (Important to wait at least 90 days since it can take up to 16 weeks to effect (induction phase)):
  - A BSA of 1% or less is recommended for target therapy.
- During maintenance or remission, monitor every 6 months.
  - A BSA of 1% or less is the target response every 6 months during maintenance evaluation.
- In Europe, successful treatment is defined as a decrease in the Psoriasis Area and Severity Index (PASI) score of 75% or greater. The PASI is a scoring instrument that ranges from 0 (absence of disease) to 72 (most severe form of the disease).[17]
- Treatment failure is defined as a decrease in the PASI score of less than 50% necessitating new treatment.
- Monitor for improvement of symptoms and control of comorbid conditions. Incomplete clearance of lesions, but improvement in these metrics, can be considered at least partial treatment success. The American Academy of Dermatology/National Psoriasis Foundation (AAD-NPF) clinical guidelines on psoriasis outline other qualitative measures to be used in assessing the holistic approach to disease management.[1] It emphasizes evaluating physical, psychological, and social impact of the disease on the quality of life and daily living activities of the patients. Efficacy achievement alone may not have the overall desired effect on patients wellbeing.[1,14] Dermatology Quality of Life Scales, Dermatology Life Quality Index (DLQI), Dermatology Specific Quality of Life Instrument, and Skindex-29 are validated instruments that are used to measure these quality outcomes in patients with psoriasis by specialists.[12,18]
- Monitor for adverse effects and drug interactions, depending on agent(s) used.
- Total clearance of skin is not impossible during periods of remission; remissions may be days, months, years, and even decades in length with patients being weaned from their medications entirely or reduced to a low maintenance dose.

Patient Encounter, Part 3

The patient was started on clobetasol 0.1% ointment and phototherapy and has been doing well for several months. RH reports that his skin looks better, but he is starting to have joint pain.

Current meds: Nonmedicated moisturizer after bathing and as needed; clobetasol 0.1% ointment twice daily; phototherapy; metoprolol ER 25 mg daily

What is your main treatment goal for this patient?

What pharmacologic treatments would be appropriate for this patient at this time?

What are the monitoring parameters of your proposed treatment?

Table 68–4

Systemic Agents[3,7,11,12,18]

Drug	Mechanism of Action	Doses and Administration	Dosage Forms	Adverse Effects	Therapeutic efficacy on PASI 75	Therapeutic Application	Therapeutic Monitoring
Immunosuppressants							
Cyclosporine	An immunosuppressive agent that specifically inhibits helper T cell and keratinocyte activation and proliferation	2.5 mg/kg/day in two divided doses for at least 4 weeks This dose may be subsequently titrated and increased by 0.5 mg/kg/day every 2 weeks until there is control of plaques (max dose of 5 mg/kg /day)	Oral and IV solution	Nephrotoxicity, lowering of seizure threshold, tremor, gingival hyperplasia, hypertension, squamous cell carcinoma (cutaneous), avoid concomitant use with phototherapy due to increased photocarcinogenesis, but can be used sequentially, avoid live vaccines due to immunosuppression	~41%–71%	Recommended in severe, recalcitrant psoriasis Used in psoriasis only (children only as last line therapy)	LFTs (Baseline and routine) SCR, BUN CBC Uric acid Blood pressure Drug Interaction with cytochrome p450 substrate and inhibitors Pregnancy Therapeutic relapse after completing therapy (~3 months)
Methotrexate	Folic acid antagonist Act by interfering with purine synthesis, thus inhibiting DNA synthesis and cell replication	7.5–10 mg weekly (max of 25 mg) 2.5 mg every 12 hours times 3 doses (should be given with folate supplementation to reduce adverse effects)	Oral and injectable	Nausea, vomiting, stomatitis, fatigue, hepatotoxicity, bone marrow suppression, pulmonary fibrosis	24%–60%	First-line agent (can be used as monotherapy, but more effective in combination with TNFa agents) (can be given safely with narrow band UVB) Used in psoriasis and psoriatic arthritis (adults and children)	CBC SCR, BUN LFTs (baseline and every 3–6 months), avoid in cirrhosis and alcohol use disorders Reactivation of infections PPD test for TB Pregnancy category X
PDE 4 inhibitors							
Apremilast	Phosphodiesterase 4 (PDE4) inhibitor, with specificity for cyclic adenosine monophosphate (cAMP) that results in increased intracellular cAMP levels	Initial titration over 5 days: Day 1, 10 mg orally in AM; Day 2, 10 mg twice daily; Day 3, 10 mg in AM, 20 mg in PM; Day 4, 20 mg twice daily; Day 5, 20 mg in AM, 30 mg in PM Maintenance: Day 6 and thereafter, 30 mg orally twice daily	Oral	Diarrhea, nausea, headache, tension-type headache, weight decreased, depression, suicidal behavior, suicidal thoughts	33%	Used in psoriasis and psoriatic arthritis (adults)	Coadministration with strong CYP450 inducers (eg, rifampin, phenobarbital, carbamazepine, and phenytoin) is not recommended Reduce dose to 30 mg daily when CrCl <30 mL/min (0.5 mL/s)

Janus Kinase (JAK) Inhibitor							
Tofacitinib	Inhibits Janus kinase which are intracellular enzymes, and modulates a signaling pathway that influences the cellular processes of hemopoiesis and immune cell function	Immediate release: 5 mg twice daily Extended release: 10 mg once daily	Oral pill (immediate and extended release)	URI, headache, diarrhea, cold or flu-like symptoms	39.9%–59.2%	Used in psoriatic arthritis only (adults) (in combination with nonbioologic DMARDs) Off-label for psoriasis (can be used with methotrexate, but should not be combined with cyclosporine or biologics	Serious infection, malignancies, GI perforations, changes in CBC (reductions in lymphocytes, ANC or hemoglobin may necessitate dose changes, LFTs, or lipids, Caution with administration of live vaccines (administer zoster vaccine prior to start of therapy) When switching from IR to ER give ER tablet day after last IR dose
Oral Retinoids							
Acitretin	Stimulates differentiation and normalizes epidermal cell proliferation, not immunosuppressive	10–50 mg/day	Oral capsule	Myalgia, hair loss, hepatotoxicity, pancreatitis, hypervitaminosis A, hyperlipidemia, xerosis, epistaxis	70%–75% (dose dependent and can take 3–6 months for full treatment response)	Second line Agent (more efficacious in combination with phototherapy than monotherapy) Used in psoriasis only (adults and children)	Lipids CBC SCR, BUN (baseline and every 3 months Pregnancy category X CYP450 medications

Table 68–5

Biological Therapy[2,3,6,7,11,12,23,24,25]

Medication	Mechanism of Action	Dose and Administration	Dosage Forms	Adverse Effects	Therapeutic effects on PASI	Place in Therapy	Therapeutic Monitoring
Cytokine Modulators: Tumor Necrosis Factors							
Etanercept	Fusion protein that binds to both TNFα and TNFβ	50 mg subcutaneously twice weekly for 12 weeks then 50 mg subcutaneously weekly	Subcutaneous solution Biosimilars available: etanercept-szzs Etanercept-ykro	URI, nausea, vomiting, headaches Injection site reaction	47%–59% at weeks 12 and 24	Monotherapy for moderate–severe psoriasis (4 years and up) Monotherapy for PsA associated with any stage of psoriasis	CBC LFTs CMP hepatitis PPD (tuberculosis) Safe in pregnancy and lactation
Abatacept	Blocks T-cell activation	125 mg once weekly	Subcutaneous self-injection, IV infusion	HA, URI, cold-flu-like symptoms	Improvement of PsA symptoms	Used in psoriatic arthritis only (adults)	Signs of infection (should not be used with TNF inhibitors) Do not give live vaccines PPD prior to starting therapy (TB testing) Info lacking on use in pregnancy
Adalimumab	Human monoclonal antibody that binds TNFα inhibiting its interaction with receptors	80 mg subcutaneously, first dose then 40 mg subcutaneously on week 2, then 40 mg subcutaneously every 2 weeks	Subcutaneous solution Biosimilars available: adalimumab-adbm, adalimumab-atto adalimumab-adaz adalimumab-bwwd adalimumab-afzb adalimumab-fkjp	URI, pharyngitis, nausea, dyspepsia, fatigue, headaches Injection site reaction	53%–80% at weeks 12 and 16	First line, can be used as monotherapy for adults, monotherapy for PsA with any stage of psoriasis	CBC LFTs CMP hepatitis PPD (tuberculosis) Efficacy-limiting immunogenicity (mitigated by using with methotrexate) Safe in pregnancy and lactation
Certolizumab	Humanized antigen binding fragment of a monoclonal antibody which binds to TNFα blocking receptors	400 mg (2 injections of 200 mg each) on weeks 0,2, and 4 then every other week	Subcutaneous injection	URI Rash UTI Serious allergic reaction Lupus-like syndrome	75%–83%	Monotherapy for psoriasis and PsA	CBC LFTs CMP hepatitis Signs and symptoms of infection Safe in pregnancy and lactation
Infliximab	Chimeric monoclonal antibody that targets TNFα	5 mg/kg IV on weeks 0, 2, 6 and then 5 mg every 8 weeks (10 mg/kg dosing is reserved for IBD)	Intravenous and subcutaneous solutions Biosimilars available: infliximab-abda, infliximab-dyyb, infliximab-qbtx infliximab-qbtx infliximab-axxq	URI, pharyngitis, diarrhea, fatigue, hypersensitivity reaction, infusion-related reactions	76%–82% at weeks 10 and 24	Monotherapy PsA therapy with or without MTX associated with any stage of psoriasis	CBC CMP hepatitis PPD (tuberculosis) Efficacy-limiting immunogenicity Safe in pregnancy and lactation

Golimumab	Human monoclonal antibody that binds to both soluble and transmembrane bioactive forms of human tumor necrosis factor alfa (TNF alfa; a cytokine protein), resulting in inhibition of TNF alfa biological activity by preventing the binding of TNF alfa to its receptors	50 mg SC once monthly 2 mg/kg 30-minute IV infusion at 0, 4, then every 8 weeks	Subcutaneous and IV solution	Hypertension, rash, ALT/SGPT level raised, AST/SGOT level raised, dizziness, paresthesia, bronchitis, sinusitis, URI, new or worsening heart failure	Improvement in symptoms and inhibition of structural damage	Used in psoriatic arthritis only (adults) alone or with methotrexate	LFTs Infection Edema
Cytokine Modulators: Interleukin inhibitors							
Ustekinumab	Human monoclonal antibody that targets IL12/23 p40	45–90 mg subcutaneously on week 0 and 4, then every 12 weeks (45 mg if <100 kg vs 90 mg >100 kg)	Subcutaneous solution	Headache, URI, pharyngitis, abdominal pain	66%–78% at weeks 12 and 28 Less effective than TNF for PsA, does not have label for prevention of joint destruction	First line, can be used as monotherapy Used in psoriasis (people over 12 years old) and psoriatic arthritis (adults) Monotherapy PsA with any stage of psoriasis	CBC CMP hepatitis PPD (TB testing) Signs of serious infection (increased with methotrexate) Efficacy-limiting immunogenicity occurs: antibodies are produced resulting in lowered serum levels, and loss of efficacy Uncertain pregnancy and lactation risk
Secukinumab	Human monoclonal antibody that antagonizes IL17A	300 mg subcutaneously at weeks 0, 1, 2, 3, and 4 then 300 mg every 4 weeks	Subcutaneous solution	Nasopharyngitis, diarrhea, URI	82%–86% at week 12	First line, can be used as monotherapy Used in psoriasis and psoriatic arthritis (adults) (FDA approved) Monotherapy PsA at any psoriasis stage	CBC CMP hepatitis PPD (TB testing) Signs of serious infection (increased with methotrexate) Contraindicated in inflammatory bowel disease, Caution in patients with chronic or recurrent infection Rare antibodies (< 0.4%) and not associated with a loss of efficacy No studies in human pregnancy

(*Continued*)

Table 68–5

Biological Therapy[2,3,6,7,11,12,23,24,25] (*Continued*)

Medication	Mechanism of Action	Dose and Administration	Dosage Forms	Adverse Effects	Therapeutic effects on PASI	Place in Therapy	Therapeutic Monitoring
Ixekizumab	Human monoclonal antibody that inhibits the release of proinflammatory cytokines and chemokines by selectively binding with interleukin 17A cytokine	160 mg (two 80 mg injections) subcutaneously at week 0, followed by 80 mg subcutaneously at weeks 2, 4, 6, 8, 10, and 12, then 80 mg subcutaneously every 4 weeks	Subcutaneous solution	Injection site reaction, neutropenia, URI, hypersensitivity reaction	71%–100% at week 12 If neutralizing antibodies develop, can reduce drug concentrations resulting in a loss of efficacy	First line, can be used as monotherapy Used in psoriasis and psoriatic arthritis (adults) (FDA approved) Monotherapy for PsA associated with psoriasis	Caution in patients with chronic or recurrent infection, CBC CMP hepatitis PPD (TB testing) Signs of serious infection (increased with methotrexate) No studies in human pregnancy
Brodalumab	Human monoclonal IgG2 antibody that blocks the release of proinflammatory cytokines and chemokines by selectively binding to human interleukin-17 receptor A (IL-17RA) and inhibiting its interactions with cytokines IL-17A, IL-17F, IL-17C, and IL-17A/F heterodimer and IL-25	210 mg subcutaneously on weeks 0, 1, and 2, then every 2 weeks thereafter	Subcutaneous solution	Diarrhea, mycosis, arthralgia, headache, pain in throat, fatigue, neutropenia, cryptococcal meningitis, suicidal thoughts	67%–86% at week 12	Second line Used in psoriasis (adults) and psoriatic arthritis	PPD (tuberculosis) Caution in patients with chronic or recurrent infection Contraindicated in inflammatory bowel disease No studies in human pregnancy
Guselkumab	Human monoclonal antibody Blocks interleukin 23 (IL-23)	100 mg SC Weeks 0 and 4, then every 8 weeks	Subcutaneous solution	URI, HA, joint pain, diarrhea	70%	Used in psoriasis only (adults)	CBC CMP PPD (tuberculosis) Hepatitis Safety in pregnancy is unknown Signs of infection
Tildrakizumab	Monoclonal antibody designed to selectively block IL-23	100 mg SC Weeks 0 and 4, then every 12 weeks	Subcutaneous injection	URI, HA, joint pain, diarrhea	61%–66%	Used in psoriasis only (adults)	CBC CMP PPD (tuberculosis) Hepatitis Safety in pregnancy is unknown If antibodies develop, can lower serum concentrations and reduce efficacy
Risankizumab	Monoclonal antibody that selectively inhibits IL-23	150 mg (two 75 mg injections) administered by subcutaneous injection Week 0, 4, and every 12 weeks thereafter	Subcutaneous self-injection	URI, HA, joint pain, diarrhea	77%	Used in psoriasis only (adults)	CBC CMP PPD (tuberculosis) Hepatitis Safety in pregnancy is unknown

Patient Care Process

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. Identify allergies to medications and other substances.
- Review the medical history, history of psoriasis (signs, symptoms, treatments), and physical assessment findings (eg, BMI, BSA % covered in lesions/plaques)
- Speak with patient and review records to identify lifestyle habits (note tobacco use), preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.
- Identify sources of stress that could worsen psoriasis.
- Document pertinent family medical history (eg, heart disease, stroke, diabetes, dyslipidemia).

Assess the Information:

- Determine whether patient is taking any substance that could adversely affect psoriasis control or interact with prescribed medications.
- Based on the medical history, determine whether patient has any contraindications to therapy.
- Determine the severity and type of psoriasis.
- Identify comorbidities associated with psoriasis.
- Document location and BSA % covered by lesions/plaques.
- Assess efficacy, safety, and patient adherence of current and past pharmacotherapy.
- Identify significant adverse drug effects or interactions.

Develop a Care Plan:

- If patient is not at desired level of remission, determine pharmacologic treatment (**Figure 68–1**).
- Select lifestyle modifications likely to be effective, safe, and applicable to the patient.
- Choose optimal medications and doses for the patient (**Tables 68–2** to **68–5**). Use combination therapy when appropriate to take advantage of complementary mechanisms of action and to reduce side effects.

Implement the Care Plan:

- Educate the patient about changes in drug therapy, medication administration, potential new adverse effects, and how to manage and report adverse effects.
- Address any patient concerns about psoriasis and its management.
- Discuss importance of medication adherence and lifestyle modifications to prolong remission.
- Determine whether the patient has insurance coverage or whether recommended agents are included on the institution's formulary.
- Educate patient about the involvement of dermatologists (eg, when biologic therapy is warranted).

Follow-up: Monitor and Evaluate:

- Follow up at 6-to-12-week intervals to assess effectiveness and safety of therapy until remission is achieved.
- Review medication adherence and BSA % covered measurements, evaluating the degree of control.
- Once in remission, monitor patient twice yearly to assess control and pertinent lab monitoring. Determine whether the patient is experiencing any adverse reactions or drug interactions.

SUMMARY

Psoriasis is a chronic disease with no current cure but requires lifelong management. No two cases are identical and treatment must be tailored to the patient with the help of a dermatologist. The disease can severely impact the quality of life of the patients by affecting physical, psychological, and social well-being. AAD-NPF guidelines recommend a holistic approach, assessing all areas of life in caring for patients that live with this disease.

Abbreviations Introduced in This Chapter

BSA	Body surface area
cAMP	Cyclic 3'-5'-adenosine monophosphate
DISH	Diffuse idiopathic skeletal hyperostosis
IF-©	Interferon-*gamma*
IL-2	Interleukin-2
IL-10	Interleukin-10
IL-12/23	Interleukin-12 and interleukin-23
LFT	Liver function test
MI	Myocardial infarction
NB-UVB	Narrowband ultraviolet B
NSAIDS	Nonsteroidal anti-inflammatory drugs
PASI	Psoriasis Area and Severity Index
PGA	Physician Global Assessment
PPD	Purified protein derivative
PUVA	Psoralen ultraviolet A therapy
PsA	Psoriatic arthritis
PUVA	Psoralens + ultraviolet A
RePUVA	Oral retinoid + PUVA
ReUVB	Acitretin + ultraviolet B
RRR	Regular rate and rhythm
SCAT	Short-contact anthralin therapy
TNF	Tumor necrosis factor
UVB	Ultraviolet B

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69 Anemia

Maribel A. Pereiras

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Discuss common causes of anemia.
2. Identify common signs and symptoms of anemia.
3. Describe diagnostic evaluation required to determine the etiology of anemia.
4. Develop a treatment regimen considering the underlying cause and patient-specific variables.
5. Compare and contrast oral and parenteral iron preparations.
6. Explain the optimal use of folic acid and vitamin B_{12} in patients with macrocytic anemia.
7. Evaluate the proper use of epoetin and darbepoetin in patients with anemia caused by cancer chemotherapy or chronic kidney disease.
8. Develop a plan to monitor the outcomes of pharmacotherapy for the treatment of anemia.

INTRODUCTION

KEY CONCEPT Anemia is a deficiency of erythrocytes with a corresponding reduction in the concentration of hemoglobin (Hgb) that results in reduced oxygen-carrying capacity of the blood. Some patients with anemia may be asymptomatic initially, but eventually, the lack of oxygen to tissues results in fatigue, lethargy, shortness of breath, headache, edema, and tachycardia. Common causes include acute or chronic blood loss, decreased functional red blood cell (RBC) production, and increased RBC destruction. Determination of the underlying cause of anemia is essential for successful management.

EPIDEMIOLOGY AND ETIOLOGY

Anemia is a common diagnosis with a prevalence that varies widely based on age, gender, race/ethnicity, and geographic location (Table 69–1).[1,2] As per the World Health Organization, anemia is a serious global issue affecting up to 42% of young children (< 5 years old) and 40% of pregnant women. Patients with specific comorbidities such as cancer and chronic kidney disease (CKD) also have a significantly higher rate of anemia. The incidence of anemia in cancer patients ranges from 30% to 90%. Contributing factors include the underlying malignancy and myelosuppressive antineoplastic therapy.[3] The prevalence of anemia in patients with CKD ranges from 15% to 20% in stages 1 through 3 and up to 70% in stage 5.[4]

A decrease in erythrocyte production can be multifactorial. One common cause is nutritional deficiencies (iron, vitamin B_{12}, and folic acid) that are often easily treatable and most commonly seen in up to a third of elderly patients.[5] Women of childbearing potential are also another group that is at risk of iron deficiency anemia (IDA), given poor dietary intake or iron loss through monthly menstrual cycles. Patients with cancer or CKD generally have dysregulations in iron and erythropoietin (EPO) hemostasis leading to a risk of developing anemia. Patients with chronic immune-related diseases such as rheumatoid arthritis and systemic lupus erythematosus are also at increased risk to develop anemia as a complication of their disease. Anemia related to chronic inflammatory conditions is termed anemia of chronic disease (ACD).[5]

Drug therapy is the mainstay of treatment for anemias caused by reduced RBC production and is the focus of this chapter. Anemia due to the destruction of erythrocytes, such as with blood loss, trauma, or hemolytic anemia, will not be discussed.[6]

PATHOPHYSIOLOGY

Erythropoiesis

Erythropoiesis begins with a pluripotent stem cell in the bone marrow undergoing differentiation and ends with the appearance of RBCs in peripheral blood. The production of RBCs is stimulated by EPO, a hormone secreted by the kidney in response to cellular hypoxia. EPO stimulates RBC production by inducing differentiation of RBC precursors in the bone marrow to become **reticulocytes** (Figure 69–1). Reticulocytes become erythrocytes after 1 to 2 days in the bloodstream.[7] This process is also dependent upon a steady supply of important ingredients, iron, folic acid, and vitamin B_{12}.

Decreased Production Anemias

▶ *Nutritional Deficiencies*

Diets poor in nutritional supplements may contribute to a decrease in erythrocyte production. Socioeconomics, religious choices, or geographical location may determine dietary lifestyle choices. Diets that are low or absent in meat consumption may increase the risk of IDA, while diets that lack animal products (such as dairy or eggs) may lead to B_{12} deficiency anemia. Those with dietary restrictions should be counseled on maintaining a balanced diet and to be inclusive of foods that are rich in

Table 69–1

Prevalence of Anemia[1,2]

Children (1–5 years)	43%
Males (17–84 years)	29%
Males (85+ years)	26%
Females (15–49 years, pregnant)	38%
Females (15–49 years, nonpregnant)	29%
Females (85+ years)	20%

supplementation. If the dietary restrictions are severe, the use of supplemental products may be necessary.

Deficiencies in folic acid and vitamin B_{12} may hinder the process of erythrocyte maturation. Folic acid and vitamin B_{12} are required for the formation of DNA. Significant decreases in the amount of either folic acid or B_{12} inhibit DNA synthesis and consequently RBC production.[7,8] Poor diet can contribute to folic acid and vitamin B_{12} deficiencies. Pernicious anemia is a specific severe vitamin B_{12} anemia caused by the malabsorption of vitamin B_{12}. Normal B_{12} absorption and transport is depicted in Figure 69–2. In pernicious anemia, there is an absence of intrinsic factor, a glycoprotein produced by gastric parietal cells, which binds to vitamin B_{12} and facilitates its absorption in the ileum. This condition results in B_{12} deficiency despite adequate dietary B_{12} intake.[9] Aside from the vital role vitamin B_{12} plays in red cell and DNA production, it also serves a critical role in neurological function. Therefore, severe vitamin B_{12} anemias may also manifest neurological dysfunction.

Iron is also essential for RBC production. It is required in the nucleus formation of the iron-porphyrin heme ring, along with globin chains, which creates hemoglobin. Lack of iron leads to a decrease in Hgb synthesis and decreased RBC production. Normal homeostasis of iron transport and metabolism is depicted in Figure 69–3.[10] Approximately 1 to 2 mg of iron is absorbed through the duodenum daily, and the same amount is lost via blood loss, desquamation of mucosal cells, or menstruation. Daily iron requirements also increase during growth and pregnancy.

IDA typically occurs because of inadequate absorption of iron or excessive blood loss. Inadequate absorption may occur in patients who have congenital or acquired intestinal conditions, such as inflammatory bowel disease, celiac disease, or bowel resection. Achlorhydria and diets poor in iron may also contribute to iron-deficient states. Iron deficiency may also occur following excessive iron loss. Common etiologies include excessive menstruation, ulcers, neoplastic lesions, and excessive bleeding following surgery or trauma.[10,11]

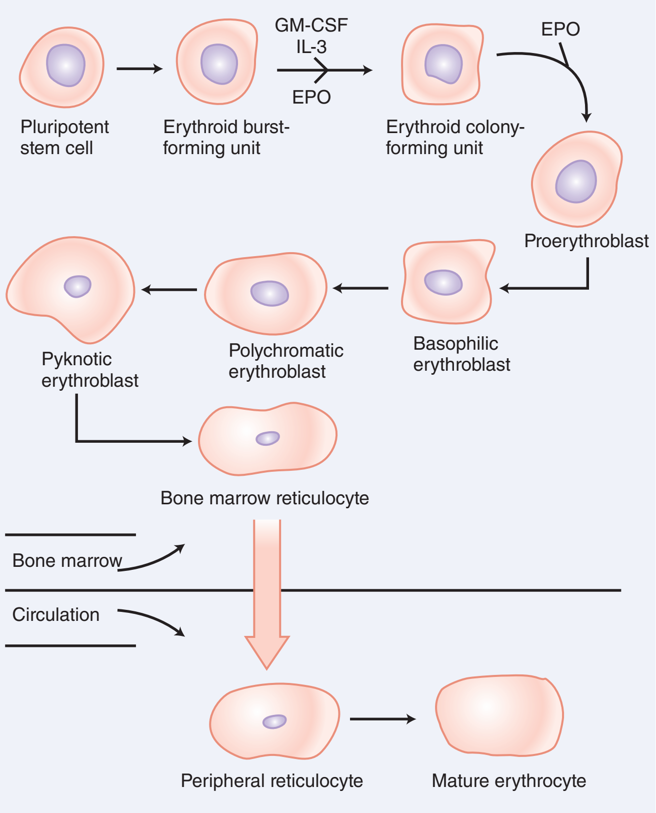

FIGURE 69–1. The process of erythropoiesis.

▶ *Dysregulation of Iron Homeostasis and Impaired Marrow Production*

Chronic diseases associated with ACD include infection, autoimmune disease, CKD, and cancer. A major contributing factor for the development of ACD is disturbance of iron homeostasis related to the activation of the immune system. Hepcidin is an acute-phase protein expressed in response to the upregulation of inflammatory cytokines. Increased expression of hepcidin causes decreased iron absorption from the gastrointestinal (GI) tract and inhibition of iron release from macrophages. In addition, immune activation can cause upregulation of cytokines that impair the proliferation and differentiation of erythroid precursors. Decreased production and blunted responsiveness to EPO can also contribute to ACD; this is best documented in patients with CKD. Finally, disruption of erythropoiesis secondary to infiltration of the bone marrow by cancer can lead to anemia.[3,5,10-12]

TREATMENT

Desired Outcomes

KEY CONCEPT The goal of anemia therapy is to increase Hgb to levels that improve red cell oxygen-carrying capacity, alleviate symptoms, and prevent complications from anemia. Normal Hgb values are 14.0 to 17.5 g/dL (140–175 g/L or 8.69–10.9 mmol/L) for males and 12.3 to 15.3 g/dL (123–153 g/L or 7.63–9.50 mmol/L) for females. It is important to note that continuation of therapy should be assessed primarily by the resolution of clinical symptoms. Patients who experience a resolution in their symptoms (eg, shortness of breath, tachycardia, fatigue, dizziness) may not require aggressive therapy to maintain their Hgb values within normal limits. Hypoxia and cardiovascular sequelae due to anemia can be avoided if Hgb levels are greater than 7.0 g/dL (70 g/L or 4.34 mmol/L).[11] In patients with acute coronary syndrome, consideration for transfusions can be given when Hgb levels are 8 g/dL (80 g/L or 4.96 mmol/L) or less.[44]

General Approach to the Anemic Patient

KEY CONCEPT The underlying cause of anemia must be determined and used to guide therapy. A complete blood count (CBC) is the laboratory evaluation that provides objective RBC characteristics useful in determining etiology and appropriate treatment. The mean corpuscular volume and determination of iron, ferritin, folate, and vitamin B_{12} levels are required to correctly diagnose a patient's anemia. Figure 69–4 and Table 69–2 illustrate how laboratory test results determine the correct diagnosis.

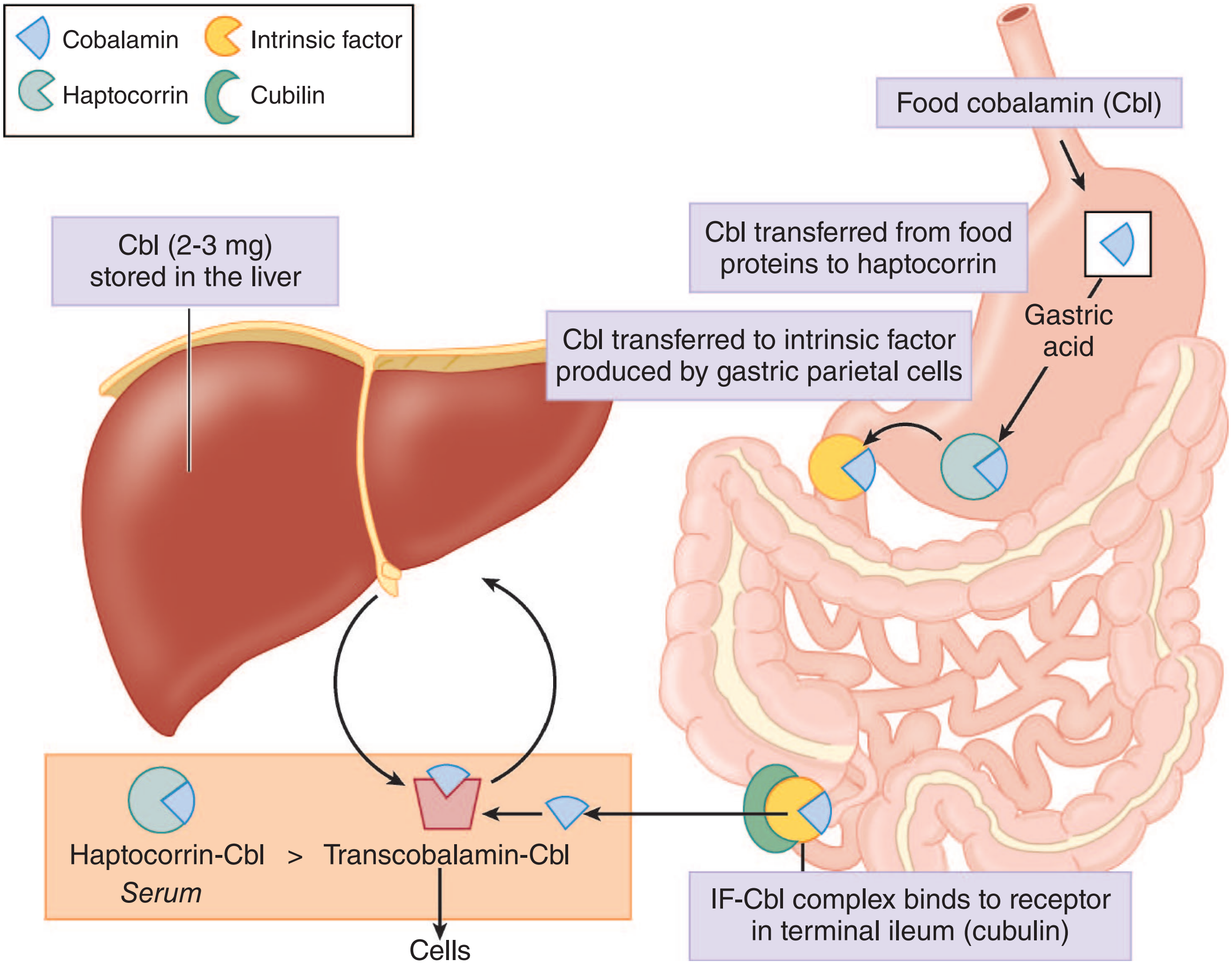
Cobalamin
Intrinsic factor
Haptocorrin
Cubilin
Food cobalamin (Cbl)
Cbl (2-3 mg) stored in the liver
Cbl transferred from food proteins to haptocorrin
Gastric acid
Cbl transferred to intrinsic factor produced by gastric parietal cells
Haptocorrin-Cbl > Transcobalamin-Cbl
Serum
Cells
IF-Cbl complex binds to receptor in terminal ileum (cubulin)

FIGURE 69–2. Vitamin B_{12} absorption and transport. (Reproduced, with permission, from Aster JC, Bunn HF. Pathophysiology of Blood Disorders. 2nd ed. New York: McGraw Hill; 2017.)

Clinical Presentation and Diagnosis of Anemia

Signs and Symptoms

Generally, the signs and symptoms of anemia are nonspecific and may include the following:

- Fatigue, lethargy, dizziness
- Shortness of breath
- Headache
- Edema
- Tachycardia

Other findings that may be present in some patients include the following:

- Dry skin, chapped lips
- Nail brittleness or spoon-shaped nails
- Hunger for ice, starch, or clay (termed **pica**)
- Cognitive impairment, gait abnormalities, irritability, peripheral neuropathy (vitamin B_{12} anemia)

Medical History

Inquire about the following conditions:

- History of blood loss, such as hemorrhoids, melena, or menorrhagia (IDA)
- Dietary habits (vegan/vegetarian), malnourishment, or recent weight loss (vitamin B_{12} or folate deficiency)
- Recent GI surgeries (gastric bypass) (vitamin B_{12} or folate deficiency)
- Alcoholism (folate deficiency)
- Cancer or CKD

(*Continued*)

Clinical Presentation and Diagnosis of Anemia (Continued)

- Chronic autoimmune disorders or infections, such as HIV infection or rheumatoid arthritis (anemia of chronic disease)

Physical Examination

These findings aid the clinician in determining the severity of the anemia:

- Orthostatic hypotension and tachycardia secondary to volume depletion
- Cutaneous changes such as pallor, jaundice, and nail brittleness

Laboratory Evaluation

Table 69–2 describes common tests used to determine the etiology of anemia. A diagnostic and treatment algorithm for anemia is outlined in Figure 69–4.

1. A CBC is a necessary first step in evaluating a patient with anemia. If the Hgb and Hct are less than the normal range, the patient is anemic. Subsequent evaluations of RBC indices and the peripheral smear often are necessary to determine the etiology (and ultimately, the treatment) of the anemia.
2. Evaluating the mean corpuscular volume (MCV) is the next step in an anemia workup. It is classified as microcytic, normocytic, or macrocytic if the MCV is below, within, or above the normal range of 80 to 96 fL/cell, respectively.

Microcytic Anemia and Iron Evaluation

Iron studies (see Table 69–2) should be evaluated in the setting of a low MCV. These include the following:

- Serum iron
- Serum **ferritin**—the best indirect determinant of body iron stores. It is commonly decreased in patients with IDA
- Total iron-binding capacity (TIBC)—quantifies the iron-binding capacity of transferrin and is increased in IDA
- **Transferrin saturation** (serum iron/TIBC)—indicates the amount of transferrin that is bound with iron; it is lower in IDA

Macrocytic Anemia

- Evaluate folic acid and vitamin B_{12} levels in the setting of an elevated MCV
- Further investigation such as administering radiolabeled B_{12} (ie, Schilling test) to determine if there is a lack of intrinsic factor or use of intrinsic factor antibodies

Normocytic Anemia

- Evaluate reticulocytes and CBC
- High reticulocyte counts may indicate RBC loss via acute blood loss, hemolysis, or splenic sequestration
- Low serum iron with normal to increased ferritin consistent with ACD

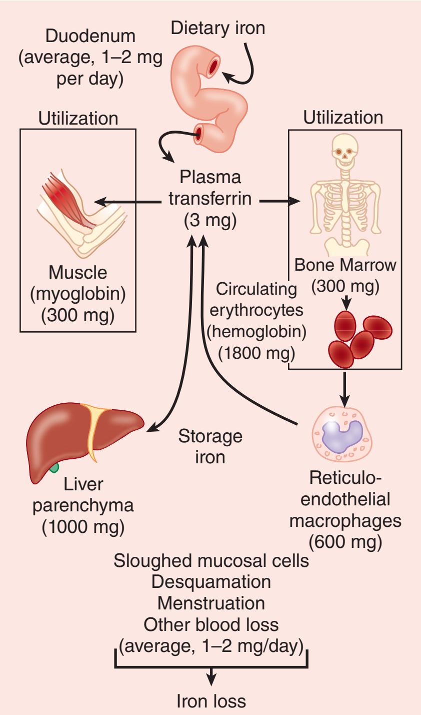

FIGURE 69–3. The distribution of iron use in adults. (From Andrews N. Disorders of iron metabolism. N Engl J Med. 1999;341(26): 1986–1995.)

Nonpharmacologic Therapy

The primary nonpharmacologic treatment of anemia is transfusion of RBCs. Safety concerns, cost, and the limited availability of this therapy support efforts to establish the "optimum" threshold for administering RBC transfusions. A Cochrane review concluded it is appropriate to use "restrictive transfusion triggers in patients free of serious cardiac disease." The authors concluded a reasonable "trigger for transfusion" for patients without significant cardiovascular disease is 7.0 g/dL (70 g/L or 4.34 mmol/L).[13] The Transfusion Requirements In Critical Care trial reported no significant differences in hospital mortality between patients randomly assigned to maintain Hgb levels of 7.0 to 9.0 g/dL (70–90 g/L or 4.34–5.59 mmol/L) and 10.0 to 12.0 g/dL (100–120 g/L or 6.21–7.45 mmol/L).[14] Typically, only patients with acute symptoms (ie, dyspnea, chest pain) and Hgb concentrations in the range of 7.0 to 9.0 g/dL (70–90 g/L or 4.34–5.59 mmol/L) require blood transfusions.

Anemia can be attributed to diets poor in iron, folic acid, or vitamin B_{12}. However, in the United States, nutrient-poor diets rarely cause anemia. Therefore, ingesting a diet that is rich in iron, folic acid, or vitamin B_{12} should be encouraged but is rarely the sole modality of treatment. Food sources of iron, folic acid, and vitamin B_{12} are listed in Table 69–3.

Pharmacologic Therapy

▶ *Iron Deficiency Anemia*

KEY CONCEPT The gold standard treatment of IDA is oral iron therapy that provides 150 to 200 mg of elemental iron daily in

Patient Encounter 1, Part 1

A 58-year-old man was admitted to the emergency department. His wife found him at home passed out on the floor with several beer cans around him. According to his wife, he had been suffering from depression for being laid off from work during the COVID pandemic and had taken up drinking. For the last 2 months, she estimates he drank anywhere from 3 to 5 cans of beer a day with more on the weekends. She reported him as moody and even on his "good days" noted him to be weak, tired, and stumbling about as he walked. He has a medical history of hypertension, diabetes, and he is on several medications. Surgical history includes gastric bypass surgery, 6 years ago. Upon physical exam, he appears pale and is found to be tachycardic and dyspneic.

What aspects of this patient's history suggest he may be anemic?

What laboratory assessments are needed to make a diagnosis and therapeutic plan?

How would the requested laboratory parameter(s) aid your decision-making?

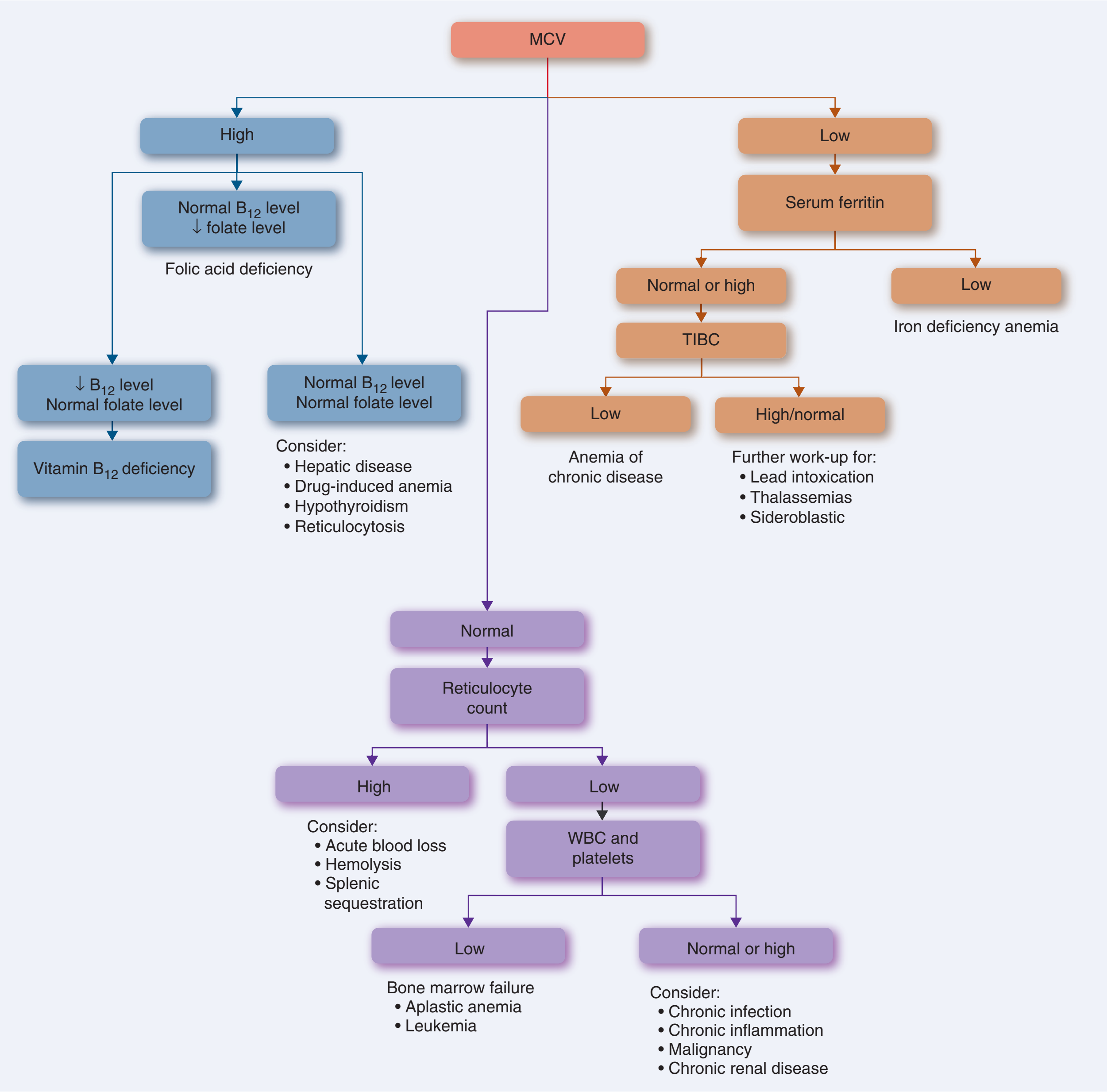
MCV
High
Low
Normal B_{12} level
↓ folate level
Folic acid deficiency
Serum ferritin
Normal or high
Low
Iron deficiency anemia
TIBC
↓ B_{12} level
Normal folate level
Normal B_{12} level
Normal folate level
Low
High/normal
Vitamin B_{12} deficiency
Consider:
• Hepatic disease
• Drug-induced anemia
• Hypothyroidism
• Reticulocytosis
Anemia of chronic disease
Further work-up for:
• Lead intoxication
• Thalassemias
• Sideroblastic
Normal
Reticulocyte count
High
Low
Consider:
• Acute blood loss
• Hemolysis
• Splenic sequestration
WBC and platelets
Low
Normal or high
Bone marrow failure
• Aplastic anemia
• Leukemia
Consider:
• Chronic infection
• Chronic inflammation
• Malignancy
• Chronic renal disease

FIGURE 69–4. The anemia evaluation process. (ACD, anemia of chronic disease; A_2, hemoglobin A_2 type; F, hemoglobin F type; MCV, mean corpuscular volume; Pb, lead; TIBC, total iron-binding capacity.)

Table 69–2

Pertinent Laboratory Tests in the Evaluation of Anemia

Test Name	Normal Range	Description/Significance
CBC		
Hgb	Males: 14.0–17.5 g/dL (140–175 g/L or 8.69–10.9 mmol/L) Females: 12.3–15.3 g/dL (123–153 g/L or 7.63–9.50 mmol/L)	Amount of Hgb in the blood; signifies oxygen-carrying capacity of the blood and determines whether a patient is anemic
Hct	Males: 40.7%–50.3% (0.407–0.503) Females: 36.1%–44.3% (0.361–0.44.3)	The percent of blood that the erythrocytes encompass; also indicates anemia; the Hgb is measured, and the Hct is calculated
RBC	Males: $4.5–5.9 \times 10^6$ cells/μL ($4.5–5.9 \times 10^{12}$ cells/L) Females: $4.1–5.1 \times 10^6$ cells/μL ($4.1–5.1 \times 10^{12}$ cells/L)	The number of erythrocytes in a volume of blood; also indicates anemia, but seldom used
RBC Indices		
MCV	80–97.6 μm^3/cell (80–97.6 fL/cell)	A widely used laboratory value to measure RBC "size"; higher values indicate **macrocytosis** and lower values indicate **microcytosis**
MCH	27–33 pg/cell	Amount of Hgb per RBC; may be decreased in IDA
MCHC	32–36 g/dL (320–360 g/L)	Hgb divided by the Hct; also low in IDA
Iron Studies		
Serum iron		
Males	45–160 mcg/dL (8.1–28.6 μmol/L)	Measures amount of iron bound to transferrin; low in IDA
Females	30–160 mcg/dL (5.4–28.6 μmol/L)	
Serum ferritin		
Males	20–250 ng/mL (20–250 mcg/L; 45–562 pmol/L)	Ferritin is the protein–iron complex found in macrophages used for iron storage; low in IDA
Females	10–150 ng/mL (10–150 mcg/L; 22–337 pmol/L)	
TIBC	220–420 mcg/dL (39.4–75.2 μmol/L)	Measures the capacity of transferrin to bind iron; high in IDA
TSAT	15%–50% (0.15–0.50)	TSAT (%) = (serum iron/TIBC) × 100; a saturation of less than 15% (0.15) is common in IDA
Other Tests		
RBC distribution width (RDW)	11.5%–14.5% (0.115–0.145)	A higher value means the presence of many different sizes of RBCs; the MCV is therefore less reliable when RDW is larger
Reticulocyte count (erythrocyte precursors)		Should be elevated in patients who are responding to treatment
Males	0.5%–1.5% of RBCs (0.005–0.015)	
Females	0.5%–2.5% of RBCs (0.005–0.025)	
Folic acid (plasma)	3.1–12.4 ng/mL or mcg/L (7.0–28.1 nmol/L)	Used to determine folic acid deficiency
Folic acid (RBC)	125–600 ng/mL (283–1360 nmol/L)	Used to determine folic acid deficiency
Vitamin B_{12}	180–1000 pg/mL (133–738 pmol/L)	Used to determine vitamin B_{12} deficiency
EPO level	2–25 mIU/mL (2–25 IU/L)	Patients may benefit from EPO therapy if they are anemic, and EPO levels are normal or mildly elevated

EPO, erythropoietin; Hct, hematocrit; Hgb, hemoglobin; IDA, iron deficiency anemia; MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; MCV, mean cell volume; RDW, RBC distribution width; TIBC, total iron-binding capacity; TSAT, transferrin saturation.

Table 69–3

Food Sources of Iron, Vitamin B_{12}, or Folic Acid[41-43]

Nutrient	Food Sources
Iron	Red meat, organ meats, seafood, wheat germ, egg yolks, white beans, lentils, kidney beans, nuts and dried fruit, fortified cereals/breads
Vitamin B_{12}	Eggs, milk, yogurt, fish/seafood, poultry, meat, fortified cereals
Folic acid	Dark green vegetables (spinach, asparagus, brussels sprouts, broccoli), liver, peanuts, beans (kidney beans), fruits, fortified cereals, chickpeas, enriched pasta/breads/rice

divided doses. Many different iron products and salt forms are available. Typically, iron sulfate is the most commonly used formulation. Table 69–4 lists commonly prescribed oral iron products and the amount of elemental iron provided by each.

Iron supplementation resolves anemia by replenishing iron stores to levels necessary for RBC production and maturation. After absorption, iron binds to transferrin in the plasma and is transported to the muscles (for myoglobin), liver (for storage), or bone marrow (for red cell production). Reticulocytosis should occur in 7 to 10 days, and Hgb values should rise by about 1.0 g/dL (10 g/L or 0.62 mmol/L) per week. Patients should be reassessed if Hgb does not increase by 2.0 g/dL (20 g/L or 1.24 mmol/L) in 3 weeks.[15]

The preferred regimen for oral iron is 50 to 65 mg of elemental iron, two to three doses daily on an empty stomach.

Table 69–4

Oral Iron Products and Elemental Iron Content[37-40]

Salt Form	Brand Name(s)	Percent of Elemental Iron	Formulation Types
Ferrous sulfate	FeroSul Fer-In-Sol Slow Fe	~20	Elixir, liquid, solution Tablet—slow and extended release
Ferrous sulfate, anhydrous	N/A	~30	Tablet
Ferrous gluconate	Ferate	~12	Tablets
Ferrous fumarate	Ferretts Ferrimin Hemocyte	33	Tablets
Polysaccharide–iron complex	Niferex Ferrex NovaFerrum	Dose expressed as elemental iron	Liquid Capsule

Patient Encounter 1, Part 2

Laboratory parameters are ordered, and the following is reported

CBC

- WBC: 8.70×10^3/μL (8.70×10^9/L)
- Hgb: 8.3 g/dL (83 g/L; 5.15 mmol/L)
- Hct: 24.8% (0.248)
- Plt: 135×10^3/μL (135×10^9/L)

Red Blood Cell Indices

- MCV: 120.4 μm^3 (120.4 fL)
- MCH: 28.4 pg/cell
- MCHC: 35.3 g/dL (353 g/L; 21.9 mmol/L)

Others

- RBC count: 3.9×10^6/μL (3.9×10^{12}/L)
- RDW: 22% (0.22)

Iron Studies

- Serum iron: 100 mcg/dL (17.9 μmol/L)
- Serum ferritin: 123 ng/L (123 mcg/L; 276 pmol/L)
- TIBC: 300 mcg/dL (53.7 μmol/L)
- Transferrin saturation: 36% (0.36)

B$_{12}$ and Folate

- Serum folate: 4.3 ng/mL (9.77 nmol/L)
- Serum B$_{12}$: 106 pg/mL (78.201 pmol/L)

Is this a macrocytic or microcytic anemia?

Specifically, what is the etiology of the anemia?

Recommend the most appropriate drug regimen (drug, dosage form, and schedule).

Administration on an empty stomach (1 hour before or 2 hours after a meal) is preferred for maximal absorption. If patients develop intolerable GI side effects (ie, heartburn, nausea, bloating) after taking iron on an empty stomach, they should be advised to take it with meals. Enteric coated iron supplements are also available that may help with tolerability. However, the use of food intake or enteric coated products does decrease absorption. Some data suggests that coadministration of vitamin C may improve oral absorption although there is little evidence to support this.[27] New data is emerging regarding the optimal dosing schema for iron supplementation based on additional information regarding iron absorption and the effect on hepcidin. A study by Motretti and colleagues suggests that lower doses and less frequent dosing may improve the amount of iron absorbed. This data requires further evaluation but may offer a more convenient dosing schedule while minimizing side effects.[17,18] Common toxicities associated with oral iron include abdominal pain, nausea, heartburn, constipation, and dark stools.[16]

Potentially clinically significant drug–drug interactions involving iron products include fluoroquinolones, tetracyclines, eltrombopag, and mycophenolate mofetil. Iron decreases the absorption of these drugs. The absorption of iron is influenced by gastric acidity. Limited data supports drugs that decrease gastric acidity (antacids, proton pump inhibitors, and H2-receptor antagonists) may impair the absorption of iron. If concurrent administration cannot be avoided, to minimize this interaction, oral iron should be administered at least several hours before or after the affected drug. The absorption can also be affected by certain disease states that may limit the absorption, such as celiac disease, inflammatory bowel disease, or patients who have had gastric surgeries.[11]

Parenteral iron therapy is indicated when patients cannot tolerate oral formulations, have decreased intestinal absorption, or are noncompliant. Five parenteral iron formulations are available in the United States.[19-24] Table 69–5[20-24] provides details pertinent to the use of these products. Iron dextran (ID) was available in two formulations, as a high- and low-molecular-weight iron product. Dexferrum (the high-molecular-weight [HMW] product) is associated with a much higher incidence of life-threatening adverse effects, typically anaphylactic-like reactions, and this formulation has been discontinued.[25] Although total dose infusion (TDI), where the total replacement dose of iron administered in one dose is not an approved method of administration in the United States, low-molecular-weight ID is approved for TDI in Europe. TDI administration achieves similar patient outcomes while lowering costs. Sodium ferric gluconate complex, iron sucrose, ferumoxytol, and ferric carboxymaltose received FDA labeling for the treatment of patients with anemia and CKD in the last decade.[19-24] Although the occurrence of life-threatening adverse events caused by parenteral iron is extremely low, the absolute rate of life-threatening events is substantially higher for HMW ID.[21]

The dose of iron dextran is calculated by the following equation: dose (mL) = 0.0442 (desired Hgb − observed Hgb) × body weight + (0.26 × body weight). The body weight that should be used is lean body weight for adults and children weighing more than 15 kg and actual body weight for children weighing 5 to 15 kg. Hemoglobin should be expressed in units of g/dL (hemoglobin expressed in g/L × 0.10, or mmol/L × 1.61). The dose in milligrams can be calculated based on a standard concentration of 50 mg of elemental iron per milliliter.[19] Prescribing information recommends administering iron dextran in 100-mg aliquots daily until the total dose is achieved. However, anecdotal evidence reports that the total calculated dose can be administered safely over 4 to 6 hours on 1 day. Because of the risk of anaphylaxis, a

Table 69–5

Parenteral US Iron Products

Product (Brand Name)	Iron dextran (INFeD)	Sodium ferric gluconate (Ferrlecit)	Iron sucrose (Venofer)	Ferumoxytol (Feraheme)	Ferric carboxymaltose (Injectafer)
Carbohydrate type	Dextran polysaccharide	Gluconate	Sucrose	Polyglucose sorbitol carboxymethylether	Carboxymaltose
Molecular weight (Daltons)	165,000	289,000–444,000	34,000–60,000	750,000	150,000
Maximum dose approved (mg)	100	125	200	510	750
Total dose infusion	Yes	No	No	No	No
Test dose needed?	Yes	Yes	No	No	No
Premedications	Yes for TDI only	Yes for TDI only	No	No	No
Box warning	Yes	Yes	No	No	No
Rate of infusion undiluted[a]	50 mg/min	12.5 mg/min	40 mg/min	30 mg/sec	100 mg/min

[a] From FDA product labeling.

Data from Auerbach M, Adamson JW. How we diagnose and treat iron deficiency anemia. Am J Hematol. 2016; 91:31–38.

test dose of iron dextran (0.5 mL over at least 30 seconds) must be administered to patients before their first dose of iron dextran. Patients should be monitored for signs of anaphylaxis for at least 1 hour before administering the remaining total dose. Other adverse effects include arthralgias, arrhythmias, hypotension, flushing, and pruritus.[19]

▸ *Vitamin B_{12} and Folic Acid Anemia*

KEY CONCEPT Anemia caused by vitamin B_{12} deficiency (also known as pernicious anemia) or folic acid deficiency is treated by replacing the missing nutrient. Both folic acid and vitamin B_{12} are essential for erythrocyte production and maturation.

Oral and parenteral vitamin B_{12} (cyanocobalamin) replacement therapies are equally effective in patients able to absorb B_{12}. Vitamin B_{12} is absorbed completely following parenteral administration, whereas oral vitamin B_{12} is absorbed poorly via the GI tract and primarily within the terminal ileum. Consequently, cyanocobalamin is commonly administered as an intramuscular injection of 1000 mcg/day for 1 week, followed by 1000 mcg/week for a month or until the Hgb normalizes. Lifelong maintenance therapy (1000 mcg/month IM) is required for patients with pernicious anemia. An alternative maintenance regimen for pernicious anemia is oral cyanocobalamin (1000–2000 mcg/day); however, level of cobalamin must be monitored frequently to ensure adequate absorption. In patients with severe neurological signs or CNS symptoms, oral therapy is not recommended. If the etiology was a dietary deficiency or reversible malabsorption syndrome, oral therapy may be utilized, and treatment can be discontinued after the underlying cause is corrected and vitamin B_{12} stores normalized. A common oral dosing regimen is from 1000 to 2000 mcg/day. If parenteral cyanocobalamin is used initially, oral vitamin B_{12} can be useful as maintenance therapy. Typically, resolution of neurologic symptoms, disappearance of megaloblastic RBCs, and increased Hgb levels occur within a week of therapy.[26] Vitamin B_{12} is well tolerated and reported adverse effects include injection-site pain, pruritus, and rash.[27]

Patient Encounter 1, Part 3

The patient is diagnosed with vitamin B_{12} deficiency anemia and is started on parenteral cyanocobalamin for 1 month followed by 1000 mcg of oral cobalamin taken daily. He is also encouraged to improve his nutritional intake, take steps to stop drinking, and recommended to a behavioral health center for more support. At his first weekly visit, he reports enrolling in the behavioral program and a new sense of "direction." A follow-up CBC a month later reveals an Hgb of 10 g/dL (100 g/L or 6.2 mmol/L), previously 8.3 g/dL (83 g/L or 5.15 mmol/L). He states he has noticed improvement in mood and has more energy. He is also making better choices in his dietary habits. Upon occasion, he will miss "a dose or two," given his other medications he also must remember to take.

What hemoglobin level would constitute a therapeutic response in this patient?

How can compliance be improved in this patient?

The effective dose of folic acid is 1 mg/day by mouth. Absorption of folic acid is rapid and complete. However, patients with malabsorption syndromes or short gut syndrome may require doses up to 5 mg/day and longer therapy durations. Reticulocytosis occurs within days of commencing therapy. Typically, a patient's Hgb will start to rise after 2 weeks of therapy and normalize after 2 to 4 months of therapy. Folic acid is well tolerated. Nonspecific adverse effects include allergic reactions, flushing, and rash.

▸ *Anemia of Chronic Disease*

KEY CONCEPT Decreased RBC transfusion requirements are a goal of therapy in patients with ACD treated with the EPO-stimulating agent (ESAs). However, in 2007, the FDA product labeling for epoetin and darbepoetin was revised to include new data documenting safety concerns. Subsequently, the Centers for Medicare and Medicaid Services (CMS) implemented more restrictive ESA coverage determination guidelines. In 2010, the FDA implemented a risk evaluation and mitigation strategy (REMS) for ESAs administered to treat patients with cancer who are undergoing chemotherapy, but in 2017, the FDA decided the REMS program was no longer needed.[28] Table 69–6 summarizes the FDA-labeled dosing regimens for patients whose anemia of

Table 69–6

ESA Products and Usual Doses for Anemia from Cancer/Chemotherapy, CKD, and Zidovudine/HIV Infection in Adult Patients[a]

	Type of ESA	Biosimilar Available	Cancer/Chemotherapy Dosing Regimens	CKD Dosing Regimens	Zidovudine/HIV Dosing Regimen[d]
Epoetin-α (Epogen, Procrit, or biosimilar)	First generation	Yes	150 U/kg SC three times per week 40,000 units SC once every week	50–100 U/kg SC or IV three times per week	100 U/kg IV or SC three times per week
Darbepoetin-α (Aranesp or biosimilar)	Second generation	No	2.25 mcg/kg SC once every week 500 mcg SC fixed dose every 3 weeks	0.45 mcg/kg SC or IV once every week[b] 0.75 mcg/kg SC or IV once every 2 weeks[b] 0.45 mcg/kg SC or IV once every 4 weeks[c]	Not recommended
Methoxy polyethylene glycol–epoetin beta (Mircera)	Third generation, continuous ESA	No	NA	Not on prior ESA therapy: 0.6 mcg/kg SC or IV every 2 weeks. One hemoglobin stable may give monthly with a dose that is double the dose given every 2 weeks[e,f]	NA

[a] Indications and dosage regimens per FDA product labeling.

[b] For patients on dialysis.

[c] For patients not on dialysis.

[d] FDA-labeled indication for Procrit (epoetin-α), not Epogen (epoetin-α) or darbepoetin.

[e] IV is preferred for those on hemodialysis.

[f] For patients on ESA therapy, there is conversion dosing based on the total weekly epoetin alfa dose, prefer to product package insert for details.

chronic disease is related to cancer chemotherapy, CKD, or zidovudine treatment.

Epoetin, a recombinant human EPO, binds to the EPO receptors on RBC precursor cells in the bone marrow and results in increased RBC production. Darbepoetin, a synthetic EPO analog, differs from epoetin in that it is a glycosylated protein and exhibits a longer half-life, allowing for a longer dosing interval. Clinical practice guidelines consider epoetin and darbepoetin to be therapeutic equivalents.[3,29] KEY CONCEPT ESAs should only be used to prevent a transfusion and should not be initiated unless the hemoglobin is less than 10.0 g/dL (100 g/L, 6.21 mmol/L), and chemotherapy is planned for a minimum of 2 additional months. Over the last few years, a biosimilar agent for the reference product of epoetin has been developed. A biosimilar is a biological product that has been approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as the reference product, and that there are no clinically meaningful differences between the biosimilar and the reference product.[47] The biosimilar, epoetin alfa-epbx, utilizes the same dosing, schedules and indications as the reference product; however, it has not been deemed interchangeable. ESA-labeled dosing regimens for treatment of patients receiving chemotherapy are summarized in Table 69–6.

Within the ESA therapeutic category, there also exists a continuous EPO receptor activator (CERA). Methoxy polyethylene glycol–epoetin beta is a novel third-generation pegylated epoetin beta (PEG–EPO) product. This product has the longest half-life of the ESAs. It is estimated to last 6 times longer than darbepoetin alfa and up to 20 times longer than epoetin. However, this medication is only indicated for use in patients with chronic kidney disease.

Anemia Due to Chemotherapy in Patients with Cancer Postmarketing outcome data documented that cancer patients administered ESAs had an increased risk of thrombotic events, shorter progression-free and overall survival.[30] ESAs increased mortality of patients while on a study (combined hazard ratio [cHR] 1.17; 95% confidence interval [CI] 1.06–1.30) and worsened overall survival (cHR 1.06; 95% CI 1.00–1.12). This corresponds to a 17% increased risk of mortality for patients treated with ESAs and a 6% increase of mortality overall. Based on these data, the FDA revised ESA product labeling, restricting their administration to patients with chemotherapy-induced anemia without curative

Patient Encounter 2, Part 1

A 34-year-old woman presents to her obstetrician for her prenatal visit. She is 16 weeks pregnant and her children at home are 2 and 4 years old. She has been fatigued for the last 2 months and feels it has been from caring for her two children and working part-time. Her food habits have been irregular, as she had severe morning sickness up until recently. She has also developed a fondness for sucking on ice chips. Her physical examination is notable for pallor and pale conjunctiva. Medical history is negative.

What aspects of this patient's history suggest she may be anemic?

What laboratory assessments are required to make an appropriate diagnosis and therapeutic plan?

Patient Encounter 2, Part 2

Laboratory results:

CBC

- WBC: 5.7 × 10^3/mm^3 (5.7 × 109/L)
- Hgb: 6.7 g/dL (67 g/L; 4.16 mmol/L)
- Hct: 20.8% (0.208)
- Plt: 210 × 103/µL (210 × 109/L)

Red Blood Cell Indices

- MCV: 71 µm^3 (71 fL)
- MCH: 23 pg/cell
- MCHC: 28.3 g/dL (283 g/L; 17.6 mmol/L)

Iron Studies

- Serum iron: 27 mcg/dL (4.8 µmol/L)
- Serum ferritin: 6.9 ng/mL (6.9 mcg/L; 16 pmol/L)
- TIBC: 459 mcg/dL (82.2 µmol/L)
- Transferrin saturation: 11% (0.11)

B$_{12}$ and Folate

- Serum B$_{12}$: 657 pg/mL (484.86 pmol/L)
- Serum folate: 10 ng/mL (22.7 nmol/L)

Is this a macrocytic or microcytic anemia?

Specifically, what is the etiology of the anemia?

Recommend the most appropriate drug regimen (drug, dosage form, and schedule).

intent. The 2019 update of the joint American Society of Clinical Oncology/American Society of Hematology clinical practice guideline on the use of ESAs in patients with cancer adopted FDA recommendations for more restrictive use of ESA in patients with cancer.[29]

In 2008, CMS published more restrictive coverage criteria for ESA treatment of chemotherapy-associated anemia. Patients should be monitored every 4 weeks. If Hgb has not increased by 1.0 g/dL (10 g/L, 0.62 mmol/L) after 4 weeks and remains less than 10.0 g/dL (100 g/L, 6.21 mmol/L), a one-time dose escalation of 25% is appropriate. If Hgb increases by more than 1.0 g/dL (10 g/L, 0.62 mmol/L), or is more than 10.0 g/dL (100 g/L, 6.21 mmol/L), the ESA should be discontinued. At 8 weeks if Hgb has increased by 1 g/dL (10 g/L, 0.62 mmol/L) but remains less than 10.0 g/dL (100 g/L, 6.21 mmol/L), continued ESA administration is covered. However, if after 8 weeks Hgb fails to increase by 1 g/dL (10 g/L, 0.62 mmol/L), CMS payment of therapy is not covered. CMS covers ESA therapy for up to 8 weeks after the completion of chemotherapy for patients achieving responses.[3,31]

Patient Encounter 2, Part 3

The patient is diagnosed with iron deficiency anemia (IDA) and is started on ferrous sulfate 325 mg po three times daily to be taken on an empty stomach. A follow-up CBC 1 month later reveals an Hgb of 7.8 g/dL (78 g/L; 4.84 mmol/L), previously 6.7 g/dL (67 g/L; 4.16 mmol/L). She reports a slight improvement in mood and more energy. She no longer craves the ice chips as intensely as before. However, she struggles to be compliant and has developed constipation.

What hemoglobin level would constitute a therapeutic response in this patient?

What recommendation(s) would you make regarding the compliance to help with constipation?

"Functional" iron deficiency exists when total iron stores are normal or increased, but disruption of iron homeostasis prevents utilization of the stored iron for erythropoiesis. "Functional" iron deficiency has been described in patients with ACD. Therefore, it is imperative that patients starting ESA therapy have laboratory studies performed to assess iron stores. If results document that a patient has suboptimal iron stores, iron replacement therapy is indicated prior to initiation of ESA therapy. In addition, a workup to assess for rationales for iron deficiency should be explored. The updated 2019 ASCO/ASH guidelines also state that iron supplementation may be used to help improve ESA response in patients with chemotherapy-associated anemia without iron deficiency.[29]

Anemia Due to CKD Anemia is common in patients with CKD. Early treatment of anemia in patients with CKD on dialysis has been associated with slower disease progression and lower risk of death. It is essential to evaluate and treat anemia in patients before they progress to stage 5 CKD (glomerular filtration rate [GFR] less than 15 mL/min/1.73 m^2 [0.14 mL/s/m^2]).[32]

Patients with CKD typically develop normocytic, normochromic anemia as a result of EPO deficiency. However, a thorough workup of anemia should be performed to rule out other etiologies.[32] The 2012 KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease recommends that ESA therapy be started when the hemoglobin is between 9.0 and 10.0 g/dL (90–100 g/L) in dialysis patients. For those CKD patients not on dialysis, the guidelines recommend that ESAs be started when the Hgb is less than 10.0 g/dL (10 g/L) and should also be based on patient-specific scenarios—if the rate of Hgb decline predicts the need for an RBC transfusion and if a goal of therapy is to either reduce the risk of RBC transfusion–related risks or reduce the chance of alloimmunization.[32,33] This dosing strategy was adopted to decrease the risk of serious adverse cardiovascular events. ESA-labeled dosing regimens for patients with CKD are summarized in Table 69–6.[34-36]

Although EPO deficiency is the primary cause of CKD anemia, iron deficiency may also exist. Iron stores in patients with CKD should be maintained so that transferrin saturation is greater than 20% (0.20) and serum ferritin is greater than 100 ng/mL (100 mcg/L or 225 pmol/L). If iron stores are not maintained appropriately, epoetin, darbepoetin, or methoxy polyethylene glycol–epoetin beta will not be effective. Most CKD patients will require iron supplementation.[32]

Anemia Due to Zidovudine in HIV-Infected Patients Early clinical trials evaluating the efficacy of zidovudine in patients with HIV documented that nearly 50% of patients treated with zidovudine developed anemia requiring RBC transfusions. Subsequently, results from numerous clinical trials reported that epoetin resulted in statistically significant decreases in transfusion requirements for patients with HIV who have serum EPO levels less than 500 mU/mL (500 U/L). Currently, epoetin has a labeled indication for the treatment of anemia in patients with EPO levels

Patient Care Process

Collect Information:

- Review the medical and surgical history in conjunction with any physical assessment findings
- Speak with the patient/family member to evaluate lifestyle habits, particularly dietary preferences, beliefs, health goals, and socioeconomic factors

Assess the Information:

- Based on physical examination and review of systems, determine if the patient exhibits signs or symptoms of anemia
- Review current medications and assess if they could be contributing to anemia
- Evaluate CBC, if anemia is present, assess RBC indices to determine if the anemia is microcytic, normocytic, or macrocytic
- Assess iron, folic acid, and vitamin B_{12} studies to determine etiology of anemia

Develop a Care Plan:

- Determine whether a transfusion or pharmacotherapy is indicated. If pharmacotherapy is needed, decide whether oral or intravenous therapy is indicated [41]
- When initiating ESAs, assess the patient's iron status
- Discuss the importance of medication adherence to oral therapy
- Choose oral medications and doses that are optimal for the patient
- Select lifestyle and diet modifications that are likely to be effective and safe for the patient

Implement the Care Plan:

- Educate the patient on medication administration, potential new adverse effects, and how to report adverse effects
- Review signs and symptoms of anemia with the patient and address any concerns about anemia and its management
- Determine whether the patient has insurance coverage or recommended agents are included on the institution's formulary

Follow-up: Monitor and Evaluate:

- Follow up monthly to assess efficacy and tolerance of therapy until resolution of symptoms and Hgb goal is achieved
- Monitor for resolution of symptoms such as fatigue, shortness of breath, lethargy, headache, edema, and tachycardia
- Monitor the CBC monthly
- Monitor compliance of prescribed therapy and for side effects, such as:
  - Oral iron: nausea, vomiting, abdominal pain, heartburn, constipation, and dark stools
  - Parenteral iron: anaphylaxis (test dose required for iron dextran and observe for 1 hour after), injection-site pain/irritation, arthralgias, myalgias, flushing, malaise, and fever
  - Folic acid: bad taste, nausea, rash, and allergic reactions
  - Vitamin B_{12}: pain and erythema at injection site
  - ESAs: hypertension (monitor blood pressure), thrombosis (eg, deep vein thrombosis/pulmonary embolism, myocardial infarction, cerebrovascular accident, and transient ischemic attack), arthralgias, and headache

less than 500 mU/mL (500 U/L) and administered zidovudine doses less than 4200 mg/week.[34]

OUTCOME EVALUATION

KEY CONCEPT Patients should be monitored for Hgb response, symptom resolution, and adverse effects at appropriate intervals, and treatment regimens adjusted accordingly. The goal of anemia therapy is to correct the underlying etiology of the anemia, normalize the Hgb, and alleviate associated symptoms.

- To ensure response for patients with IDA, monitor CBC with special attention to occurrence of reticulocytosis and iron studies.
- A 1.0 g/dL (10 g/L or 0.62 mmol/L) per week increase in Hgb is desirable in patients with IDA. Reevaluate patients with increases less than 2.0 g/dL (20 g/L or 1.24 mmol/L) in 3 weeks.
- For patients with folic acid deficiency, monitor Hgb periodically and reevaluate patients who fail to normalize Hgb levels after 2 months of therapy.
- For patients with vitamin B_{12} deficiency, monitor for resolution of neurologic symptoms (ie, confusion and paresthesias), if applicable, and Hgb levels weekly until the levels normalize.[42]
- For cancer patients treated with chemotherapy without curative intent, initiate ESA treatment when Hgb levels are less than 10.0 g/dL (100 g/L or 6.21 mmol/L) and monitor Hgb levels weekly. If Hgb levels exceed 1.0 g/dL (10 g/L or 0.62 mmol/L) or 10.0 g/dL (100 g/L or 6.21 mmol/L), hold therapy until the Hgb level drops below 10.0 g/dL (100 g/L or 6.21 mmol/L). Restart the ESA at the lowest dose sufficient to reduce transfusions.
- For patients with CKD on dialysis, initiate ESA treatment when Hgb levels are less than 10.0 g/dL (100 g/L or 6.21 mmol/L) and monitor Hgb levels weekly. If Hgb levels approach or exceed 11.0 g/dL (110 g/L or 6.83 mmol/L), reduce or hold further doses until the level drops below 10.0 g/dL (100 g/L or 6.21 mmol/L). Restart the ESA at the lowest dose sufficient to reduce transfusions.

- For patients with CKD not on dialysis, initiate ESA treatment when Hgb levels are less than 10.0 g/dL (100 g/L or 6.21 mmol/L) and when the following additional criteria apply:
    - The rate of hemoglobin decline indicates the likelihood of a transfusion AND
    - Reducing the risks of alloimmunization and/or RBC transfusion is a goal. Monitor Hgb levels weekly. If Hgb levels exceed 10.0 g/dL (100 g/L or 6.21 mmol/L), reduce or hold further doses until the level drops below 10.0 g/dL (100 g/L or 6.21 mmol/L). Restart the ESA at the lowest dose sufficient to reduce transfusions.

Abbreviations Introduced in This Chapter

ACD	Anemia chronic disease
CKD	Chronic kidney disease
EPO	Erythropoietin
ESA	Erythropoietin-stimulating agent
GFR	Glomerular filtration rate
Hct	Hematocrit
Hgb	Hemoglobin
IDA	Iron deficiency anemia
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
RBC	Red blood cells
TIBC	Total iron-binding capacity

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Coagulation and Platelet Disorders

Anna Dushenkov and Paiboon Jungsuwadee

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the basics of the regulation of hemostasis and thrombosis.
2. Select appropriate nonpharmacological and pharmacological therapy for a patient with hemophilia in a given clinical situation.
3. Calculate an appropriate factor-concentrate dose for a product, given the percentage correction desired based on clinical situation.
4. List possible complications from hemophilia-induced bleeding episodes.
5. Choose an appropriate treatment strategy for patients with factor VIII or IX inhibitors.
6. Devise a treatment plan for a patient with a specific variant of von Willebrand disease (vWD).
7. Describe various recessively inherited coagulation disorders (RICDs) and the role of specific factor replacement in RICD management.
8. Recommend first-and second-line treatment approaches for immune thrombocytopenia (ITP).
9. Identify basic clinical features, causes, and management of select thrombotic microangiopathies (TMAs).

INTRODUCTION

Components of Hemostatic System

Following vessel injury, the endothelium is activated, and a series of physiological responses to prevent bleeding are initiated. The endothelial response involves vasoconstriction, platelet plug formation, coagulation, and fibrinolysis regulation. Under normal circumstances, platelets circulate in the blood in an inactive form. After injury, platelets undergo activation, which consists of (a) adhesion to the subendothelium, (b) secretion of granules containing chemical mediators (eg, adenosine diphosphate, thromboxane A2, and thrombin), and (c) aggregation. The chemical factors that are released from the injured tissue and platelets activate coagulation cascade and formation of thrombin. In turn, thrombin catalyzes conversion of fibrinogen to fibrin and its subsequent incorporation into the platelet plug. In parallel with coagulation, the fibrinolytic system is activated locally. Plasminogen is converted to plasmin, which dissolves the fibrin mesh (Figure 70–1).[1]

INHERITED COAGULATION DISORDERS

HEMOPHILIA

Epidemiology and Etiology

Hemophilia A (classic hemophilia) and B (Christmas disease) are coagulation disorders (RICDs) that result from defects in the genes encoding for plasma coagulation proteins, factor VIII (FVIII) and factor IX (FIX), respectively. The incidences of hemophilia A and B are estimated at 1 in 5000 and 1 in 30,000 male births. The disease manifests as mostly spontaneous bleedings that are either intra-articular, with 70%–80% of episodes that can lead to painful muscle atrophy and arthropathy in turn resulting in poor quality of life or intracranial hemorrhages (ICHs) that are much less common but potentially fatal.[2,3]

Pathophysiology

The pathophysiology of hemophilia is based on the deficiency of FVIII or FIX resulting in inadequate thrombin generation and impaired coagulation cascade (Figure 70–1). Hemophilias are X-linked recessive diseases (both factor VIII [*F8*] and IX [*F9*] genes are located on the X-chromosome). Generally, males carrying a defective allele for either *F8* or *F9* on their X-chromosome do not transmit the gene to their sons. However, their daughters are obligate carriers. More than 1000 mutations in *F8* and *F9* genes have been identified as causes of clinical hemophilia.[1] Consequently, hemophilia is not a result of a single genetic mutation. However, inversion at intron 22 of the *F8* gene accounts for 40% of severe hemophilia A cases, and this mutation is assessed during carrier and prenatal testing when there is a known intron 22 inversion in the family.[4] As for hemophilia B, the *F9* gene mutations appear to be the most common contributing factors. According to the European Association for Haemophilia and Allied Disorders (EAHAD) database (http://dbs.eahad.org), point mutations of the *F9* gene account for 71.9%.[5]

Complications of Hemophilia

The severity of bleeding associated with hemophilia correlates with the degree of FVIII or FIX deficiency as measured against the normal plasma level. Table 70–1 summarizes the age at onset and laboratory and clinical manifestations of hemophilia A and B.[6]

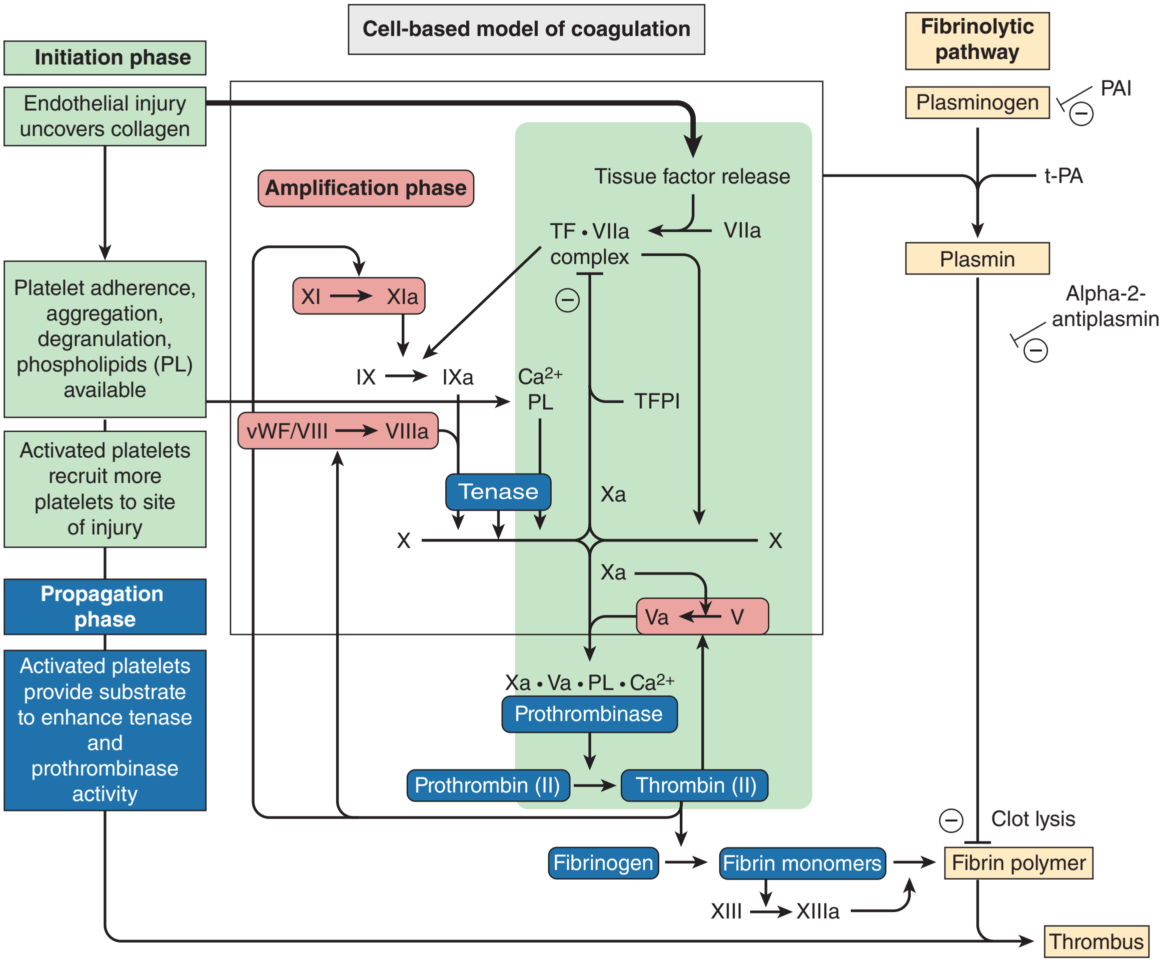
Cell-based model of coagulation
Initiation phase
Endothelial injury uncovers collagen
Platelet adherence, aggregation, degranulation, phospholipids (PL) available
Activated platelets recruit more platelets to site of injury
Propagation phase
Activated platelets provide substrate to enhance tenase and prothrombinase activity
Amplification phase
Tissue factor release
TF • VIIa complex
VIIa
XI → XIa
IX → IXa
Ca2+ PL
TFPI
vWF/VIII → VIIIa
Tenase
Xa
X
X
Xa
Va ← V
Xa • Va • PL • Ca2+
Prothrombinase
Prothrombin (II) → Thrombin (II)
Fibrinogen → Fibrin monomers → Fibrin polymer
XIII → XIIIa
Fibrinolytic pathway
Plasminogen
PAI
t-PA
Plasmin
Alpha-2-antiplasmin
Clot lysis
Thrombus

FIGURE 70–1. Coagulation and thrombolytic cascade model. This model shows successive activation of coagulation factors proceeding from the top to the bottom where thrombin and fibrin are generated. (Ca^{2+}, calcium; PAI, plasminogen activator inhibitor; PL, phospholipids; TF, tissue factor [thromboplastin]; TFPI, tissue factor pathway inhibitor; t-PA, tissue plasminogen activator; vWf, von Willebrand factor. All clotting factors are shown as Roman numerals and the addition of an "a" indicates "activated.") (From Hammer GD, McPhee SJ. Blood disorders. Pathophysiology of Disease: An Introduction to Clinical Medicine, 8th ed.; 2019, Figure 6–5.)

Table 70–1

Laboratory and Clinical Manifestations of Hemophilia

	Severe (< 0.01 IU/mL [10 IU/L])	Moderate (0.01–0.05 IU/mL [10–50 IU/L])	Mild (> 0.05 IU/mL [50 IU/L])
Age at onset	1 year or less	1–2 years	2 years–adult
Neonatal symptoms			
PCB	Usual	Usual	Rare
ICH	Occasional	Uncommon	Rare
Muscle/joint hemorrhage	Spontaneous	Minor trauma	Minor trauma
CNS hemorrhage	High risk	Moderate risk	Rare
Postsurgical hemorrhage (without prophylaxis)	Frank bleeding, severe	Wound bleeding, common	Wound bleeding
Oral hemorrhage following trauma, tooth extraction	Usual	Common	Common

CNS, central nervous system; ICH, intracranial hemorrhage; PCB, postcircumcisional bleeding.

Normal range of factor VIII/IX activity level is 0.5–1.5 IU/mL (500–1500 IU/L). 1 IU/mL (1000 IU/L) corresponds to 100% of the factor found in 1 mL of normal plasma.

Treatment

▶ *Desired Outcomes*

Patients with hemophilia are cared for by interdisciplinary teams all who share the same short- and long-term management goals.[7] The short-term goals of hemophilia treatment include the following:

- Decrease the number of bleeding episodes per year or bleeding frequency
- Normalize or improve clotting factor concentrate levels

The long-term goals of hemophilia treatment include the following:

- Maintain clinical joint function
- Normalize orthopedic joint score
- Normalize radiologic joint score
- Maintain quality-of-life measurements

▶ *General Approach to Treatment*

KEY CONCEPT Intravenous factor replacement with recombinant or plasma-derived products to treat or prevent bleeding is the mainstay treatment of hemophilia. Primary prophylaxis is defined as the regular administration of factor concentrates in the absence of documented joint disease and initiated before the age of three.[8] Primary prophylaxis is recommended for individuals who have not had a bleeding episode but have severe factor deficiency (FVIII or IX activity levels < 1%) as it is efficacious in preventing bleeding and associated complications.[9] In addition, several studies have shown the benefit of prophylaxis in reducing morbidity in severe hemophilia A and B in both children and adults.[10]

▶ *Nonpharmacologic Therapy*

Supportive Care Rest, ice, compression, elevation (RICE) can be used during the bleeding episode, following with casts, splints, and crutches after the bleeding has been controlled.

Surgery Surgical arthroscopic synovectomy reduces replacement therapy–resistant disease and repetitive hemarthrosis of a single joint. This procedure removes inflamed joint tissue. Patients may have decreased range of motion after the surgery.

Orthotics Joint prostheses do not deal with the deformities directly. Orthotics in hemophilia serves as an important supportive measure before or after surgery.

▶ *Pharmacologic Therapy*

Hemophilia A

DDAVP Primary therapy is based on disease severity and type of hemorrhage.[11] Most patients with mild-to-moderate disease and minor bleeding episodes can be treated with 1-desamino-8-D-arginine vasopressin (desmopressin acetate [DDAVP]), a synthetic analogue of the antidiuretic hormone, vasopressin. DDAVP causes release of von Willebrand factor (vWF) and FVIII from the endothelial storage sites. DDAVP increases plasma FVIII levels by two- to four-fold within 60 minutes after an infusion or 90 minutes after an intranasal administration.[12] The recommended dose is 0.3 mcg/kg, IV (infused over 15–30 minutes) or subcutaneously (if < 1.5 mL) or 150 mcg (in patients weighing < 50 kg) to 300 mcg (in patients weighing 50 kg or more) intranasally via concentrated nasal spray, which may be repeated after 24 hours.[11] Desmopressin infusion may be administered daily for up to 3 days. FVIII levels should be obtained after administration. Facial flushing, hyper- or hypotension, gastrointestinal upset, and headache are the common side effects of desmopressin. Water retention and hyponatremia may occur; patients should be instructed to limit water intake while taking DDAVP. Serious side effects include seizures related to hyponatremia and myocardial infarction. Due to higher incidence of hyponatremia-related seizures in patients less than 2 years old, the use of desmopressin is not recommended in this population. Tachyphylaxis, an attenuated response with repeated administration, may occur after several doses.[13] DDAVP should not be used in severe life-threatening bleeding due to delayed response, and

Clinical Presentation and Diagnosis of Hemophilia A and B

Hemophilia A and B are clinically indistinguishable.

Symptoms

- Ecchymosis
- Hemarthrosis—bleeding into joint spaces[a] (especially knee, elbow, and ankle)
  - Joint pain, swelling, and erythema
  - Cutaneous warmth
  - Decreased range of motion
- Muscle hemorrhage
  - Swelling
  - Pain with motion of affected muscle
  - Signs of nerve compression
  - Potential life-threatening blood loss, especially with thigh bleeding
- Mouth bleeding with dental extractions or trauma
- Genitourinary bleeding
- Gastrointestinal bleeding
- Hematuria
- Intracranial hemorrhage (spontaneous or following trauma), with headache, vomiting, change in mental status, and focal neurologic signs
- Excessive bleeding with surgery

Diagnostic Parameters/Laboratory Testing

- Family history
- Normal prothrombin time (PT)
- Normal platelet count
- Prolonged activated partial thromboplastin time (aPTT)
- Low FVIII level (hemophilia A)
- Low FIX level (hemophilia B)

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[a] Hallmark of hemophilia; inadequately managed recurrent hemarthrosis leads to deformity and chronic pain (hemophilic arthropathy).

the increase in FVIII may not be sufficient for proper clotting. DDAVP is usually used to treat mild hemophilia A.

According to the manufacturer, the use of DDAVP is contraindicated in patients with creatinine clearance less than 50 mL/min (0.83 mL/s); however, it has been used off-label in patients with impaired renal function.

Antifibrinolytic Therapy Aminocaproic acid and tranexamic acid are antifibrinolytic agents that reduce plasminogen activity leading to clot stabilization and inhibition of clot lysis. These agents are usually used as adjuncts in dental procedures or in difficult-to-control menorrhagia episodes and must be administered with appropriate factor concentrates to form a clot.[11]

Factor VIII Replacement Patients with severe hemophilia A may receive primary (before the first major bleed) or secondary (after the first major bleed) prophylaxis. Patients with hemophilia who experience a major bleed require FVIII replacement.[7] The therapy may include recombinant (produced via transfection of mammalian cells with the human *F8* gene) or plasma-derived (concentrate from pooled plasma) FVIII (Table 70–2). Newer generation plasma-derived coagulation factor concentrates are considerably safer after advancements in viral testing and inactivation technology. Recombinant factor VIII (rFVIII) products are stabilized with sucrose, trehalose, and mannitol or produced in human cell lines, eliminating the concern for viral transmission.[11]

Several strategies have been utilized to extend the half-lives of recombinant FVIII and FIX (EHL rFVIII and EHL rFIX, respectively).[14-17] Those strategies include fusion of the rFVIII or rFIX to a fragment-crystallizable region (Fc region) of immunoglobulin as in ie, Eloctate for rFVIII or Alprolix for rFIX, or to recombinant albumin as in ie, Idelvion for rFIX. Other strategies are PEGylation of the recombinant clotting factors as in ie, Adynovate, Esperoct for rFVIII or Rebinyn for rFIX, or as a single chain construct as in ie, Afstyla for rFVIII.

The severity of hemorrhage and its location are the major determinants of percentage correction to target, as well as duration of therapy (Table 70–3). The normal range of FVIII activity level is 1 IU/mL (1000 IU/L), which corresponds to 100% of the factor found in 1 mL of normal plasma. Minor bleeding may be treated with a goal of 25% to 30% (0.25–0.30 IU/mL [250–300 IU/L]) of normal activity, whereas serious or life-threatening bleeding requires greater than 80% of normal activity. FVIII is a large molecule that remains in the intravascular space, and its estimated volume of distribution is around 50 mL/kg. Generally, FVIII levels increase by 2% (0.02 IU/mL [20 IU/L]) for every 1 U/kg of FVIII concentrate infused. To calculate FVIII replacement dose, the following equation can be used:

$$\text{Dose of FVIII (U)} = \text{weight (kg)} \times (\text{desired percentage increase}) \times 0.5$$

Thus, to increase FVIII levels by 50% (eg, from 0% to 50%) in a 70-kg (154-lb) patient, an IV dose of 1750 U is required. The median half-life of FVIII ranges from 9.4 hours (in 1–6-year olds) to 10.4 hours (in 10–65-year olds).[18,19] Half the initial dose is given every half-life (every 8–12 hours) to maintain the desired FVIII level. Although intermittent bolus infusions of FVIII concentrates have been used successfully, continuous infusion protocols can be used in patients requiring prolonged treatment of acute hemorrhage to avoid dangerously low trough levels and decrease the overall cost of therapy. FVIII can be administered as a continuous infusion at 2 to 4 U/kg/hour with daily factor level monitoring to ensure appropriate rate of infusion.[20,21]

Hemophilia B

Factor IX Replacement Hemophilia B therapy may include recombinant (produced via transfection of mammalian cells with the human *F9* gene) or plasma-derived (concentrate from pooled plasma) FIX (Table 70–2). Guidelines for choosing the factor-concentrate formulation for hemophilia B are similar to the guidelines for hemophilia A. However, older generation FIX concentrates containing other vitamin K–dependent proteins, called prothrombin complex concentrates (PCCs), have been associated with thrombogenic side effects, and these products are not the first-line treatment for hemophilia B. Being a small protein, FIX molecules pass into both the intravascular and the extravascular spaces. Therefore, the volume of distribution of FIX is twice that of FVIII. Consequently, 1 U of FIX administered per kilogram of body weight yields a 1% rise in the plasma FIX level (0.01 IU/mL [10 IU/L]). To calculate the FIX replacement dose, the following equation can be used:

$$\text{Dose of FIX (U)} = \text{weight (kg)} \times (\text{desired percentage increase}) \times \text{F}$$

where for example, F for Benefix is 1.2 for adults and 1.4 for children less than 15 years old.[22] Thus, to increase FIX levels by 50% (eg, from 0% to 50%) in a 70-kg (154-lb) 14-year-old patient, the required dose of FIX is 4900 U IV. The half-life of FIX ranges from 16 to 17 hours; therefore, doses are given every 18 to 24 hours.

Administration of EHL products might overcome the need for frequent, several times per week infusions, resulting in up to estimated 50% fewer infusions per year of treatment.[23]

With the rapidly increasing use of EHL formulations, it has become evident that there is a lack of standardized treatment algorithms that would maximize patients outcomes.[24] Several population-based pharmacokinetic models eg, Web Accessible Population Pharmacokinetic Service for Hemophilia (WAPPS-Hemo, www.wapps-hemo.org), were designed to guide practitioners in EHL products' dosing and frequency of administration.

▶ Treatment of Patients With FVIII or FIX Inhibitors

FVIII and FIX inhibitors are antibodies that develop in response to replacement therapy in approximately 30% and 5% of hemophilia A and hemophilia B patients, respectively. This is the most serious complication with no difference between plasma-derived and recombinant products in their potential for inhibitor development. The antibodies bind to and neutralize the activity of infused factor concentrates. Other complications include anaphylaxis.[25] Although the inhibitors do not increase hemorrhage frequency, their existence challenges treatment of bleeding episodes. Titers of inhibitors are measured and reported in Bethesda units (BU), and this measurement is used to guide therapy (Figure 70–2). Management of acute bleeding in patients with factor inhibitors includes the administration of FVIII concentrates, PCCs, aPCC, recombinant factor VIIa (rFVIIa), and recombinant porcine FVIII.[26] Immune tolerance induction can be attempted to prevent future bleeding episodes.

FVIII concentrates can be used in patients with low inhibitor levels to control acute bleeding episodes. The dose of FVIII is determined based on clinical response (Figure 70–2).

PCCs contain vitamin K–dependent factors II, VII, IX, and X. These agents bypass FVIII, at which the antibody is directed (Figure 70–2). However, PCCs carry the risk of serious thrombotic complications. The only aPCC agent available, FEIBA (Factor Eight Inhibitor Bypassing Activity), has a higher concentration of activated factors.

Table 70–2

Selected Clotting Factor Products

Brand Name	Product Type	Viral Inactivation/Exclusion Method	Stabilizer	Half-life, h (Adult)
Factor VIII				
Alphanate	Plasma-derived FVIII/vWF	Solvent-detergent, dry heat	Human albumin	17.9 ± 9.6
Hemofil M	Plasma-derived FVIII	Solvent-detergent/Immunoaffinity chromatography	Human albumin	14.8 ± 3.0
Humate-P	Plasma-derived FVIII/vWF	Cryoprecipitate-pasteurization	NS	12.2
Koāte-DVI	Plasma-derived FVIII	Solvent-detergent, dry heat	Human albumin	16.1
Advate[III]	Recombinant FVIII	Solvent-detergent/Immunoaffinity chromatography	Trehalose, mannitol	12.0 ± 2.9[€]
Adynovate[III]	Recombinant FVIII; PEGylated	Solvent-detergent/Immunoaffinity chromatography	Trehalose, mannitol	14.7 ± 3.8
Afstyla[III]	Recombinant B-domain truncated FVIII; Single chain	NS/Immunoaffinity chromatography	Sucrose	14.2
Eloctate[IV]	Recombinant B-domain deleted FVIII; Fc fusion	Detergent and nanofiltration/Affinity chromatography	Sucrose	19.7
Esperoct[IV]	Recombinant B-domain truncated FVIII; GlycoPEGylated	Detergent and nanofiltration/Affinity chromatography	NS	21.7
Helixate FS[II]	Recombinant FVIII	Solvent-detergent/Immunoaffinity chromatography	Sucrose	13.7 ± 1.8
Jivi	Recombinant B-domain deleted FVIII	Filtration/Chromatography	Sucrose	18.6 ± 4.6
Kogenate FS[II]	Recombinant FVIII	Solvent-detergent/Immunoaffinity chromatography	Sucrose	13.7± 1.8
Kovaltry[III]	Recombinant FVIII	Detergent and nanofiltration/Affinity chromatography	Sucrose	14.3 ± 3.7
Novoeight[III]	Recombinant FVIII	Detergent and nanofiltration/Affinity chromatography	Sucrose	12.0
Nuwiq[IV]	Recombinant B-domain deleted FVIII	Solvent-detergent and nanofiltration/Chromatography	Sucrose	17.1 ± 11.2
Recombinate[I]	Recombinant FVIII	NS/Immunoaffinity chromatography	Human albumin, rvWF	14.6 ± 4.9
ReFacto[II]	Recombinant B-domain deleted FVIII	NS/Chromatography	Human albumin	13.7 ± 3.7
Xyntha[III]	Recombinant B-domain deleted FVIII	Solvent-detergent, nanofiltration/Affinity chromatography	Sucrose	11.2 ± 5.0
Factor IX				
AlphaNine SD	Plasma-derived FIX	Solvent-detergent and nanofiltration/Affinity chromatography	NS	21
Mononine	Plasma-derived FIX	Nanofiltration/Immunoaffinity chromatography	Mannitol	22.6
Profilnine	Plasma-derived Factors II, IX, X	Solvent-detergent and nanofiltration/Chromatography	NS	24.7 ± 8.3
Alprolix[IV]	Recombinant FIX; Fc fusion	Detergent and nanofiltration/NS	Sucrose, mannitol	86
BeneFIX[III]	Recombinant FIX	Nanofiltration/Chromatography	Sucrose	18.8 ± 5.4
Idelvion[III]	Recombinant FIX; rAlbumin fusion	Solvent-detergent and nanofiltration/NS	Sucrose, mannitol	118
Ixinity[III]	Recombinant FIX	Solvent-detergent and nanofiltration/Chromatography	Trehalose, mannitol	24 ± 7
Rebinyn	Recombinant FIX; PEGylated	Detergent and nanofiltration/Immunoaffinity chromatography	Sucrose, mannitol	114.9
Rixubis[III]	Recombinant FIX	Solvent-detergent and nanofiltration/Chromatography	Sucrose, mannitol	26.7 ± 3
APCC				
Feiba VH or NF	Plasma-derived Factors II, VIIa, IX, X	Nanofiltration and vapor heat	NS	NS
PCC				
Profilnine SD	Plasma-derived Factors II, IX, X	Solvent-detergent and nanofiltration/Chromatography	NS	24.7 ± 8.3
Other				
NovoSeven RT	Recombinant FVIIa	NS/Chromatography	Sucrose, mannitol	3.3 ± 0.3
Vonvendi	Recombinant vWF	Immunoaffinity purification	Trehalose, mannitol	19.1 ± 4.3
Wilate	Plasma-derived FVIII/vWF complex	Solvent-detergent and dry heat/Ion-exchange chromatography	Sucrose	10.6 ± 2.7

[€], Adolescent (12 to < 16 years)

[I], first generation; [II], second generation; [III], third generation; [IV], fourth generation of recombinant factor products; NS, not specified

APCC, activated prothrombin complex concentrate; NS, not specified; PCC, prothrombin complex concentrate; vWF, von Willebrand factor.

Table 70–3

Guidelines for Replacement Dosing With Factor VIII and Factor IX

Type of Hemorrhage	Desired Plasma FVIII Level (% of Normal)	Desired Plasma FXI Level (% of Normal)	Duration of Therapy (days)
CNS, intracranial, retropharyngeal, retroperitoneal, surgical prophylaxis	80–100	80–100	FVIII: every 8–12 hours over 10–14 days FIX: every 12 hours over 10–14 days
Mild hemarthrosis, mucosal (eg, epistaxis), superficial hematoma	30	20–30	FVIII: every 8–12 hours over 1–2 days FIX: every 12–24 hours over 1–2 days

rFVIIa is a bypassing agent designed to generate thrombin only at tissue injury sites, where it binds tissue factor. Due to its local action, rFVIIa is associated with fewer systemic thrombotic events than PCC. rFVIIa is used effectively in surgeries and spontaneous bleeds.[27]

Recombinant porcine FVIII serves as a third-line agent (only after FVIIa and aPCC have failed) due to the relatively high incidence of cross-reactivity with FVIII inhibitors.

Induction of immune tolerance, which is often performed with the goal of eliminating the inhibitor, is accomplished by the administration of repetitive doses of FVIII or FIX with or without immunosuppressive therapy. It is effective in 70% of patients with hemophilia A and 30% of patients with hemophilia B.

Approval of emicizumab introduced a new era in the management of hemophilia when therapeutic agents are not the replacement factors but rather molecules that either mimic the function of the missing coagulation protein or modulate the coagulation cascade.[2,28] Emicizumab is a bispecific humanized monoclonal immunoglobulin G4 (IgG4) antibody that recognizes both FIXa and factor X (FX). Emicizumab bridges FIXa and FX, therefore, resembling the function of missing FVIIIa needed for hemostasis.[29] Emicizumab is administered subcutaneously with a varying frequency between 1 and 4 weeks injection.[30] The selection of a weight-based dosing regimen should take into consideration patient's preferences, which can drive meaningful adherence.

Gene therapy is a modality that offers a potential for hemophilia cure when after a single treatment, patient will no longer develop bleeding or other disease complications. Sustainable expression of FIX was achieved in a small number of patients with hemophilia B after an injection of adeno-associated viral vector carrying FIX variant gene coupled with the sequences optimizing expression and targeting the liver. Patients demonstrated a reduced annualized bleeding rate along with a decreased need for factor replacement. These successful results prompted extensive research in gene therapy for hemophilia A where recently similar promising outcomes have been reported.[31]

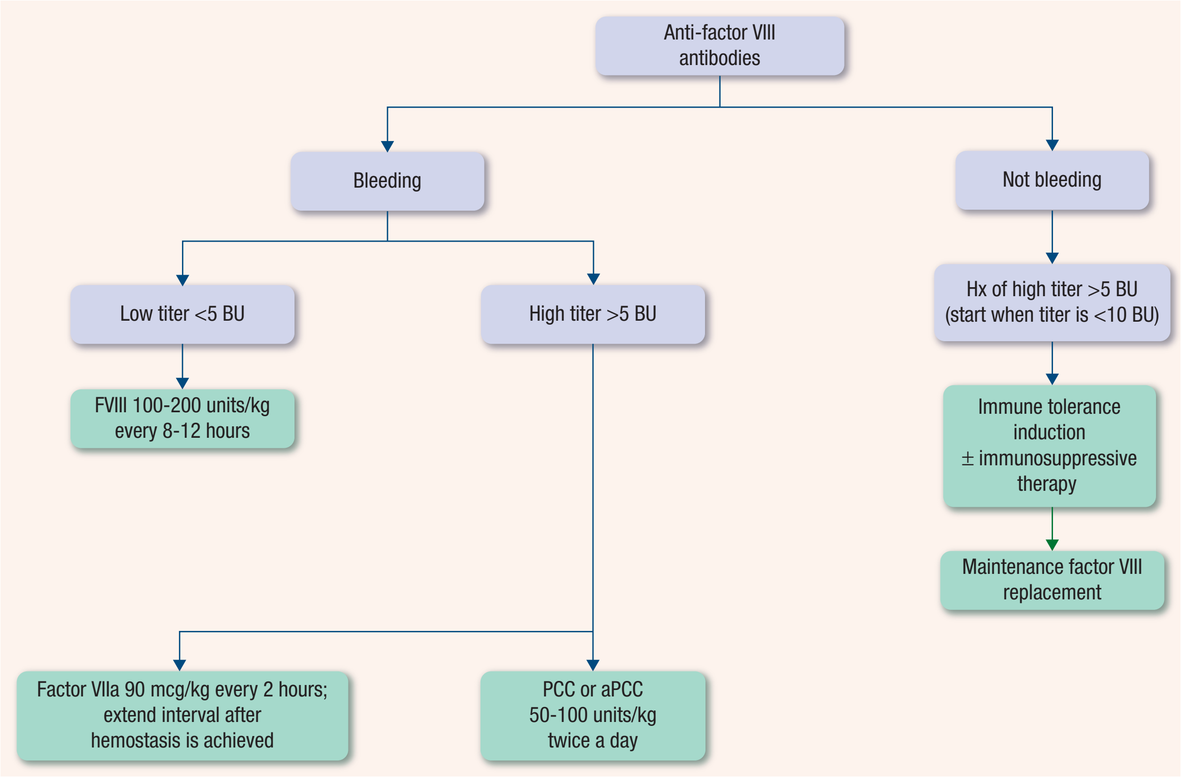

Anti-factor VIII antibodies
Bleeding
Not bleeding
Low titer <5 BU
High titer >5 BU
Hx of high titer >5 BU (start when titer is <10 BU)
FVIII 100-200 units/kg every 8-12 hours
Immune tolerance induction ± immunosuppressive therapy
Maintenance factor VIII replacement
Factor VIIa 90 mcg/kg every 2 hours; extend interval after hemostasis is achieved
PCC or aPCC 50-100 units/kg twice a day

FIGURE 70–2. Treatment algorithm for the management of patients with hemophilia A and factor VIII antibodies. (aPCC, activated prothrombin complex concentrate; BU, Bethesda unit; PCC, prothrombin complex concentrate). (From DiPiro JT, Yee GC, Posey L, Haines ST, NolinFigure TD, Ellingrod V. Coagulation disorders. Pharmacotherapy: A Pathophysiologic Approach, 11th ed.; 2020, Figure 119–1.)

▶ *Treatment of Pain Associated with Hemophilia*

Pain commonly occurs in patients with hemophilia. Acute bleeding episodes and long-term joint destruction are common sources of pain. Acetaminophen and opioid analgesics are recommended to control mild-to-moderate and severe pain, respectively. Nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin should generally be avoided because these drugs bind to platelets and increase the risk of bleeding. Selective cyclooxygenase-2 (COX-2) inhibitors can be used with caution.[32]

Outcome Evaluation

The main goal of hemophilia treatment is to prevent bleeding episodes and their long-term complications. Clinicians should evaluate patients for the following:

- Musculoskeletal status, including joint range of motion and radiologic assessment, as indicated.
- Number and type of bleeding episodes to assess adequacy of prophylactic treatment and home therapy.
- Development of inhibitors due to the use of clotting-factor concentrates, especially in patients with severe disease and those poorly responding to treatment.
- Following the age-appropriate vaccination schedules in hemophiliacs without the evidence of immunity.

VON WILLEBRAND DISEASE

Epidemiology and Etiology

Von Willebrand disease (vWD) is the most common inherited bleeding disorder caused by a deficiency or dysfunction of vWF. It is classified based on the quantitative deficiency of vWF or qualitative abnormalities of vWF. Based on population studies, the prevalence of vWD is 0.6% to 1.3%. In contrast to hemophilia, the majority of vWD cases are inherited as an autosomal dominant disorder, suggesting equal frequency in males and females.[33,34]

Pathophysiology

vWF is a large multimeric glycoprotein with two main functions in hemostasis: to aid platelet adhesion to injured blood vessel walls and to carry and stabilize factor VIII in plasma. Table 70–4 represents three main vWD phenotypes, their frequency, and genetic transmission.[35]

Patient Encounter 1, Part 1: vWD

A 15-year-old girl without significant past medical history is referred to a hematology clinic with a complaint of having heavy menstrual bleeds with normal menstrual cycle but with clots, size of about a quarter and soaking through a pad within an hour. The bleeds usually last for 10 days. Her mother reports history of spontaneous nosebleeds and easy bruising in male and female members of the family.

What are this patient's risk factors for vWD?

What additional information for developing a treatment plan do you need to collect?

Treatment

▶ *Desired Outcomes*

Unlike in hemophilia, the bleeding tendency in vWD is less frequent and generally less severe. Consequently, chronic prophylaxis is usually unwarranted. The goal of mainstay therapy in vWD is:

- To stop spontaneous bleeding as necessary
- To prevent surgical and postpartum bleeding

▶ *Nonpharmacologic Therapy*

Local measures, including pressure and ice, may be used to control superficial bleeding.

▶ *Pharmacologic Therapy*

Systemic therapy is used to prevent bleeding associated with surgery, childbirth, and dental extractions and to treat bleeding that cannot be controlled with local measures. The two systemic approaches involve using desmopressin (DDAVP), which stimulates the release of endogenous vWF, or administering products that contain vWF. The National Heart, Lung, and Blood Institute issued comprehensive evidence-based guidelines for the diagnosis and management of vWD.[34]

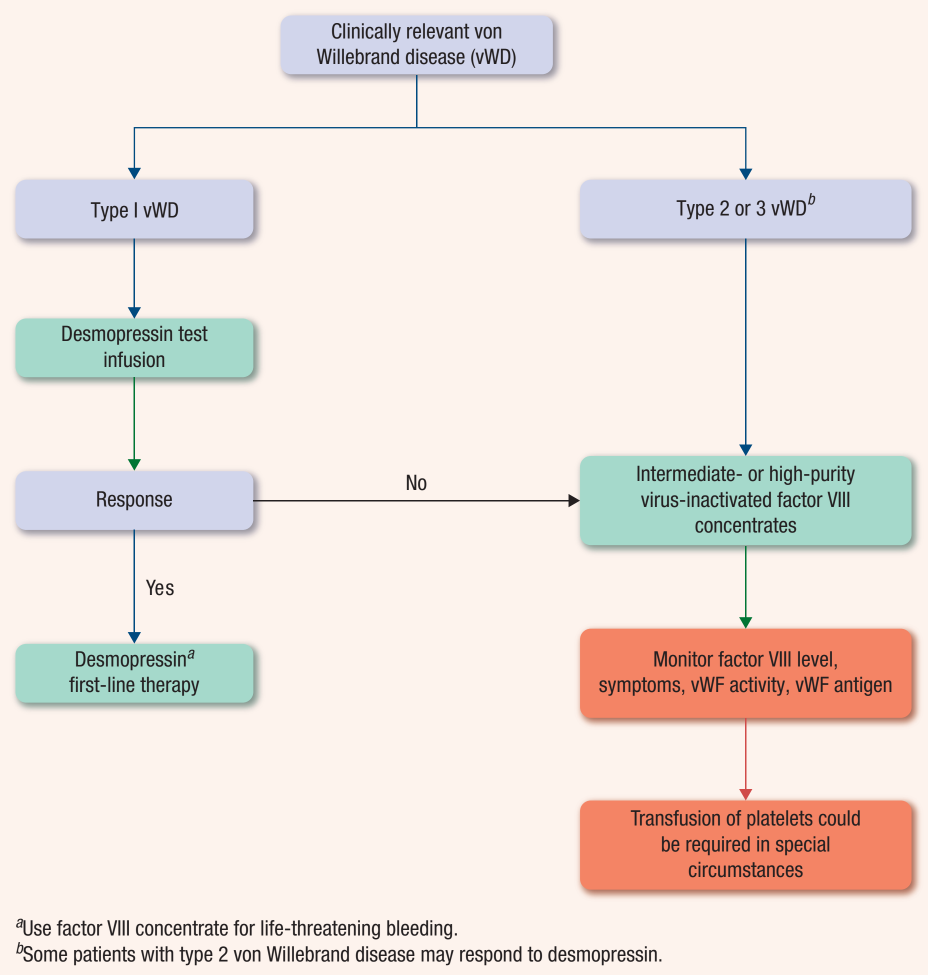
The general approach to the treatment of vWD is depicted in Figure 70–3.

DDAVP Most patients with type 1 vWD (functionally normal vWF) and minor bleeding episodes can be treated with desmopressin, which induces the release of factor VIII and vWF from the endothelial cells through interaction with vasopressin V2

Table 70–4

Classification of vWD

Phenotype	Mechanism of Disease	Percentage of Cases	Genetic Transmission
Type 1 vWD	Partial (mild-to-moderate) quantitative deficiency of vWF and FVIII	70–80	Autosomal dominant
Type 2 vWD	Qualitative abnormalities of vWF	10–30	
2A	Decreased platelet-dependent vWF function owing to the lack of larger multimers	10–20	Autosomal dominant (or recessive)
2B	Decreased vWF function due to increased affinity to platelet GPIb and resultant sequestration or loss	5	Autosomal dominant
2M	Defective platelet-dependent vWF functions not associated with multimer defects	Uncommon	Autosomal dominant (or recessive)
2N	Defective vWF binding to FVIII	Uncommon	Autosomal recessive
Type 3 vWD	Severe quantitative deficiency of vWF	Rare	Autosomal recessive


Clinically relevant von Willebrand disease (vWD)
Type I vWD
Type 2 or 3 vWD[b]
Desmopressin test infusion
Response
No
Yes
Intermediate- or high-purity virus-inactivated factor VIII concentrates
Desmopressin[a] first-line therapy
Monitor factor VIII level, symptoms, vWF activity, vWF antigen
Transfusion of platelets could be required in special circumstances

[a] Use factor VIII concentrate for life-threatening bleeding.
[b] Some patients with type 2 von Willebrand disease may respond to desmopressin.

FIGURE 70–3. General approach to treatment of vWD. (From DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V. Coagulation disorders. Pharmacotherapy: A Pathophysiologic Approach, 11th ed.; 2020, Figure 119–2.)

receptors. The recommended dose is the same as that used to treat mild FVIII deficiency (0.3 mcg/kg IV infused over 15–30 minutes or 150–300 mcg intranasally via concentrated nasal spray; may repeat after 24 hours). This therapy is generally ineffective in individuals with type 2A disease, who secrete abnormal vWF. It is recommended for individuals with type 2B disease who respond to DDAVP. The drug may increase the risk of postinfusion thrombocytopenia, in which case a concomitant platelet infusion is administered. Patient with type 3 vWD, who lack releasable stores of vWF, do not respond to DDAVP therapy.[36]

The individual responsiveness to desmopressin is inconsistent, and a test dose administered at the time of diagnosis or prior to therapy is the best predictor of response. Generally, DDAVP is more effective in individuals with vWD than in patients with hemophilia, with an average two- to five-fold increase in vWF and FVIII levels over the baseline. In patients with an adequate response, desmopressin is the first-line therapy because it allows for once-daily administration (elevates plasma levels for 8–10 hours), does not pose a threat in terms of viral transmission, and costs substantially less than the plasma-derived products.

Antifibrinolytic Therapy Fibrinolysis inhibitors and oral contraceptives are used successfully in the management of epistaxis and menorrhagia or as adjuvant treatments.[37] Fibrinolysis inhibitors include aminocaproic acid (25–60 mg/kg, orally or IV [or 4–5 g] every 4–6 hours, to a maximum dose of 24 g/day) and tranexamic acid (10 mg/kg, IV every 8 hours). Oral tranexamic acid is FDA approved for the treatment of cyclic heavy menstrual bleeding although it is not approved for the management of patients with vWD. The IV form of tranexamic acid can be given as swish and swallow or spit every 6 to 8 hours for bleeding prophylaxis in dental surgery. Both aminocaproic acid and tranexamic acid are dose adjusted for patients with renal insufficiency.

Replacement Therapy KEY CONCEPT Type 1 vWD patients unresponsive to desmopressin, patients with types 2 and 3 vWD, and patients undergoing major surgery require replacement therapy with plasma-derived, intermediate- and high-purity virus-inactivated FVIII concentrates containing vWF. Ultra-high-purity plasma-derived and recombinant FVIII concentrates should not be used for the treatment of vWD because those products do not contain vWF.

Table 70–5 provides typical dosing guidelines and target levels of replacement therapy—concentrates to control various types of hemorrhage.

Vonicog alfa is the first recombinant vWF approved for the perioperative management of bleeding and on-demand treatment and control of bleeding episodes in patient with vWD older than 18 years of age.[38]

Table 70–5

Replacement Therapy in vWD

Condition	Therapy	Recommended Dosage
Major surgery	Maintain vWF:RCo and FVIII levels at least 100 IU/dL (1000 IU/L) followed by 50 IU/dL (500 IU/L) for 7–14 days	40–60 U/kg[a] loading dose, followed by 20–40 U/kg every 12–24 hours
	To minimize risk of thrombosis: vWF:RCo levels should not exceed 200 IU/dL (2000 IU/L), and FVIII levels should not exceed 250 IU/dL (2500 IU/L)	DDAVP may be added after a few days
Minor surgery	Prophylaxis: maintain vWF:RCo and FVIII levels at least 30 IU/dL (300 IU/L) (preferably > 50 IU/dL [> 500 IU/L])	30–60 U/kg loading dose, followed by 20–40 U/kg every 12–48 hours
	Minor surgery: maintain vWF:RCo and FVIII levels at least 30 IU/dL (300 IU/L) (preferably > 50 IU/dL [> 500 IU/L]) for 3–5 days	DDAVP may be added after a few days

[a] vWF concentrates are dosed based on vWF:RCo units concentration in the preparation to achieve the desired vWF:RCo levels.

Clinical Presentation and Diagnosis of vWD

Clinical manifestations vary depending on the subtype. Patients with mild disease may be asymptomatic into adulthood.

Symptoms

- Bruising
- Mucocutaneous bleeding
- Epistaxis
- Oral cavity bleeding
- Menorrhagia
- Gastrointestinal bleeding
- Joint and deep tissue bleeding
- Postoperative bleeding

Laboratory Testing

- Low or normal vWF antigen concentration in plasma (vWF:Ag)
- Low or normal factor VIII coagulation assay (FVIII:C)[a]
- Low ristocetin cofactor activity (vWF:RCo)[b]

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[a] FVIII coagulation assay measures the ability of vWF to bind and maintain adequate levels of FVIII.

[b] Ristocetin cofactor activity (vWF:RCo) assay measures the ability of vWF to interact with intact platelets (normal 50–200 IU/dL [500–2000 IU/L]).

Outcome Evaluation

The main goal of vWF treatment is to prevent bleeding with surgery or dental procedures. Clinicians should evaluate patients every 6 to 12 months for the following:

- Number and type of bleeding episodes to assess the need for prophylactic treatment.
- Ensure adequate levels of vWF and FVIII prior to minor and major surgical procedures and for the treatment of bleeding.
- Vaccination against hepatitis A and B is recommended in all patients with vWF deficiency with no evidence of immunity.

OTHER CLOTTING FACTOR DEFICIENCIES

Etiology and Epidemiology

RICDs refer to relatively rare deficiencies in factors II, V, VII, and X to XIII resulting in either decreased clotting factor production or production of a dysfunctional molecule with reduced activity.[39] The clinical severity of bleeding varies and generally is poorly correlated with the factor blood levels. Table 70–6 illustrates these clotting factor deficiencies and some of their characteristics.

Pathophysiology

The RICDs are rare genetic disorders. Mutations in the genes responsible for the respective clotting factors result in impaired functionality or production of the factor.

Table 70–6

Clotting Factor Deficiency Characteristics

Factor Deficient	Inheritance Pattern	Estimated Incidence	Laboratory Abnormalities	Severity and Site of Bleeding
II	Autosomal dominant or recessive	Extremely rare	Prolonged PT and aPTT	Mild-to-moderate umbilical cord, joint, and mucosal tract
V	Autosomal recessive	1:1,000,000	Prolonged PT and aPTT	Mild-to-moderate mucosal tract
VII	Autosomal recessive	1:500,000	Prolonged PT	Mild-to-severe mucosal tract and joint
X	Autosomal recessive	1:1,000,000	Prolonged PT and aPTT	Mild-to-severe umbilical cord, joint, and muscle
XI	Autosomal recessive	4% of Ashkenazi Jews: otherwise rare	Prolonged aPTT	Mild-to-moderate posttraumatic bleeding
XII	Unknown	Unknown	Prolonged aPTT	No bleeding
XIII	Autosomal recessive	< 1:2,000,000	Normal PT and aPTT	Moderate-to-severe umbilical cord, intracranial, and joint bleeding; recurrent miscarriages, impaired wound healing

aPTT, activated partial thromboplastin time; PT, prothrombin time.

Patient Encounter 1, Part 2: vWD

Medications: None

Allergies: NKA

PE/ROS:

Well-nourished, well-developed (WNWD) female, otherwise healthy. Wt 52 kg.

Labs:

Platelet count: 205 × 10^3/mm^3 (205 × 10^9/L) (normal 140–440 × 10^3/mm^3 [140–440 × 10^9/L])

aPTT: 40 seconds (normal 25–40 seconds)

PT: 14 seconds (normal 11–15 seconds)

FVIII-C: 51% (normal 50%–150%)

vWF:RCo: 25 IU/dL or 250 IU/L (normal 50–200 IU/dL or 500–2000 IU/L)

vWF-Ag: 28 IU/dL or 280 IU/L (normal 50–200 IU/dL or 500–2000 IU/L)

Given this additional information, is this patient's presentation consistent with vWD?

Define treatment goals for this patient.

Treatment

▶ *Desired Outcomes*

Therapeutic interventions for RICDs improve hemostasis via replacement of deficient blood coagulation factors while minimizing the development of immune tolerance.[40]

Hemostatic levels should be maintained for the following conditions:

- Spontaneous bleeding—until bleeding stops
- Minor surgery—for 2 to 3 days
- Major surgery—until incision site has healed

▶ *Nonpharmacologic Therapy*

Transfusional Therapies

KEY CONCEPT The primary treatment of RICDs is single-donor fresh frozen plasma (FFP) that contains all coagulation factors. Disadvantages of FFP treatment include the risk of the patient becoming volume overloaded, especially when repeated infusions are administered to improve and maintain hemostasis; risk of infections; and risk of inhibitor development. PCCs licensed for the treatment of hemophilia B also contain significant levels of vitamin K–dependent factors and may be used for treatment of RICD. Table 70–7 lists the recommended RICD treatment schedules in different clinical scenarios.

Table 70–7

Treatment of Factor Deficiencies

Factor Deficient	Major Surgery	Spontaneous Bleeding
II	1. PCC: 20–30 U/kg 2. FFP: 15–20 mL/kg	1. FFP: 15–20 mL/kg
V	1. FFP: 15–20 mL/kg	1. FFP: 15–20 mL/kg
VII	1. rFVIIa: 15–30 mcg/kg every 4–6 hours	1. rFVIIa: 15–30 mcg/kg every 4–6 hours
X	1. PCC: 20–30 U/kg 2. FFP: 15–20 mL/kg	1. PCC: 20–30 U/kg 2. FFP: 15–20 mL/kg
XI	1. FFP: 15–20 mL/kg	1. FFP: 15–20 mL/kg
XIII	1. Pasteurized plasma concentrate: 10–20 U/kg 2. FFP: 15–20 mL/kg 3. Cryoprecipitate (1 bag per 10 kg)	1. FFP: 3–5 mL/kg

Numbers indicate lines of therapy. FFP, fresh frozen plasma; PCC, prothrombin complex concentrates.

▶ *Pharmacologic Therapy*

Less severe hemorrhages may be treated successfully either with antifibrinolytic amino acids alone or in combination with factor replacement therapy. Tranexamic acid and aminocaproic acid may be administered IV or orally (for doses, see vWD, Pharmacologic Therapy mentioned earlier).

PLATELET DISORDERS

Platelets, in combination with other factors such as blood vessel wall and coagulation factors, play a key role in hemostasis. Normal platelet count is 150 to 450 × 10^3/mm^3 (150–450 × 10^9/L). Thrombopoietin, a hormone synthesized in the liver, regulates platelet production. Several congenital and iatrogenic disorders may result in low platelet count; among them, drug-induced thrombocytopenia, infection-induced thrombocytopenia, disseminated intravascular coagulation (DIC), congenital thrombocytopenia, and idiopathic immune thrombocytopenia (ITP). Two types of thrombocytopenic disorders and their treatments are discussed below.

IMMUNE THROMBOCYTOPENIA

Epidemiology and Etiology

ITP is one of the most common causes of acquired thrombocytopenia. The estimated incidence is 1.9 to 6.4 cases per 100,000 persons in children and 3.3 cases per 100,000 in adults.[41] ITP is an acquired disorder caused by immune-mediated destruction of platelets, resulting in shortened platelet life span.

Childhood-onset and adult-onset ITP present very differently. Adult-onset ITP is generally chronic (longer than 6 months) and affects women two to three times more often than men. By contrast, childhood-onset ITP is acute in onset and usually follows an infectious illness, and both sexes are equally affected. Childhood ITP typically resolves on its own within 4 to 6 weeks without major sequelae. ITP occurs in about 1 of every 1000 pregnancies. In pregnant women with preexisting ITP, both maternal and fetal complications may occur, requiring separate management.

Pathophysiology

ITP can be primary or secondary. Primary ITP can occur due to the formation of autoimmune IgG antibodies directed at patient's platelets' surface glycoproteins, GPIIb/IIIa and GP1b/IX/V; abnormal production of megakaryocytes in the bone marrow; or T-cell defects that lead to destruction of platelets. The majority of adult ITP cases are due to primary causes.

Secondary ITP occurs due to an underlying disorder, such as autoimmune (eg, rheumatoid arthritis, systemic lupus erythematosus [SLE]) or infectious diseases (eg, human immunodeficiency virus [HIV], hepatitis C virus [HCV],

Patient Care Process: Hemophilia A/B, vWD, and RICD

Collect Information:

- Obtain complete medical and medication history.
- Evaluate CBC, vital signs, and coagulation studies. If a bleeding disorder is diagnosed, evaluate specific coagulation assays to determine the etiology of the bleeding disorder.

Assess the Information:

- Identify appropriate goals of therapy based on patient's presentation.
- Based on patient data, determine if patient has contraindications to potential therapeutic options.

Develop a Care Plan:

- Institute nonpharmacological therapy to minimize minor bleeding.
- Depending on the diagnosis and disease severity, select appropriate pharmacotherapy with desmopressin, antifibrinolytic medications, and/or disease-specific factor replacement therapies.
- Recommend prophylactic therapies before major and minor surgical procedures based on bleeding risk assessment.
- Evaluate pain and treat if necessary, selecting medications that do not increase the risk of bleeding.

Implement the Care Plan:

- Address any patient's concerns about coagulation disorder and its management.
- Educate the patient and/or patient's caregivers about coagulation disorder, efficacy/safety of replacement therapies, and medication/activities to avoid.
- Discuss importance of medication adherence and follow-up monitoring to achieve optimal outcomes. Determine whether there are any barriers to adherence.
- Review vaccination history and recommend appropriate vaccinations.
- Determine the patient's ability to afford prescribed pharmacotherapy.

Follow-up: Monitor and Evaluate:

- If clotting factor replacement is utilized, continuously evaluate its efficacy and test for inhibitors development if loss of efficacy is observed.
- Monitor number/severity of bleeding episodes, joint count/joint destruction, and pain associated with some coagulation/bleeding disorders.
- Determine whether the patient is experiencing any adverse reactions or drug interactions.

or *Helicobacter pylori* infections).[42] Platelets survival time is significantly shorter in patients with ITP (from minutes to 2–3 days compared with normal 7–10 days). Sequestration in spleen, liver, and bone marrow is partially responsible for decreased platelet survival.

Treatment

▶ *Desired Outcomes*

The goal of ITP treatment is to maintain sufficient hemostasis, keeping in mind patient's preferences and ensuring adequate quality of life.[43]

▶ *General Approach to Treatment*

KEY CONCEPT The treatment of ITP is determined by platelet count and intensity of bleeding. (Table 70–8). In some cases, especially in children where up to 80% of cases resolve spontaneously regardless of pharmacologic interventions, observation might be sufficient. In patients, who are corticosteroid-dependent and whose thrombocytopenia does not resolve within 3 months, the selection of a second-line treatment should be personalized with consideration of availability of medical and social infrastructure,

Patient Encounter 1, Part 3: vWD: Creating a Care Plan

Based on the information presented, create a care plan for this patient.

What additional pharmacologic interventions can be considered for this patient if first line fails?

Clinical Presentation and Diagnosis of ITP

General

The typical patient is well with the exception of bleeding.

Symptoms

- Petechiae
- **Purpura**, **wet purpura**
- **Ecchymosis**
- Cutaneous bleeding
- Mucosal site bleeding
- Epistaxis
- Gingival bleeding
- Hematuria
- Menorrhagia
- Intracranial hemorrhage (rare)

Diagnostic Criteria

- Platelet count less than $100 \times 10^3/\text{mm}^3$ ($100 \times 10^9/\text{L}$)
- Otherwise normal complete blood count with differential
- Normal reticulocyte count
- Normal peripheral blood smear (no hemolysis or blast cells)
- History and physical examination ruling out other possible causes of thrombocytopenia[30]

Other Laboratory Testing

Laboratory testing to evaluate other causes that can lead to secondary ITP, such as HCV, HIV, and *Helicobacter pylori*.

Table 70–8

Guidelines for the Management of Adult ITP

Platelets ≥ $30 \times 10^3/\text{mm}^3$ (30×10^9/L), no bleeding or minor mucocutaneous bleeding	Observation
Platelets < $30 \times 10^3/\text{mm}^3$ (30×10^9/L), no bleeding or minor mucocutaneous bleeding	Prednisone (0.5–2 mg/kg/day IV/PO) or dexamethasone (40 mg IV/PO × 4 days) If corticosteroids contraindicated: Anti-D immune globulin (50–75 mcg/kg/day IV × one dose) IVIg (1 g/kg/day IV × one dose, repeat as necessary)
Platelets < $30 \times 10^3/\text{mm}^3$ (30×10^9/L), bleeding symptoms after an adequate trial of first-line agents	Splenectomy Rituximab (375 mg/m² IV once weekly for four doses) Eltrombopag (25–75 mg PO daily) Romiplostim (1–10 mcg/kg subcutaneously once weekly) Immunosuppressants
Hemorrhage	Platelet transfusion IVIg (1 g/kg/day IV × one dose, repeat as necessary) Methylprednisolone (1 g/day IV for 3 days)

disease duration, severity and frequency of bleedings, and patient's values and preferences.[43]

▶ *Nonpharmacologic Therapy*

Splenectomy In adults, splenectomy is generally considered after 3 to 6 months if the patient continues to require 10 to 20 mg/day of prednisone to maintain the platelet count greater than $30 \times 10^3/\text{mm}^3$ (30×10^9/L). Splenectomy may also be considered for urgent treatment of neurologic symptoms or for managing a relapse despite an adequate trial of corticosteroids, IV immunoglobulin (IVIg), or anti-Rh(D). Even though individual patient response cannot be predicted, the majority (66%–88%) of refractory adult patients have a favorable response to splenectomy within several days; however, some patients will have no response or will experience a relapse sometime after splenectomy.

In children, splenectomy is usually reserved due to the self-limited nature of ITP and risk of infectious complications following splenectomy. However, splenectomy is recommended in children with an ITP duration greater than 1 year with significant bleeding symptoms and unresponsive or intolerant of pharmacological therapies. Between 70% and 80% of children attain complete remission following splenectomy. Laparoscopic splenectomy is preferable to open splenectomy because it speeds the recovery and shortens the duration of hospitalization. The major complication of splenectomy is bacterial sepsis, occurring at incidence rates of approximately 1%. Immunizations with *Haemophilus influenzae* type b, pneumococcal, and meningococcal vaccines are indicated in all patients 2 weeks prior to splenectomy.[44] Additional complications include thrombosis and pulmonary hypertension.

Patient Encounter 2, Part 1: ITP

A 23-year-old female with history of a short respiratory illness presented with gingival bleeding, requiring swishing with icy water and nonitchy ecchymotic rash on her left forearm. Patient denied any history of hematemesis, epistaxis, hemoptysis, hematuria, melena, or trauma.

What patient information is suggestive of ITP?

What additional information for developing a treatment plan do you need to collect?

Platelets Transfusions Platelets transfusions are indicated if a patient has severe life-threatening bleeding, such as intracranial hemorrhage. In such situations, platelets transfusions are administered along with IVIg and glucocorticoids (discussed later).[45]

Additional Considerations Patients with severe thrombocytopenia may need to restrict their participation in extreme contact sports. Medications that inhibit platelet aggregation (eg, NSAIDs) should be avoided.

▶ *Pharmacologic Therapy*

The general approach to management of ITP in adults is summarized in Table 70–8.

Glucocorticoids Glucocorticoids may decrease splenic sequestration of antibody-coated platelets, diminish antibody generation, and increase platelet output by the bone marrow. In adults, the response rate to oral prednisone (1 mg/kg/day) is 50% to 75%, with patients usually responding within the first 1 to 2 weeks. The duration of therapy depends on the platelet count response. Guidelines advocate for a longer course of prednisone therapy (21 days), followed by a taper. High-dose dexamethasone (40 mg orally or intravenously daily) administered for 4 days in 14- to 28-day cycles has also been used successfully and may be superior to prednisone especially in cases when rapid response is desired.[46] In children, oral or parenteral corticosteroids (prednisone, dexamethasone, methylprednisolone) can be used; various dosage regimens have been studied with no drug or dosage regimen showing superiority.[43]

IV Immunoglobulin (IVIg) IVIg impairs the clearance of platelets coated with IgG by activating inhibitory receptor FcRγIIb. Roughly 80% of adults will respond to IVIg, but remission usually is not sustained. In adults, IVIg infusion (1 g/kg/day given as a single dose, repeated if necessary) is reserved for situations, in which rapid increase in platelet count is necessary, such as life-threatening bleeding and very low platelet count, or for patients who have contraindications to glucocorticoids. If treatment is indicated in children, a single dose of IVIg (0.8–1 g/kg) is usually effective. The use of IVIg is complicated by serious adverse effects, shortages and high cost.

Anti-Rh(D) Anti-Rh(D) can be used only in Rh(D)-positive patients who have not had splenectomy. It is as efficacious as IVIg and is generally less expensive. Anti-Rh(D) is a desirable

Patient Encounter 2, Part 2: ITP

PE/ROS:

Wt 60 kg; vital signs within normal limits.

Skin: round, macular, bluish in color, ecchymotic rash, 4 cm in diameter, located on left forearm. Oral cavity: bleeding gingival surfaces noted.

The rest of the examination is unremarkable.

Medications: None

Allergies: NKA

Labs:

WBC: $5.8 \times 10^3/\text{mm}^3$ (5.8×10^9/L) (normal $3.5–10.5 \times 10^3/\text{mm}^3$ [$3.5–10.5 \times 10^9$/L])

Platelet count: $9 \times 10^3/\text{mm}^3$ (9×10^9/L); manual count: $15 \times 10^3/\text{mm}^3$ (15×10^9/L) (normal $140–440 \times 10^3/\text{mm}^3$ [$140–440 \times 10^9$/L])

Platelet count 2 months prior: $240 \times 10^3/\text{mm}^3$ (240×10^9/L)

aPTT: 35 seconds (normal 25–40 seconds)

PT: 11 seconds (normal 10–12 seconds)

Hgb: 12.1 g/dL (121 g/L or 7.5 mmol/L) (normal 12.0–15.5 g/dL or 120–155 g/L or 7.50–9.61 mmol/L)

Hct: 35% (normal 34.9%–44.5%)

Peripheral blood smear:

WBC: few activated lymphocytes and neutrophils with left shift

RBC: normocytic and normochromic

Platelets: giant platelets seen

Disseminated intravascular coagulation ruled out based on laboratory test and blood film

HCV: negative

HIV: negative

Helicobacter pylori **antibody:** negative

Pregnancy: negative

Given this additional information, is this patient's presentation consistent with ITP?

Define treatment goals for this patient.

modality in chronic ITP when the goal is to circumvent long-term exposure to corticosteroids. The initial dose is 50 mcg/kg intravenously, with dose adjustment based on hemoglobin levels. Administration of anti-Rh(D) may increase the platelet count in about 70% to 80% of children with ITP. Response to anti-Rh(D) lasts for about 3 to 5 weeks, and substantial numbers of patients treated repetitively with anti-Rh(D) can postpone or avoid splenectomy. Rare fatal intravascular hemolysis has been reported with the use of anti-Rh(D); close monitoring for 8 hours after drug administration is recommended.

Immunosuppressants Immunosuppressant therapy is generally utilized for patients who are refractory to or intolerant of all other ITP treatments. Rituximab, an anti-CD20 antibody, at a dose of 375 mg/m^2 once weekly for four doses, can induce long-term response in 21% to 27% of patients.[43] Progressive multifocal leukoencephalopathy (PML) has been rarely reported with rituximab use. Rituximab can be considered a second- or third-line therapy in patients who have experienced treatment failure with corticosteroids, IVIg, or splenectomy. Screening for hepatitis B infection is required prior to rituximab initiation.

Azathioprine and cyclophosphamide produce response rates of 20% to 40% in adult patients who are treated for 2 to 6 months. Other medications used in ITP include vincristine, vinblastine, cyclosporine, danazol, and mycophenolate mofetil; due to major toxicities and lack of adequate evidence-based recommendations, their use is reserved for refractory ITP.

All immunizations should be up to date prior initiating immunosuppressant therapy because these medications increase susceptibility to infections.

Thrombopoietic Growth Factors Thrombopoietic growth factors stimulate the bone marrow to produce enough platelets to overcome the body's premature destruction of platelets. Romiplostim and eltrombopag are thrombopoietin (TPO) mimetics that have been approved for the treatment of thrombocytopenia in adult and pediatric patients with chronic ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding, and who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Romiplostim is a TPO peptide mimetic that binds to and activates the human TPO receptor. Romiplostim works by stimulating megakaryopoiesis, which results in enhanced platelet production. The initial dose of romiplostim is 1 mcg/kg subcutaneously once weekly based on the actual body weight. The dose can be adjusted weekly by increments of 1 mcg/kg until the patient achieves a platelet count greater than or equal to $50 \times 10^3/\text{mm}^3$ (50×10^9/L). The maximum dose is 10 mcg/kg/week.[47] Studies have demonstrated efficacy of romiplostim over treatment periods of 5 years.[48]

Eltrombopag is a nonpeptide TPO receptor agonist with a low immunogenic potential that stimulates megakaryocyte proliferation and differentiation. Eltrombopag has been shown to increase platelet counts and decrease bleeding episodes in patients with ITP.[49] The usual starting dose is 50 mg by mouth once daily; it can be increased to a maximum dose of 75 mg daily in order to achieve and maintain a platelet count greater than or equal to $50 \times 10^3/\text{mm}^3$ (50×10^9/L). The starting dose should be reduced by 50% in patients with mild-to-severe hepatic impairment and in individuals of Asian descent. Eltrombopag can be taken regardless of a meal if the meal contains 50 mg or less of calcium. The drug should be administered at least 2 hours before or 4 hours after antacids, dairy, and other foods or supplements containing polyvalent ions eg, iron, zinc, magnesium, selenium, and calcium ($>$ 50 mg).[50] Studies have demonstrated its efficacy lasting over 3 years.[49,51]

Either TPO mimetic should be discontinued if platelet counts do not increase after 4 weeks at a maximum dose.

Although these agents are usually well tolerated, a number of rare but serious risks have been identified, including worsened thrombocytopenia, thrombotic/thromboembolic complications ie, portal vein thrombosis, and progression to acute myelogenous leukemia. In addition, eltrombopag's labeling carries a "boxed warning" regarding the increased risk of hepatotoxicity.

Patient Encounter 2, Part 3: ITP: Creating a Care Plan

Based on the information presented, create a care plan for this patient. If pharmacologic therapy is indicated, list first-line and alternative therapies.

Monitoring of hepatic enzymes every 2 weeks initially, followed by every 4 weeks thereafter, is recommended.

Another oral agent indicated for chronic ITP in adults who have insufficient response to previous treatment is fostamatinib, a kinase inhibitor whose place in therapy remains to be determined.

Outcome Evaluation

- Monitor platelet counts as indicated clinically.
- In adults, the goal of therapy is to maintain platelet count greater than or equal to 30 × 10^3/mm^3 (30 × 10^9/L).
- Monitor for signs and symptoms of bleeding.

THROMBOTIC MICROANGIOPATHIES

Epidemiology and Etiology

Thrombotic microangiopathies (TMAs) include a diverse variety of disorders with different pathophysiological features. Typical presentation includes small vessel (microangiopathic) hemolytic anemia with thrombocytopenia. Microvascular thrombosis occurs due to defects in the endothelium of small vessels, such as arterioles and capillaries.[52]

Primary TMAs include thrombotic thrombocytopenic purpura (TTP), shiga toxin–mediated hemolytic uremic syndrome (ST-HUS), immune or dose-related drug-induced TMA, complement-mediated TMA, metabolism-mediated TMA, and coagulation-mediated TMA. Classification and causes of primary TMA are summarized in Table 70–9. Here, we will focus on TTP and complement-mediated TMAs.

Thrombotic Thrombocytopenic Purpura

TTP is a severe systemic disorder characterized by thrombi formation within the circulation that results in the platelet consumption and subsequent thrombocytopenia.[41] TTP can occur in all ages and can be hereditary or acquired. Both types of TTP are very rare; the estimated annual incidence of acquired TTP (aTTP) is three cases per million adults.[53]

▸ *Pathophysiology*

Endothelial cells normally synthesize vWF in the form of a high-molecular-weight multimer composed of smaller identical monomers. Each monomer is able to bind platelets, and the number of monomers on the vWF multimer is directly proportional to its platelet-binding capacity. Consequently, particularly adherent ultra-large molecules of vWF (ULvWF) are broken down to smaller size by vWF-cleaving proteases such as ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeats) to avoid undesired clot formation. TTP results from inherited deficiency in the vWF-cleaving protease ADAMTS13 activity or development of autoimmune inhibitors to ADAMTS13. This, in turn, elevates circulating levels of ULvWF, leading to inappropriate platelet agglutination. Thrombocytopenia develops because the rate of aggregated platelet consumption is faster than production of megakaryocytes in the bone marrow. Microangiopathic hemolytic anemia generally follows as a consequence of red blood cells damage by platelet clumps that occlude the microcirculation. Occlusive ischemia of the brain or gastrointestinal tract is common. TTP is distinguished from other TMAs for rarely causing renal abnormalities.

▸ *Desired Outcomes*

The main goal of TTP treatment is to prevent end-organ damage.

▸ *Nonpharmacologic Therapy*

KEY CONCEPT The standard treatment for hereditary TTP is plasma infusion containing ADAMTS13 protease. For acquired TTP, urgent plasma exchange (PEX) is needed to remove ADAMTS13 inhibitor. If PEX is unavailable, treatment with plasma infusion and glucocorticoids is indicated until PEX is available.[54]

Plasma Exchange The procedure involves the removal of the patient's plasma and its substitution with donor plasma. In this manner, circulating antibody inhibitor to ADAMTS13 is removed and enzyme is replenished. PEX involves placement of two IV lines (cannulae) into two separate veins. Blood removed through one cannula is centrifuged to separate the blood cells from the plasma. The blood cells are mixed subsequently with donor plasma and returned to the patient via the second cannula. The goal is to exchange 1 to 1.5 plasma volumes (40–60 mL/kg). Generally the procedure is repeated daily until neurologic symptoms resolve and normal lactate dehydrogenase (LDH) and platelet counts are maintained for several days. Once complete remission is achieved, PEX frequency can be reduced to every other day for additional few days, with subsequent PEX discontinuation and

Table 70–9

Thrombotic Microangiopathy Syndromes

Name	Notes
• TTP (ADAMTS13 deficiency)	Hereditary presents in children, acquired usually presents in adults.
• Shiga toxin–mediated hemolytic uremic syndrome (ST-HUS)	Triggered by *Shigella dysenteriae* or *Escherichia coli* Shiga-toxin producing infection.
• Drug-induced	Can be mediated by immune reaction (eg quinine) or related to the increased dose (eg bevacizumab, sunitinib).
• Complement-mediated	Mutations in complement factor H (CFH), CD46, complement factors I (CFI), B (CBF).
• Coagulation-mediated	Genetic abnormalities in proteins mediating coagulation (eg thrombomodulin gene [THBD], diacylglycerol kinase epsilon [DGKE]).

Patient Care Process ITP

Collect Information:

- Conduct physical examination evaluating sites of bleeding. Obtain complete medical and medication history.
- Evaluate CBC, peripheral blood smear, complete metabolic panel, and Rh(D) status; order tests to rule out other diseases commonly associated with thrombocytopenia.

Assess the Information:

- Determine whether ITP is likely due to primary or secondary causes (this may change treatment focus).
- Evaluate platelet count, occupational risks of bleeding, and actual bleeding severity to determine the initial treatment approach.
- Identify relevant goals of therapy based on patient's platelet counts and the presence or absence of bleeding.
- Based on patient data, determine if patient has contraindications to potential ITP therapeutic options.

Develop a Care Plan:

- Choose medications and doses that are optimal for the patient.
- First-line treatment for patients meeting criteria for pharmacotherapy is corticosteroids for up to 21 days. Anti-Rh(D) or IVIg can be considered if corticosteroids are contraindicated or a rapid rise in platelet count is necessary. Alternatives to first-line agents include immunosuppressants and TPO mimetics, which are reserved for patients failing to respond after adequate trial of first-line agents. Surgical splenectomy is reserved for refractory ITP.

Implement the Care Plan:

- Address any patient concerns about ITP and its management.
- Educate the patient about new medications in their regimen, discuss drug administration and side effects, especially focusing on serious effects and their management.
- Discuss importance of medication adherence and follow-up monitoring to achieve optimal outcomes. Determine whether there are any barriers to adherence. Educate patient's caregivers, if applicable.
- Review vaccination history and recommend appropriate vaccinations.
- Determine patient's ability to afford prescribed pharmacotherapy.

Follow-up: Monitor and Evaluate:

- Adhere to prescriber's recommendations on appropriate frequency of follow-up (depends on severity at presentation and pharmacotherapy chosen).
- Review platelet response and bleeding to assess changes in clinical status and evaluate pharmacotherapy for efficacy and safety. In adults, once response is achieved, monitor regularly to ensure platelet counts stay above $30 \times 10^3/\text{mm}^3$ ($30 \times 10^9/\text{L}$).
- Determine whether the patient is experiencing any adverse reactions or drug interactions.

close patient follow-up. When PEX is started immediately upon diagnosis, remission and survival rates at 6 months are approximately 80%. Although generally considered safe, complications from catheter insertion or catheter infection may occur and include hemorrhage, pneumothorax, sepsis, and thrombosis. Allergic reactions to plasma can cause severe hypotension and hypoxia.[55]

Splenectomy Splenectomy is reserved for patients with frequently relapsing disease who are refractory to PEX or immunosuppressive therapy.

▶ *Pharmacologic Therapy*

Glucocorticoids Glucocorticoids can be used for their immunosuppressive effect in combination with PEX; however, as

Clinical Presentation and Diagnosis of Thrombotic Microangiopathies[a]

Onset and typical features will vary depending on precipitating cause.

1. Thrombocytopenia
    - Thrombocytopenic purpura
    - Bleeding
2. Fever (sometimes)
3. Microangiopathic hemolytic anemia
4. Neurologic symptoms (sometimes)
    - Headache, confusion, difficulty speaking, transient paralysis, numbness
5. Renal abnormalities (rare with TTP, common with other TMA types)
    - Proteinuria, hematuria, mild or severe renal insufficiency

Laboratory Testing

- Decreased ADAMTS 13 activity (< 10% or normal)—TTP
- Decreased hemoglobin, hematocrit, and platelets
- Peripheral blood smear showing schistocytes
- Decreased serum haptoglobin
- Elevated LDH
- Elevated indirect bilirubin level
- Elevated reticulocyte count
- Normal PT and aPTT
- Elevated urine protein, red blood cells, and/or serum creatinine, decreased urine output

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[a] Thrombotic microangiopathies diagnosis can be based on the presence of thrombocytopenia and microangiopathic hemolytic anemia in the absence of other possible causes.

Patient Encounter 3, Part 1: TTP

A 21-year-old African female was seen in the emergency room for severe headache, confusion, chills, nausea and vomiting, and purplish pinpoint nonitchy rash and petechiae on the abdomen. Patient has no history of gingival bleeding, hematemesis, melena, hematochezia, or autoimmune diseases including SLE and is otherwise healthy.

What patient information is suggestive of TTP?

What additional information for developing a treatment plan do you need to collect?

Patient Encounter 3, Part 2: TTP

PE/ROS:

Young WNWD female in no distress

Wt 70 kg, T 101.3°F (38.5°C), BP 128/75 mm Hg, HR 80 beats/min, RR 18 breaths/min

Neuro: patient appears confused but oriented × 3

Skin: disseminated purplish pinpoint nonitchy rash and bruises on the abdomen

The rest of the examination is unremarkable

No familial history of hematologic disorders

Medications: none

Allergies: NKA

Labs:

- Platelet count: 8×10^3/mm^3 (8×10^9/L) (normal 140–440 × 10^3/mm^3 [140–440 × 10^9/L])
- aPTT: 35 seconds (normal 25–40 seconds)
- PT: 11 seconds (normal 10–12 seconds)
- Haptoglobin: 10 mg/dL (100 mg/L) (normal 30–200 mg/dL or 300–2000 mg/L)
- LDH: 1057 U/L (17.62 μkat/L) (normal 100–250 U/L, or 1.67–4.17 μkat/L)
- Hgb: 7.1 g/dL (71 g/L; 4.34 mmol/L) (normal 12.0–15.5 g/dL or 120–155 g/L or 7.50–9.61 mmol/L)
- Hct: 22% (normal 34.9%–44.5%)
- Blood peripheral smear: numerous schistocytes (10–15 per high power field)
- SCr: 0.8 mg/dL (71 μmol/L) (normal 0.6–1.2 mg/dL [53–106 μmol/L])
- ADAMTS13 activity: less than 5% (normal ≥ 60%)
- Anti-ADAMTS13 IgG: 3.2 U/mL (normal ≤ 0.4 U/mL)
- Imaging studies: CT scan head–unremarkable
- Pregnancy test: negative

Given this additional information, is this patient's presentation consistent with TTP?

What is the likely etiology of this patient's TTP?

Define treatment goals for this patient.

Patient Encounter 3, Part 3: TTP: Creating a Care Plan

Based on the information presented, create a care plan for this patient.

monotherapy, they are not efficacious in TTP. The most commonly used agents are methylprednisolone 250 mg/day IV or prednisone 1 mg/kg/day orally for the duration of PEX therapy and for additional 1 to 2 weeks to maintain normalized platelet counts.

Immunosuppressants TTP that fails to respond adequately to PEX can be treated with immunosuppressive agents. Cytotoxic immunosuppressive therapies with the most potential benefit in refractory TTP include cyclosporine and rituximab. Other agents that had been used include bortezomib, vincristine, cyclophosphamide, azathioprine, and mycophenolate mofetil.[54]

Targeted Therapy Caplacizumab is a vWF-directed antibody fragment, recently approved for the treatment of aTTP. Caplacizumab targets the A1-domain of vWF, inhibiting the interaction between vWF and platelets thereby reducing vWF-mediated platelet adhesion and platelet consumption. In clinical trials, bleedings occurred in more than half of the patients treated with the drug. Caplacizumab should be discontinued 7 days prior to an elective procedure including dental work. The drug is administered parenterally in combination with immunosuppressive therapy and plasma exchange. If patient experiences more than two recurrences of aTTP while on treatment, caplacizumab must be discontinued.[56]

Complement-Mediated TMA

This type of TMA results from genetic mutations of various factors responsible for alternative pathway of complement activation. Generally thought to be triggered by an infectious episode in predisposed patients, uncontrolled complement activation leads to the formation of membrane attack complexes that cause endothelial damage, TMA, and renal failure.[57]

▶ *Nonpharmacologic Therapy*

Supportive therapy may include blood or platelet transfusions, maintenance of fluid balance to support adequate end-organ perfusion, and dialysis therapy. Liver–kidney transplantation provides cure for this type of TMA but is associated with significant complications.

▶ *Pharmacologic Therapy*

Eculizumab is a humanized monoclonal antibody that binds to complement component C5, thus preventing formation of C5b and subsequent formation of C5b-9 (membrane attack complex).[58] Complement genetic studies may be helpful in determining whether a patient is a good candidate to receive eculizumab (eg, patients with C5 mutations may not respond as well). For best results, treatment should be started within 48 hours of presentation; the usual adult dose is 900 mg, intravenously once weekly for four doses, followed by 1200 mg on week 5, and 1200 mg every 2 weeks thereafter. All immunizations should be up to date in patients considered for this therapy, as it can increase the risk of serious infections, including meningococcal infection. Alternatively, PEX or plasma infusion can be used if eculizumab therapy is not feasible.

Patient Care Process for Thrombotic Microangiopathy

Collect Information:

- Obtain complete medical and medication history.
- Evaluate CBC, vital signs, neurologic symptoms, complete metabolic panel, and urinalysis for the presence of thrombocytopenia, fever, anemia, and renal abnormalities. Evaluate neurologic symptoms and peripheral blood smear.

Assess the Information:

- Identify the primary cause of TMA to evaluate targeted treatment selection.
- Identify appropriate goals of therapy based on patient's presentation.
- Based on patient data, determine if patient has contraindications to potential therapeutic options.

Develop a Care Plan:

- Choose medication and doses (if applicable) that are appropriate and optimal for the patient.
- If patient meets clinical criteria for the diagnosis of acquired TTP, start daily PEX as soon as possible. Glucocorticoids and other adjunctive therapies may be considered.
- Institute supportive therapy based on patient's presentation and needs.

Implement the Care Plan:

- Educate the patient about new medications in their regimen, discuss drug administration and side effects, especially focusing on serious effects and their management.
- Address any patient concerns about specific TMA and its management.
- Discuss importance of medication adherence and follow-up monitoring to achieve optimal outcomes. Determine whether there are any barriers to adherence. Educate patient's caregivers, if applicable.
- Review vaccination history and recommend appropriate vaccinations.
- Determine patient's ability to afford prescribed pharmacotherapy.

Follow-up: Monitor and Evaluate:

- Adhere to prescriber's recommendations on appropriate frequency of follow-up (depends on severity at presentation and pharmacotherapy chosen). When platelet counts stay above 150 × 10^3/mm^3 (150 × 10^9/L) for 2 days, PEX may be discontinued; glucocorticoids may be continued for additional 1 to 2 weeks.
- Determine whether the patient is experiencing any adverse reactions or drug interactions.
- Follow patients indefinitely with periodic CBC/LDH measurements to screen for possible relapse.

Abbreviations Introduced in This Chapter

ADAMTS13	A disintegrin and metalloprotease with thrombospondin type 1 repeats (vWF-cleaving metalloprotease)
BU	Bethesda units
DDAVP	1-Desamino-8-D-arginine vasopressin (desmopressin acetate)
DIC	Disseminated intravascular coagulation
FFP	Fresh frozen plasma
HCV	Hepatitis C virus
ICH	Intracranial hemorrhage
ITP	Immune thrombocytopenia
IVIg	IV immunoglobulin
PCC	Prothrombin complex concentrate
PEX	Plasma exchange
rFVIIa	Recombinant factor VIIa
rFVIII	Recombinant factor VIII
rFIX	Recombinant factor IX
RICD	Recessively inherited coagulation disorder
TTP	Thrombotic thrombocytopenic purpura
ULvWF	Ultra-large molecules of vWF
vWD	von Willebrand disease
vWF	von Willebrand factor

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Sickle Cell Disease

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the underlying causes of sickle cell disease (SCD) and their relationship to patient signs and symptoms.
2. Identify the typical characteristics of SCD as well as symptoms that indicate complicated disease.
3. Identify the desired therapeutic outcomes for patients with SCD.
4. Recommend appropriate pharmacotherapy and nonpharmacotherapy interventions for patients with SCD.
5. Recognize when chronic maintenance therapy is indicated for a patient with SCD.
6. Describe the components of a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for SCD.
7. Educate patients about the disease state, appropriate therapy, and drug therapy required for effective treatment and prevention of complications.

INTRODUCTION

KEY CONCEPT "Sickle cell syndrome" refers to a collection of autosomal recessive genetic disorders that are characterized by the presence of at least one sickle hemoglobin (HbS) gene.[1,2]

Sickle cell disease (SCD) is a chronic illness that is associated with frequent crisis episodes. Acute complications are unpredictable and potentially fatal. Common symptoms include excruciating musculoskeletal pain, life-threatening pneumonia-like illness, cerebrovascular accidents, and splenic and renal dysfunction.[2] As the disease progresses, patients may develop organ damage from the combination of hemolysis and infarction. Because of the complexity and severity of SCD, it is imperative that patients have access to comprehensive care with providers who have a good understanding of the countless clinical presentations and the management options of this disorder.

EPIDEMIOLOGY AND ETIOLOGY

Sickle cell trait (SCT) is the heterozygous form (HbAS) of SCD in which a person inherits one normal adult hemoglobin (*HbA*) gene and one *HbS* gene. These individuals are carriers of the SCT and usually asymptomatic.[2] About 1 in 13 African American babies is born with SCT.[3] Symptomatic disease is seen in homozygous and compound heterozygous genotypes of SCD. Sickle cell anemia (SCA) is the homozygous (HbSS) state of SCD.[2] It is the most common and severe form of SCD. SCD affects both males and females equally because it is not a sex-linked disease.

KEY CONCEPT Around 100,000 Americans have SCD and it occurs in approximately 1 out of every 365 African American births.[3] HbSS (~75%) is the most common genotype, followed by HbSC (~18%), HbSβ^{+}-thalassemia (~5%), and HbSβ^{0}-thalassemia (~2%). Other variants account for fewer than 1% of patients.[2,4] For every infant diagnosed with SCD, 50 are identified as carriers.[4]

Having the *HbS* gene protects heterozygous carriers from succumbing to *Plasmodium falciparum* (malaria) infection.[1] The microorganism cannot parasitize abnormal red blood cells (RBCs) as easily as normal RBCs. Consequently, persons with heterozygous sickle gene (*SCT*) have a selective advantage in tropical regions where malaria is endemic.

The highest incidence of SCD is seen in those with African heritage, but SCD also affects persons of Indian, Saudi Arabian, Mediterranean, South and Central American, and Caribbean ancestry.[4]

Normal HbA is composed of two α-chains and two β-chains (α2β2).[1] A single substitution of the amino acid valine for glutamic acid at position 6 of the β-polypeptide chain is responsible for the production of a defective form of hemoglobin called HbS.[1] Different genetic mutations encode for other hemoglobin variants such as hemoglobin C (HbC).[1] The α-chains of HbS, HbA, and HbC are structurally identical. The chemical differences in the β-chain are responsible for RBC sickling and its associated sequelae.

The HbSS state of SCD occurs when individuals inherit the mutant *HbS* gene from both parents. The progeny of two carriers will have a 25% probability of having SCD and a 50% risk of being a carrier. β-Thalassemia can be found in conjunction with HbS. Patients with HbSS and HbSβ^{0}-thalassemia do not have normal β-globulin production and usually have a more severe course than those with HbSC and HbSβ^{+}-thalassemia.

Impaired circulation, destruction of RBCs, and vascular stasis are three known problems that are primarily responsible for the clinical manifestations of SCD (Figure 71–1).

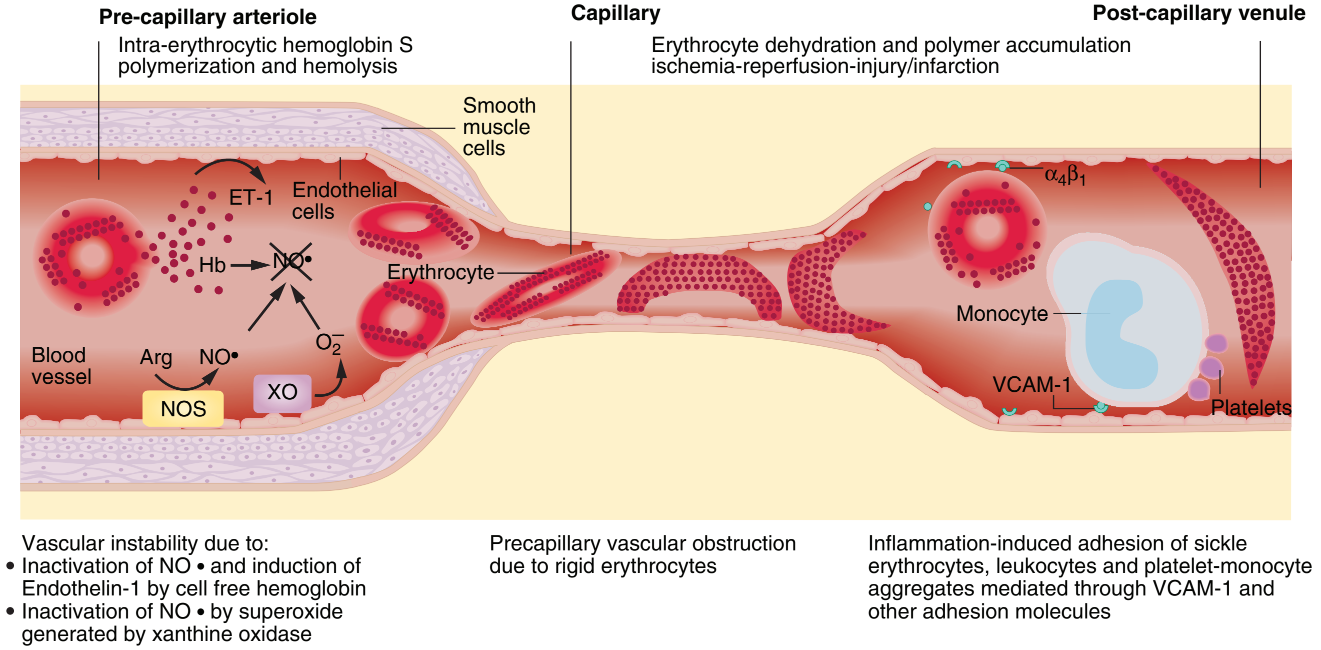
Pre-capillary arteriole
Intra-erythrocytic hemoglobin S polymerization and hemolysis
Capillary
Erythrocyte dehydration and polymer accumulation ischemia-reperfusion-injury/infarction
Post-capillary venule
Smooth muscle cells
ET-1
Endothelial cells
Hb
NO•
Erythrocyte
O_2^-
Blood vessel
Arg
NO•
NOS
XO
$\alpha_4\beta_1$
Monocyte
VCAM-1
Platelets
Vascular instability due to:
• Inactivation of NO • and induction of Endothelin-1 by cell free hemoglobin
• Inactivation of NO • by superoxide generated by xanthine oxidase
Precapillary vascular obstruction due to rigid erythrocytes
Inflammation-induced adhesion of sickle erythrocytes, leukocytes and platelet-monocyte aggregates mediated through VCAM-1 and other adhesion molecules

FIGURE 71–1. Pathophysiology of SCD. (Arg, arginine; ET-1, endothelin-1; Hb, hemoglobin; NO, nitric oxide; NOS, nitrous oxide synthase; VCAM-1, vascular cell adhesion molecule 1; XO, xanthine oxidase.) (From Kato GJ, Gladwin MT. Sickle cell disease. In: Hall JB, Schmidt GA, Kress JP, eds. Principles of Critical Care, 4th ed. New York, NY: McGraw-Hill; 2014. **Figure 96–2**.)

PATHOPHYSIOLOGY

KEY CONCEPT SCD involves multiple organ systems, and its clinical manifestations vary greatly between and among genotypes.

Sickle Hemoglobin Polymerization

The primary event in the molecular pathogenesis of SCD involves polymerization of deoxygenated HbS. HbS carries oxygen normally, and when oxygenated, the solubility of HbS and HbA are the same. Once the oxygen is unloaded to the tissues, HbS solubility decreases. This promotes hydrophobic interactions between the hemoglobin molecules and polymerization, which leads to the distortion of the RBC into the characteristic crescent or sickle shape.[1]

Viscosity of Erythrocytes and Sickle Cell Adhesion

When HbS becomes reoxygenated, the polymers within the RBCs disappear, and the cells eventually return to normal shape. Vasoocclussion is caused by a combination of factors. Repeated assaults on RBCs from sickling and unsickling can lead to cell membrane damage, loss of membrane flexibility, and rearrangement of surface phospholipids. The life span of sickled RBCs is markedly shorter (10–20 days) than that of normal RBCs (100–120 days). As intracellular membrane viscosity of HbS-containing RBCs increases, blood viscosity increases, which further contributes to vasoocclusion.[5] There is also increasing evidence that suggest sickle cells adhere to vascular endothelium.[1,5] The combined effects of decreased RBC deformability, slow transit through microcirculation, and adhesion to vascular endothelium contribute to obstruction of small and sometimes large blood vessels. The resulting local tissue hypoxia can accentuate the pathologic process of SCD.

Protective Hemoglobin Types

Fetal hemoglobin (HbF) binds oxygen more tightly than HbA and has a decreased propensity to sickling. HbA2 also possesses this characteristic but to a lesser extent. RBCs that contain HbF sickle less readily than cells without. HbF is composed of two α chains and two γ chains; therefore, it is not affected by point mutations on β chains. Irreversibly sickled cells (ISCs) are found to have low HbF concentrations. In some patients, higher HbF may ameliorate the disease.

Other Pathophysiologic Effects

Other factors may be responsible for the pathogenesis of some of the clinical features of SCD. Sickle cells can obstruct blood flow to the spleen leading to functional asplenia. Impaired splenic function can increase the propensity to infection by encapsulated organisms, particularly *Streptococcus pneumoniae*.[1] Additionally, coagulation abnormalities are not uncommon since almost every component of hemostasis is altered in SCD.

Clinical Presentation and Diagnosis of SCT

General

- Generally asymptomatic

Symptoms

- Females may have frequent urinary tract infections

Signs

- Microscopic hematuria occurs rarely
- Gross hematuria may occur spontaneously or with heavy-intensity exercise

Laboratory Tests

- Normal Hgb values

Clinical Presentation and Diagnosis of SCD

General

- Identified by neonatal screening before 2 months of age in the United States

Symptoms

- Painful vasoocclusive crises are the hallmark of SCD
- Dactylitis (hand–foot syndrome) before age 1 year
- May develop infarction of the spleen, liver, bone marrow, kidney, brain, and lungs
- Gallstones
- **Priapism** in males
- Slow-healing lower extremity ulcers after trauma or infection
- Weakness, fatigue

Signs

- Chronic hemolytic anemia is common
- Enlargement of spleen and heart
- Scleral icterus

Laboratory Tests

- Hgb 7.0 to 10.0 g/dL (70–100 g/L or 4.34–.21 mmol/L)
- Low HgF and increased reticulocytes, platelets, and white blood cells (WBCs)
- Presence of sickled cells on blood smear
- Neonatal screening: hemoglobin electrophoresis, isoelectric focusing, or DNA analysis

TREATMENT

Desired Outcomes

Multidisciplinary, regularly scheduled care is required over the lifetime of the patient with SCD, with the goal of reduction of complications and hospitalizations. Comprehensive care should include medical, educational, and psychosocial aspects as well as genetic and medication counseling.

Therapeutic interventions for SCD are targeted at preventing and/or minimizing the symptoms related to the disease and its complications. The goals of treatment are to reduce or eliminate the patient's symptoms; decrease the frequency of sickle crises, including vasoocclusive pain crises; prevent the development of complications; and maintain or improve the quality of life through decreased hospitalizations and decreased morbidity. Specific therapeutic options may:

- Maintain or increase the hemoglobin level to the patient's baseline
- Increase the HbF concentration
- Decrease the HbS concentration
- Prevent infectious complications
- Prevent or effectively manage pain
- Prevent central nervous system (CNS) damage, including stroke

General Approach to Treatment

Patients should be educated to recognize the signs and symptoms of complications that would require urgent evaluation. Patients and parents of children with SCD should be educated to seek immediate medical care when a fever develops or signs of infection occur. With acute illnesses, prompt evaluation is important, as deterioration may occur rapidly. Fluid status should be monitored to avoid dehydration or overhydration, both of which may worsen complications of SCD. Patients in acute distress should maintain oxygen saturation at 92% (0.92) or at their baseline. Any supplemental oxygen requirements should be evaluated.[4]

Nonpharmacologic Therapy

Patients should avoid smoking and excessive alcohol intake. Patients with SCD should maintain adequate hydration to help decrease blood viscosity and should be educated to avoid extreme temperature changes and dress properly in hot and cold weather. Physical exertion that leads to complications should be avoided.[4] Regular examinations, including ophthalmic, dental, renal, pulmonary, and cardiac function, are required to monitor for organ damage. A treatment overview is shown in Table 71–1.

Pharmacologic Therapy

▶ *Health Maintenance*

Immunizations Children with SCD should receive the required immunizations as recommended by the American Academy of Pediatrics and the Advisory Committee on Immunization Practices, including vaccination for meningococcal disease.[6] Additionally, influenza vaccine should be administered yearly to SCD patients 6 months of age and older, including adult patients. All adult patients with SCD should also receive the vaccine for meningococcal disease as well as a one-time dose of *Haemophilus influenzae* type b vaccine. The quadrivalent conjugate meningococcal vaccine (MenACWY) should be administered in two doses at least 2 months apart and should be revaccinated every 5 years.[7] In addition, adults should be vaccinated with the serogroup B meningococcal vaccine with either a two-dose series of MenB-4C at least 1 month apart or a three-dose series of MenB-FHbp at 0, 1 to 2, and 6 months.[7]

Because patients with SCD have impaired splenic function, they are less adequately protected against encapsulated organisms such as *S. pneumoniae*, *H. influenzae*, and *Salmonella*. **KEY CONCEPT** The use of pneumococcal vaccine in combination with penicillin prophylaxis in SCD patients has dramatically decreased the rates of morbidity and mortality; however, there are still groups of SCD children who continue to have high rates of invasive pneumococcal infections.[8,9] Infection is the leading cause of death in children with SCD younger than 3 years of age.[9] Two pneumococcal vaccines are available. The 13-valent pneumococcal conjugate vaccine (PCV 13: Prevnar) is routinely administered to infants and children and provides good protection against the 13 most common isolates seen in this age range. Administer the first dose of PCV 13 between 6 weeks and 6 months of age, followed by two additional doses at 2-month intervals and a fourth dose at 12 to 15 months of age. The 23-valent polysaccharide vaccine (PPSV 23: Pneumovax 23) is indicated for children older than 2 years and adults. Because PPSV 23 is a polysaccharide vaccine, children younger than 2 years do not respond well. 23-Valent pneumococcal polysaccharide vaccine (PPV 23) contains the 23 most common isolates of *S. pneumoniae* seen in older children and adults. Because of the different serotypes seen in the two vaccines, it is recommended that children with SCD receive both vaccines, with a dose of PPSV 23 administered after the child turns 2 years of age. The dose of PPSV 23 should be separated from the last dose of PCV 13 by at least 2 months. An additional dose of PPSV 23

Table 71–1

Management of SCD

Options and Comments	
Health Maintenance	
Infection prophylaxis	• Pneumococcal vaccines (PCV 13 and PPV 23) • Penicillin prophylaxis for children younger than 5 years of age • Annual influenza vaccine
Induction of fetal hemoglobin	• Hydroxyurea is the primary agent • Other agents are butyrates (arginine butyrate and sodium phenylbutyrate), decitabine, clotrimazole, and erythropoietin. Most not FDA approved • Combination HbF inducers have been proposed
Chronic transfusion therapy	• Primary indication: stroke prevention in pediatric patients • May also reduce pain crisis and acute chest syndrome • Goal: maintain HbS < 30% (0.30)
Emerging Therapies	
Transplantation	• May potentially cure the disease • Most experience is with HLA-matched donors; umbilical cord blood transplantation is being evaluated
L-Glutamine	• Decreases complications • FDA approved 2017
Voxelotor	• Increases hemoglobin • FDA approved 2019
Crizanlizumab	• Decreases vaso-occlusion • FDA approved 2019
Crises and Complications	
Fever and infection	• Broad-spectrum antibiotic: cefotaxime or ceftriaxone (clindamycin for cephalosporin allergy); vancomycin for staphylococcal and resistant pneumococcal organisms • Fluids
Stroke	• Acetaminophen or ibuprofen for fever • Exchange transfusion • Initiate chronic transfusion therapy to prevent recurrent strokes
Acute chest syndrome	• Broad-spectrum antibiotics (include Mycoplasma coverage) • Bronchodilator if wheezing or history of reactive airway disease • Fluids • Pain management • Transfusion
Pain crisis	• Hydration • Analgesics

should be given to children 3 to 5 years of age to ensure antibody response. This second dose should be administered 5 years after the first PPSV 23 dose. All adults with SCD should be vaccinated with both PCV 13 as well as PPSV 23. Adults and children who have not previously received PCV 13 or PPSV 23 should receive one dose of PCV 13 followed by a single dose of PPSV 23 at a minimum of 8 weeks later then an additional dose of PPSV 23 at least 5 years after the previous PPSV 23 dose.[7] If an adult or child with SCD has already received at least one dose of PPSV 23, they should additionally receive one dose of PCV 13 at least 1 year after the dose of PPSV 23.

Penicillin KEY CONCEPT Children with SCD should receive prophylactic penicillin until at least the age of 5 years, even if they have been appropriately immunized against pneumococcal infections. Penicillin V potassium is typically initiated at age 2 months, with a dose of 125 mg orally twice daily until age 3 years, then 250 mg orally twice daily until 5 years of age. Amoxicillin 20 mg/kg/day divided every 12 hours (maximum of 250 mg/dose) can also be used. The intramuscular use of benzathine penicillin 600,000 U every 4 weeks from age 6 months to 6 years is also an option for nonadherent patients. Penicillin-allergic patients may receive erythromycin 10 mg/kg twice daily. Penicillin prophylaxis usually is not continued in children older than 6 years but may be considered in patients with a history of invasive pneumococcal infection or surgical splenectomy.[4,10]

Folic Acid Folic acid supplementation with 1 mg daily is generally recommended in adult SCD patients, women considering pregnancy, and any SCD patient with chronic hemolysis.[4] Because of accelerated erythropoiesis, these patients have an increased need for folic acid. There are conflicting studies in the SCD population, especially among infants and children, but if the child has chronic hemolysis, supplementation is recommended.[11]

Fetal Hemoglobin Inducers HbF induction in patients with SCD, especially those with frequent crises, has been shown to decrease RBC sickling and RBC adhesion. A direct relationship between HbF concentrations and the severity of disease has been demonstrated in studies.[2]

Hydroxyurea Hydroxyurea is a ribonucleotide reductase inhibitor that prevents DNA synthesis and traditionally has been used in chemotherapy regimens. Studies in the 1990s found that hydroxyurea increases HbF levels as well as increasing the number of HbF-containing reticulocytes and intracellular HbF. Other beneficial effects of hydroxyurea include antioxidant properties, reduction of neutrophils and monocytes, increased intracellular water content leading to increased red cell deformability, decreased red cell

Patient Encounter 1

A 4-year-old girl with SCD is currently taking penicillin V potassium 125 mg orally twice daily, acetaminophen as needed for pain, loratadine 5-mg chewable tablet once daily for allergies, and a gummy multivitamin daily. She fully completed all her routine childhood vaccinations, including PCV 13, and is up to date. She was hospitalized at 9 months for dactylitis and also had tympanostomy tubes placed last year.

What are the general prophylaxis recommendations for children with SCD?

What interventions do you want to make today to her medication/immunization regimens?

Design an infection prevention plan for this patient.

adhesion to endothelium, and increased levels of nitric oxide, which is a regulator involved in physiologic disturbances.[12]

KEY CONCEPT Hydroxyurea reduced the frequency of hospitalizations and the incidences of pain, acute chest syndrome (ACS), and blood transfusions by almost 50% in a landmark trial in adult SCD patients with moderate-to-severe disease. Hemoglobin and HbF concentrations increased and hemolysis decreased.[12] A follow-up study demonstrated a 40% reduction in mortality over a 9-year period in patients continuing to receive hydroxyurea.[13] Not all patients responded equally; therefore, hydroxyurea may not be the best option for all patients.

The use of hydroxyurea in children and adolescents with SCD has shown similar results as in adult trials, with no adverse effects on growth and development.[4,14,15] Hydroxyurea is recommended for children with moderate-to-severe SCD and can be used in children as young as 6 months of age.[16]

The most common adverse effect of hydroxyurea is myelosuppression. Long-term adverse effects are unknown, but myelodysplasia, acute leukemia, and chronic opportunistic infections have been reported.[12] Hydroxyurea is teratogenic in high doses in animal studies and this is a concern, which should be addressed with patients. Normal pregnancies with no birth defects have been reported in some women receiving hydroxyurea, but close monitoring and weighing risk versus benefit to the patient are vitally important. Hydroxyurea is excreted in breast milk and should be avoided in lactating mothers.[12] Women of child-bearing years who take hydroxyurea should have a negative pregnancy test prior to starting hydroxyurea and should use reliable birth control during treatment.

Hydroxyurea should be considered in SCD with frequent vasoocclusive crises, repeated history of ACS, or other history of severe vasoocclusive crisis (VOC) complications.[4] The prevention of organ damage or reversal of previous damage has not been shown to occur with chronic use of hydroxyurea.[13] However, hydroxyurea treatment should be considered in all infants 9 months of age and older, as well as children and adolescents with SCD regardless of their clinical severity to reduce complications related to SCD.[17] The goals of therapy with hydroxyurea are to decrease the acute complications of SCD, improve quality of life, and reduce the number and severity of pain crises.

Hydroxyurea is available in 200-, 300-, 400-, and 500-mg capsules and as 1000-mg tablet. Extemporaneous liquid preparations can be prepared for children who cannot swallow capsules. Doses should start at 10 to 15 mg/kg daily in a single oral dose, which can be increased after 8 to 12 weeks if blood counts are stable, and there are no side effects. Individualize the dosage based on the patient's response and the toxicity seen. With close monitoring, doses can be increased by 5 mg increments up to 35 mg/kg/day.[12] In patients with renal failure, initial dosing of hydroxyurea will need to be adjusted according to the creatinine clearance, as shown in Table 71–2, with subsequent dosing titrated to response.

Closely monitor patients for efficacy and toxicity while they are receiving hydroxyurea. Monitor mean corpuscular volume (MCV), since it typically increases as the level of HbF increases. If the MCV does not increase with hydroxyurea use, the bone marrow may be unable to respond, the dose may not be adequate, or the patient may be nonadherent.[12] However, lack of increase in MCV or in HbF is not an indication to discontinue therapy; the clinical response to therapy may take 3 to 6 months. A 6-month trial on the maximum tolerated dose is required prior to consideration of discontinuation due to treatment failure, whether secondary to lack of adherence or failure to respond to therapy. HbF levels can also be monitored to assess response with a goal of increasing HbF to 15% to 20% (0.15–0.20). Assess blood counts every 2 weeks during dose titration and then every 4 to 6 weeks once the dose is stabilized. Temporary discontinuation of therapy is warranted if hemoglobin level is less than 4.5 g/dL (45 g/L or 2.79 mmol/L), absolute neutrophil count is less than $2 \times 10^3/\text{mm}^3$ (2×10^9/L), platelets are less than $80 \times 10^3/\text{mm}^3$ (80×10^9/L), or the reticulocytes are less than $80 \times 10^3/\text{mm}^3$ (80×10^9/L). Monitor for increases in serum creatinine and transaminases. Once the patient's blood counts have returned to baseline, hydroxyurea may be restarted with a dose that is 2.5 to 5 mg/kg less than the dose associated with the patient's toxicity. Doses may then be increased by 2.5 to 5 mg/kg daily after 12 weeks with no toxicity.

Administer prophylactic folic acid supplementation to SCD patients receiving hydroxyurea, because folate deficiency may be masked by the use of hydroxyurea.

5-Aza-2′-Deoxycytine (Decitabine) For patients who do not respond to hydroxyurea, or cannot tolerate the side effects of hydroyurea, 5-azacytidine, and 5-aza-2′-deoxycytidine (decitabine) may be considered, although it has not been approved by the FDA for this indication. Both induce HbF by inhibiting methylation of DNA, preventing the switch from γ- to β-globin production. Decitabine appears to be safer and more potent than 5-azacytadine. In a small study in adults refractory to hydroxyurea, decitabine 0.2 mg/kg subcutaneously one to three times weekly was associated with an increase in HbF in all patients. Additionally, RBC adhesion was reduced. Neutropenia was the only significant toxicity reported.[25]

L-Glutamine Therapy FDA approved to reduce acute complications of SCD in adults and children 5 years of age and older, L-glutamine is available as an oral powder that is administered twice daily based on body weight. The dose should be mixed immediately prior to administration with 8 oz of cold or room temperature water, milk or apple juice, or can be mixed into 4 to 6 oz of soft food, such as applesauce or yogurt. Clinical studies demonstrated significant decreases in the number of pain crises, vaso-occlusive crises hospitalizations, hospitalizations, ACS, and time to first sickle cell crisis. Adverse effects seen in studies included constipation, nausea, headache, and abdominal pain. A majority of the patients in clinical trials were also receiving hydroxyurea.[26]

Voxelotor In patients who are older than 12 years that are taking appropriately dosed hydroxyurea and continue to have vaso-occlusive crises, voxelotor is an FDA-approved option. Voxelotor

Table 71–2

Dosage Adjustments for Renal and Hepatic Dysfunction

Medication	Renal Adjustment	Hepatic Adjustment
Decitabine (Decagon)	For Scr ≥ 2 mg/dL (177 μmol/L): hold therapy until values return to baseline	For serum alanine transaminase (ALT), serum glutamic pyruvic transaminase (SGPT), or total bilirubin values more than two times the upper limit of normal: hold therapy until values return to baseline
Deferoxamine (Desferal)	Cl_{cr} 10–50 mL/min (0.17–0.83 mL/s): administer 25%–50% of usual dose Cl_{cr} < 10 mL/min (0.17 mL/s): do not use	No adjustment recommended
Deferasirox Children	> 33% increase in Scr (on two consecutive readings) and above the age-appropriate upper limits of normal: decrease daily dose by 10 mg/kg (Exjade) or 7 mg/kg (Jadenu) Scr ≥ 2 times age-appropriate upper limits of normal: discontinue treatment	Severe or persistent elevations in liver function tests: decrease the daily dose or discontinue therapy
Adults	> 33% increase in Scr above pretreatment values on two consecutive readings: decrease daily dose by 10 mg/kg (Exjade) or 7 mg/kg (Jadenu) CL < 40 mL/min (0.38 mL/s): discontinue treatment	Severe or persistent elevations in liver function tests: decrease the daily dose or discontinue therapy
Deferiprone	No adjustment necessary	No adjustment necessary
Folic acid	No adjustment necessary	No adjustment necessary
Hydroxyurea	Cl_{cr} < 60 mL/min (1.00 mL/s): initial dose of 7.5 mg/kg/day Hemodialysis: 7.5 mg/kg/day given after dialysis	Monitor patient for bone marrow toxicity
Voxelotor	No adjustment necessary	Child Pugh class C impairment: decrease dose to 1 g daily
Crizanlizumab	No adjustment necessary	No adjustment necessary

Data from Refs. [18-24,28,31].

inhibits HbS polymerization by binding to the alpha chain of HbS and increases oxygen binding. While voxelotor does not decrease VOC episodes, it does improve hemoglobin levels and reduces signs of hemolysis. It is administered once daily in oral doses of 1500 mg and can be given with or without hydroxyurea. Lower doses of 1000 mg should be given to patients with severe hepatic impairment. It is important to avoid concomitant inducers or inhibitors of hepatic CYP3A4 as there are a number of drug interactions. Adverse effects include headache, diarrhea, abdominal pain, and nausea.[27,28]

Crizanlizumab For patients who do not respond to hydroxyurea or L-glutamine, cirzanlizumab may help reduce vaso-occlusive pain crises. Crizanlizumab is a monoclonal antibody that acts against P-selectin, an adhesion molecule that is expressed on activated endothelial cells and platelets. It is FDA approved for patients greater than or equal to 16 years of age and administered as an infusion of 5 mg/kg over 30 minutes on week 0, week 2, and then every 4 weeks. The most common adverse effects include nausea, arthralgia, and fever. [29-31]

Chronic Transfusion Therapy Chronic transfusion therapy is warranted to prevent serious complications from SCD, including stroke prevention and recurrence. KEY CONCEPT Especially in children, chronic transfusions have been shown to decrease stroke recurrence from approximately 50% to 10% over 3 years. Without chronic transfusions, approximately 70% of ischemic stroke patients will have another stroke. Chronic transfusion therapy also may be used to prevent vasoocclusive pain and ACS, as well as prevent progression of organ damage.[4]

The goal of chronic transfusion therapy is to maintain the HbS level at less than 30% (0.30) of total hemoglobin concentration. Transfusions are usually administered every 3 to 4 weeks depending on the HbS concentration. For secondary stroke prevention, current studies have indicated that lifelong transfusion may be required, with increased incidence of recurrence once transfusions are stopped.[4,17]

The benefits of transfusion should be weighed with the risks. Risks associated with transfusions include alloimmunization (sensitization to the blood received), hyperviscosity, viral transmission, volume overload, iron overload, and transfusion reactions. Although the risk of contracting AIDS has decreased dramatically, hepatitis C remains a concern. All SCD patients should be vaccinated for hepatitis A and B and should be serially monitored for hepatitis C and other infections. Parvovirus occurs in 1 of every 40,000 U of RBCs and can be associated with acute anemia and multiple sickle cell complications.[4] Iron overload is a risk for patients maintained on chronic transfusions for more than 1 year. Counsel patients to avoid excessive dietary iron, and monitor serum ferritin regularly. Chelation therapy with deferoxamine, deferasirox, or deferiprone should be considered when the serum ferritin level is greater than 1500 to 2000 ng/mL (1500–2000 mcg/L; 3400–4500 pmol/L). Deferoxamine should be initiated at 20 to 40 mg/kg daily (to a maximum of 1–2 g/day) over 8 to 12 hours subcutaneously and has been associated with growth failure.[4] Monitor children receiving deferoxamine for adequate growth and development on a regular basis. Additionally, patients receiving deferoxamine should receive supplemental ascorbic acid starting 1 month after deferoxamine initiation; the ascorbic acid will increase the availability of iron for chelation. Patients with preexisting cardiac conditions should not receive ascorbic acid supplementation. Deferasirox is available in three dosage forms: a tablet (Exjade) that should be

Patient Encounter 2, Part 1

A 27-year-old African American woman with SCD is admitted to the hospital for progressive shoulder and chest pain that began 3 days ago. The patient denies injury. She complains of a nonproductive cough and a slight headache.

PMH: Sickle cell disease (HbSS); admitted for vasoocclusive crises twice over the past year; acute chest syndrome at ages 8, 9, 12, 15, 17, and 25; multiple blood transfusions

PSH: Cholecystectomy at age 13

FH: Father with SC trait. Mother with SCD.

Allergies: Sulfa drugs—hives

SH: Denies alcohol use. Is sexually active, recently married

Home Meds: Hydrocodone/Acetaminophen 7.5/325 mg two tablets every 6 hours as needed for pain; folic acid 1 mg daily by mouth; hydroxyurea 2 g orally once daily; levonorgestrel 90 mcg and ethinyl estradiol 20-mcg tablets once daily

PE:

VS: T 40.1°C (104.1°F), BP 113/62 mm Hg, P 80 beats/min, RR 29 breaths/min, O_2 Sat 96% (0.97) on 3 L nasal cannula, Ht 160 cm (5′3″), Wt 60 kg (134 lb)

Gen: Awake, alert × 3, in some distress, and obviously in pain

HEENT: Normocephalic, atraumatic. PERRLA. No lymphadenopathy

Chest: Normal to inspection and palpation. Moderate rales and wheezes

CV: RRR, no m/g/r

Abd: Soft, NT/ND

Ext: No clubbing, cyanosis, or edema. Shoulder pain with palpation

Neuro: Cranial nerves II through XII are grossly intact. Nonfocal

Labs: Hgb 6.8 g/dL (68 g/L or 4.22 mmol/L), Hct 20% (0.2 fraction), WBC 19 × 10^3/μL (19 × 10^9/L), BMP WNL

Chest X-ray shows pulmonary infiltrates.

What is your assessment of this patient's condition?

List treatment goals for this patient.

Devise a detailed therapeutic plan for this patient's hospital management.

dispersed in water, orange juice, or apple juice and taken orally 30 minutes before food, a tablet (Jadenu) that can be swallowed whole and granules (Jadenu Sprinkle) which are sprinkled on soft food.[32] Exjade should be initiated at 20 mg/kg once daily and titrated every 3 to 6 months by 5 to 10 mg/kg/day up to a maximum dose of 40 mg/kg/day. Jadenu and Jadenu Sprinkle should be initated at 14 mg/kg once daily and titrated every 3 to 6 months by 3.5 or 7 mg/kg/day to a maximum dose of 28 mg/kg/day. Exjade and Jadenu are not bioequivalent on an mg to mg basis because of bioavailability differences: when converting from one dosage form to the other, the dose for Jadenu should be about 30% less than the Exjade dose. For both products, the dose should be rounded to the whole tablet dosage form available. Exjade is available in 125, 250, and 500 mg dispersible tablets. Jadenu and Jadenu Sprinkle are available in 90-, 180-, and 360-mg tablets and packets. Deferiprone is approved for use in adults with thalassemia syndromes who have not responded adequately to other chelation therapies.[33] It is administered three times daily as an oral dosage form. Some recent studies have evaluated combination therapy for treatment of transfusion-associated iron overload. A synergistic effect has been demonstrated with the concomitant use of deferoxamine and deferiprone.[34] Monitor all chelation patients for auditory and ocular changes on a yearly basis. Exchange transfusions may also be helpful in cases of iron overload.

Patient Encounter 2, Part 2

The patient recovers from her hospitalization and comes to clinic for follow-up 2 weeks after discharge. She was discharged on her home medications. She has been feeling pretty well and her symptoms have returned to baseline. Routine laboratory tests indicate that her Clcr is now 35 mL/min/1.73 m^2 (0.33 mL/s/m^2) and her transaminases are slightly elevated. All her other laboratory values are within normal limits. She also indicates that she is interested in another form of birth control since she keeps forgetting to take her pills.

How should her medications be adjusted?

Sickle cell hemolytic transfusion reaction syndrome is a unique problem in SCD patients. Due to alloimmunization, an acute or delayed transfusion reaction may occur 5 to 20 days posttransfusion. Patients may develop symptoms suggestive of a pain crisis or worsening symptoms if they are already in crisis. A severe anemia after transfusion also may occur due to a rapid decrease in hemoglobin and hematocrit, along with a suppression of erythropoiesis. Further transfusions may worsen the clinical picture due to autoimmune antibodies. Recovery may occur only after ceasing all transfusions and is evidenced by a gradual increase in hemoglobin with reticulocytosis, which indicates the patient is now making their own RBCs.[4]

Allogeneic Hematopoietic Stem Cell Transplant Allogeneic hematopoietic stem-cell transplantation (HSCT) is the only potential cure for SCD. The best candidates are children with SCD who are younger than 16 years of age with severe complications, who have an identical human leukocyte antigen (HLA)-matched donor, usually a sibling. The transplant-related mortality rate is between 5% and 10%, and graft rejection is approximately 10%. In a recent review, the overall survival rate was 95% and the event-free survival was 92% in children with SCD who received a transplant from an HLA-matched sibling.[35] Other risks include secondary malignancies, development of seizures or intracranial bleeding, and infection in the immediate posttransplant period.[4,36]

Experience with HSCT in adult patients with SCD is still somewhat limited. The use of less intense preparative regimens has made HSCT more available for the older patient with SCD. The best results have been seen in the use of progenitor cells (from bone marrow, cord blood, or peripheral blood stem cells) from matched sibling or related donors. The largest published trial to date in adults undergoing nonmyeloablative transplant involved 30 patients with an 87% rate of disease-free survival.[36]

▶ *Acute Complications*

Transfusions for Acute Complications Red cell transfusion is indicated in patients with acute exacerbations of baseline anemia; in cases of severe vasoocclusive episodes, including ACS, stroke, and acute multiorgan failure; and in preparation for procedures that will require the use of general anesthesia or ionic contrast products. Transfusions also may be useful in patients with complicated obstetric problems, refractory leg ulcers, refractory and prolonged pain crises, or severe priapism. Hyperviscosity may occur if the hemoglobin level is increased to greater than 10.0 to 11.0 g/dL (100–110 g/L or 6.21–6.83 mmol/L). Volume overload leading to congestive heart failure is more likely to occur if the anemia is corrected too rapidly in patients with severe anemia and should be avoided.[4]

Infection and Fever KEY CONCEPT Any fever greater than 38.5°C (101.3°F) in an SCD patient should be immediately evaluated, and the patient should have a blood culture drawn and be started on antibiotics that provide empirical coverage for encapsulated organisms.[4]

Patients who should be hospitalized include the following:

- Infants younger than 1 year of age
- Patients with a previous sepsis or bacteremia episode
- Patients with temperatures in excess of 40°C (104°F)
- Patients with white blood cell (WBC) counts greater than $30 \times 10^3/\text{mm}^3$ ($30 \times 10^9/\text{L}$) or less than $0.5 \times 10^3/\text{mm}^3$ ($0.5 \times 10^9/\text{L}$) and/or platelets less than $100 \times 10^3/\text{mm}^3$ ($100 \times 10^9/\text{L}$) with evidence of other acute complications
- Acutely ill-appearing individuals

Broad IV antibiotic coverage for the encapsulated organisms can include ceftriaxone or cefotaxime. For patients with true cephalosporin allergy, clindamycin may be used. If staphylococcal infection is suspected due to previous history or the patient appears acutely ill, vancomycin should be initiated. Macrolide antibiotics, such as erythromycin or azithromycin, may be initiated if mycoplasma pneumonia is suspected. While the patient is receiving broad-spectrum antibiotics, their regular use of penicillin for prophylaxis can be suspended. Fever should be controlled with acetaminophen or ibuprofen. Because of the risk of dehydration during infection with fever, increased fluid may be needed.[1,4]

Bone infarcts or sickling in the periosteum usually is indicated by pain and swelling over an extremity. Osteomyelitis should also be considered. *Salmonella* species are the most common cause of osteomyelitis in children with SCD, followed by *Staphylococcus aureus*.[1] Select an appropriate antibiotic to cover the suspected organisms empirically.

Cerebrovascular Accidents Acute neurologic events, such as stroke, will require hospitalization and close monitoring. Patients should have physical and neurologic examinations every 2 hours.[4] Acute treatment may include exchange transfusion or simple transfusion to maintain hemoglobin at approximately 10.0 g/dL (100 g/L or 6.21 mmol/L) and HbS concentration at less than 30% (0.30). Patients with a history of seizure may need anticonvulsants, and interventions for increased intracranial pressure should be initiated if necessary. Children with history of stroke should be initiated on chronic transfusion therapy.[4]

Early detection of ischemic stroke can be done with the use of transcranial Doppler ultrasonography. In the Stroke Prevention Trial in Sickle Cell Anemia (STOP) study, screening with this method followed by chronic transfusion therapy significantly reduced the incidence of stroke.[37-39] Screening is recommended in all patients older than 2 years.

Clinical Presentation and Diagnosis of ACS in SCD

General

- Occurs in 15% to 43% of patients and is responsible for 25% of deaths
- Risk factors include young age, low HbF level, high Hgb and WBCs, winter seasons, reactive airway disease
- Recurrences are up to 80% and can lead to chronic lung disease

Symptoms

- Patients may complain of cough, fever, dyspnea, chest pain

Signs

- Temperature greater than 38.5°C (101.3°F)
- Hypoxia
- New infiltrate on chest X-ray

Laboratory Tests

- CBC with reticulocyte count
- Blood gases
- Oxygen saturation
- Cultures (blood and sputum)

Other

- Closely monitor pulmonary status

Acute Chest Syndrome ACS will require hospitalization for appropriate management of symptoms and to avoid complications. Patients should be encouraged to use incentive spirometry at least every 2 hours. Incentive spirometry helps the patient take long, slow breaths to increase lung expansion. Appropriate management of pain is important, but analgesic-induced hypoventilation should be avoided. Patients should maintain appropriate fluid balance because overhydration can lead to pulmonary edema and respiratory distress. Infection with gram-negative, gram-positive, or atypical bacteria is common in ACS, and early use of broad-spectrum antibiotics, including a macrolide, quinolone, or cephalosporin, is recommended. Fat emboli, from infarction of the long bones, may lead to ACS. Oxygen therapy should be utilized in any patient presenting with respiratory distress or hypoxia. Oxygen saturations, measured by pulse oximeter, should be maintained at 92% (0.92) or above. Exchange transfusions are often indicated when there is a rapid progression of ACS symptoms, such as increased needs for supplemental oxygen, increased respiratory distress, or progression of pulmonary infiltrates, and patients who present with wheezing may require inhaled bronchodilators.[4,40]

The use of corticosteroids is controversial. Although they may decrease the inflammation and endothelial cell adhesion seen with ACS, their use has also been associated with higher readmission rates for other complications.

Clinical Presentation and Diagnosis of Priapism in SCD

General

- Mean age of initial episode is 12 years of age
- Most male patients with SCD will have one episode by age 20
- Repeated episodes can lead to fibrosis and impotence

Symptoms

- Patients may complain of painful and unwanted erection lasting anywhere from less than 2 hours (stuttering type) to more than 2 hours (prolonged type)

Signs

- Urinary obstruction

Laboratory Tests

- CBC with reticulocyte count

Other

- Monitor for duration of episode
- Prolonged episodes should be considered medical emergencies

Priapism By age 18, approximately 90% of male patients with SCD will have had at least one episode of priapism. Stuttering priapism, where erection episodes last anywhere from a few minutes to less than 2 hours, resolves spontaneously. Erections lasting more than 2 hours should be evaluated promptly. Goals of therapy are to provide pain relief, reduce anxiety, provide detumescence, and preserve testicular function and fertility. Initial treatment should include aggressive hydration and analgesia. Transfusion may or may not be helpful but should be considered in anemic patients. Avoid the use of ice packs due to the risk of tissue damage.[4]

Both vasoconstrictors and vasodilators have been used in the treatment of priapism. Vasoconstrictors are thought to work by forcing blood out of the cavernosum and into the venous return. Aspiration of the penile blood followed by intracavernous irrigation with epinephrine (1:1,000,000 solution) has been effective with minimal complications.[37] In severe cases, surgical intervention to place penile shunts has been used, but there is a high failure rate, and the risk of complications, from skin sloughing to fistulas, limits its use.

Pseudoephedrine dosed at 30 to 60 mg daily taken at bedtime has been used to prevent or decrease the number of episodes of priapism.[4] Terbutaline 5 mg has been used orally to prevent priapism, with mixed results.[41,42] Leuprolide, a gonadotropin-releasing hormone, also has been used for this indication. Hydroxyurea may be helpful in some patients.[41,43] The use of antiandrogens is under investigation.[4]

▶ *Treatment of Acute Complications*

Aplastic Crisis Most patients in aplastic crisis will recover spontaneously, and therefore, treatment is supportive. If anemia is severe or symptomatic, transfusion may be indicated. Infection with human parvovirus B19 is the most common cause of aplastic crisis. Isolate infected patients because parvovirus is highly

Clinical Presentation and Diagnosis of Acute Aplastic Crisis in SCD

General

- Transient suppression of RBC production in response to bacterial or viral infection
- Most commonly due to infection with parvovirus B19

Symptoms

- Patients may complain of headache, fatigue, dyspnea, pallor, or fever
- Patients may also complain of upper respiratory or GI infection symptoms

Signs

- Temperature greater than 38.5°C (101.3°F) may occur
- Hypoxia
- Tachycardia
- Acute decrease in Hgb with decreased reticulocyte count

Laboratory Tests

- CBC with reticulocyte count
- Chest X-ray
- Parvovirus titers
- Cultures (blood, urine, and throat)

Clinical Presentation and Diagnosis of Sequestration Crisis in SCD

General

- Acute exacerbation of anemia due to sequestration of large blood volume by the spleen
- More common in patients with functioning spleens
- Onset often associated with viral or bacterial infections
- Recurrence is common and can be fatal

Symptoms

- Sudden onset of fatigue, dyspnea, and distended abdomen
- Patients may present with vomiting and abdominal pain

Signs

- Rapid decrease in Hgb and Hct with elevated reticulocyte count
- Splenomegaly
- May exhibit hypotension and shock

Evaluation

- Vital signs
- Spleen size changes
- Oxygen saturations
- CBC with reticulocyte count
- Cultures (blood, urine, throat)

contagious. Pregnant individuals should avoid contact with infected patients because midtrimester infection with parvovirus may cause hydrops fetalis and still birth.[1,4]

Sequestration Crisis RBC sequestration in the spleen in young children may lead to a rapid drop in hematocrit, resulting in hypovolemia, shock, and death. Treatment is RBC transfusion to correct the hypovolemia, as well as broad-spectrum antibiotics, because infections may precipitate the crisis.[1,4]

Recurrent episodes are common and can be managed with chronic transfusion and splenectomy. Observation is used commonly in adults because their episodes are milder. Splenectomy is usually delayed until after 2 years of age to lessen the risk of postsplenectomy septicemia. Patients with chronic hypersplenism should be considered for splenectomy.[4,44]

Vasoocclusive Pain Crisis The mainstay of treatment for VOC includes hydration and analgesia (Table 71–3). Pain may involve the extremities, back, chest, and abdomen. **KEY CONCEPT** Patients with mild pain crisis may be treated as outpatients with rest, warm compresses to the affected (painful) area, increased fluid intake, and oral analgesia. Patients with moderate-to-severe crises should be hospitalized. Infection should be ruled out because it may trigger a pain crisis, and any patient presenting with fever or critical illness should be started on empirical broad-spectrum antibiotics. Patients who are anemic should be transfused to their baseline. IV or oral fluids at 1.5 times maintenance are recommended. Close monitoring of the patient's fluid status is important to avoid overhydration, which can lead to ACS, volume overload, or heart failure.[4]

Aggressive pain management is required in patients presenting in pain crisis. Assess pain on a regular basis (every 2–4 hours), and individualize management to the patient. The use of pain scales may help with quantifying the pain rating. Obtain a good medication history of what has worked well for the patient in the past. Use acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) for treatment of mild-to-moderate pain. Patients with bone or joint pain who require IV medications may be helped by the use of ketorolac, an injectable NSAID. Because of the concern for side effects, including GI bleeding, ketorolac should be used only for a maximum of 5 consecutive days.

Table 71–3

Management of Acute Pain of SCD

Principles

Treat underlying precipitating factors.
- Avoid delays in analgesia administration.
- Use pain scale to assess severity.
- Choice of initial analgesic should be based on previous pain crisis pattern, history of response, current status, and other medical conditions.
- Schedule pain medication; avoid as-needed dosing.
- Provide rescue dose for breakthrough pain.
- If adequate pain relief can be achieved with one or two doses of morphine, consider outpatient management with a weak opioid; otherwise hospitalization is needed for parenteral analgesics.
- Frequently assess to evaluate pain severity and side effects; titrate dose as needed.
- Treating adverse effects of opioids is part of pain management.
- Consider nonpharmacologic intervention.
- Transition to oral analgesics as the patient improves; choose an oral agent based on previous history, anticipated duration, and ability to swallow tablets; if sustained-release products are used, a fast-release product is also needed for breakthrough pain.

Analgesic Regimens

Mild-to-moderate pain:

Hydrocodone + acetaminophen:
- Dose based on hydrocodone—children: 0.2 mg/kg per dose every 6 hours; adults: 5–10 mg/dose

Anti-inflammatory agents:
- Use with caution in patients with renal failure (dehydration) and bleeding
- Ibuprofen (oral): children: 10 mg/kg every 6–8 hours; adults: 200–400 mg/dose
- Naproxen: 5 mg/kg every 12 hours; adults: 250–500 mg/dose
- Ibuprofen + hydrocodone: Each tablet contains 200 mg ibuprofen and 7.5 mg hydrocodone per tablet; only for older children who can swallow tablets

Moderate-to-severe pain:

Morphine—children:
- 0.1–0.15 mg/kg per dose every 3–4 hours; adults: 5–10 mg/dose
- Continuous infusion: 0.04–0.05 mg/kg/hour; titrate to effect

Hydromorphone—children:
- 0.015 mg/kg per dose every 3–4 hours; adults: 1.5–2 mg/dose
- Continuous infusion: 0.004 mg/kg/hour; titrate to effect

IV anti-inflammatory agents:
- Ketorolac: 0.5 mg/kg up to 30 mg/dose every 6 hours

Patient-controlled analgesics:
- Morphine: 0.01–0.03 mg/kg/hour basal; demand 0.01–0.03 mg/kg every 6–10 minutes; 4 hours lockout 0.04–0.06 mg/kg
- Hydromorphone: 0.003–0.005 mg/kg/hour basal; demand 0.003–0.05 mg/kg every 6–10 minutes; 4 hours lock out 0.4–0.6 mg/kg

Clinical Presentation and Diagnosis of Vasoocclusive Crisis in SCD

General

- Most often involves the bones, liver, spleen, brain, lungs, and penis
- Precipitating factors include infection, extreme weather conditions, dehydration, and stresses
- Recurrent acute crises result in bone, joint, and organ damage and chronic pain

Symptoms

- Patients may complain of deep throbbing pain, local tenderness

Signs

- Erythema and swelling of painful area
- Dactylitis in young infants
- Temperature greater than 38.5°C (101.3°F)
- Leukocytosis

Laboratory tests

- CBC with reticulocyte count
- Urinalysis
- Abdominal studies (if symptoms exist)
- Cultures (blood and urine)
- Liver function tests and bilirubin
- Chest X-ray

Monitor the total amount of acetaminophen given daily, because many products contain acetaminophen. Maximum daily dose of acetaminophen for adults is 3 g/day, and for children, five doses over a 24-hour period.[45] Add an opioid if pain persists or if pain is moderate-to-severe in nature. Combining an opioid with an NSAID can enhance the analgesic effects without increasing adverse effects.[46-49]

Severe pain should be treated with an opioid such as morphine, hydromorphone, methadone, or fentanyl. Moderate pain can be effectively treated in most cases with a weak opioid such as codeine or hydrocodone, usually in combination with acetaminophen. Meperidine should be avoided because of its relatively short analgesic effect and its toxic metabolite, normeperidine. Normeperidine may accumulate with repeated dosing and can lead to CNS side effects including seizures.

IV opioids are recommended for treatment of severe pain because of their rapid onset of action and ease in titration. Intramuscular injection should be avoided. Analgesia should be individualized and titrated to effect, either by scheduled around-the-clock doses or continuous infusion. The use of continuous infusion will avoid fluctuations in blood levels between doses observed with bolus dosing. As-needed dosing of analgesia is only appropriate for breakthrough pain or uncontrolled pain. Patient-controlled analgesia (PCA) is commonly used and allows the patient to have control over his or her analgesic breakthrough dosing. As the pain crisis resolves, the pain medications can be tapered. Physical therapy and relaxation therapy can be helpful adjuvants to analgesia.[46–47]

Tolerance to opioids is seen when patients have had continuous long-term use of the medications and can be managed during acute crises by using a different potent opioid or using a larger dose of the same medication. Adverse effects associated with the use of opioids include respiratory depression, itching, nausea and vomiting, constipation, and drowsiness. Patients on continuous infusions of opioids should be on continuous pulse oximeter to assess oxygen saturations. Monitor the patient for oxygen saturations less than 92% (0.92). Oxygen should be administered as needed to keep the saturation above 92% (0.92). Itching can be managed with an antihistamine such as diphenhydramine. Nausea and vomiting can be treated and managed with the administration of antiemetics such as promethazine or 5HT3 antagonists, but the use of promethazine is contraindicated in children younger than 2 years of age. Assess stool frequency in all patients on a continuous opioid, and start stool softeners or laxatives as needed. Excessive sedation is difficult to control, and the concurrent use of an opioid with diphenhydramine or other sedative medications can exacerbate the drowsiness, leading to hypoxemia. A continuous very low dose of naloxone, an opioid antagonist, has been used successfully when the adverse effects such as itching are unbearable.[50]

As patients age and their SCD advances, most will present with some level of chronic pain, which should be treated with the lowest dose of oral analgesic, typically a combination of hydrocodone and acetaminophen on an as-needed basis. Neuropathic pain can result from repeated vaso-occlusive crises and may require the regular use of medications such as gabapentin, amitriptyline, or pregabalin.

OUTCOME EVALUATION

SCD treatment and prevention are considered successful when complications are minimized. The major outcome parameters are a decrease in morbidity and mortality, measured by the number of hospitalizations, and the extent of end-organ damage seen over time. Today, with longer survival for SCD, chronic manifestations of the disease contribute to the morbidity later in life (Table 71–4). Thirty years ago, complications from SCD contributed to high mortality. It was estimated that approximately 50% of patients with SCD did not survive to reach adulthood.[1] Since that time, data suggest improvement in mortality rates for patients with SCD. The survival age for individuals with HbSS has increased to at least the fifth decade of life. Recent reports suggest 85% survival to 18 years of age.[4] SCD is a chronic disease and cannot be cured, except in some patients with transplant.

Starting with birth, SCD patients should have regularly scheduled health assessments and interventions when necessary. Obtain a urine analysis, complete blood count, liver function tests, ferritin or serum iron level and total iron-binding capacity, blood urea nitrogen (BUN), and creatinine on at least a yearly basis and more often for children younger than 5 years of age to monitor for complications. All SCD patients should have regular screening of their hearing and vision.

All patients and parents of children with SCD should have a plan for what to do in the event of symptoms of infection or pain. Obtain a medication history when patients are admitted to the hospital. Assess adherence with prophylactic penicillin and childhood immunization schedules in all pediatric SCD patients.

Table 71–4

Chronic Complications of SCD

System	Complications
Auditory	Sensorineural hearing loss due to sickling in cochlear vasculature with hair cell damage
Cardiovascular	Cardiomegaly, myocardial ischemia, murmurs, and abnormal ECG; patients with SCD have lower BP than the normal population; normal BP values for SCD should be used for diagnosis of hypertension ("relative" hypertension); heart failure usually is related to fluid overload
Dermatologic	Painful leg ulcers; failure to heal occurs in 50% of patients; recurrences are common
Genitourinary	Renal papillary necrosis, hematuria, hyposthenuria, proteinuria, nephrotic syndrome, tubular dysfunction, chronic renal failure, impotence, priapism
Growth and development	Delay in growth (weight and height) and sexual development; decreased fertility; increased complications during pregnancy; depression may be more prevalent than in general population, especially in patients with unstable disease
Hepatic and biliary	Cholelithiasis, biliary sludge, acute and chronic cholecystitis, and cholestasis (can be progressive and life-threatening)
Neurologic	"Silent" brain lesions on MRI are associated with poor cognitive and fine motor functions; pseudotumor cerebri (rare)
Ocular	Retinal or vitreous hemorrhage, retinal detachment, transient or permanent visual loss; central retinal vein occlusion
Pulmonary	Pulmonary fibrosis, pulmonary hypertension, cor pulmonale
Renal	Hematuria, hyposthenuria (inability to concentrate urine maximally), tubular dysfunction, enuresis during early childhood, acute renal failure can also occur
Skeletal	Aseptic necrosis of ball-and-socket joints (shoulder and hip); prostheses may be needed due to permanent damage; bone marrow hyperplasia resulting in growth disturbances of maxilla and vertebrae
Spleen	Asplenia (autosplenectomy or surgical splenectomy)

Patient Care Process

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. Identify allergies to medications and other substances.
- Review the medical history and physical assessment findings.
- Speak with the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.
- Review available laboratory tests.

Assess the Information:

- Based on physical examination and review of systems, determine whether the patient is experiencing any signs or symptoms of an acute or chronic SCD complication (Tables 71–1 and 71–4).
- Assess the safety, efficacy, and patient adherence of current pharmacotherapy.
- Identify any significant adverse drug effects or interactions.
- Assess the patient's medication history. Does the patient take any medications routinely for SCD? Which analgesics have been helpful to the patient in the past? Are they taking appropriate doses to achieve the desired effect? If not, why?
- Determine if the patient is up to date on their immunizations. Have they received their annual influenza vaccine? Are they missing any vaccines?

Develop a Care Plan:

- Choose medications and doses that are optimal for the patient.
- Select lifestyle modifications that are likely to be effective and safe for the patient.
- Determine whether drug doses are optimal.
- If the patient is having an acute complication of SCD, arrange for referral and/or admission to the hospital.

Implement the Care Plan:

- Educate the patient about changes in drug therapy, medication administration, potential new adverse effects, and how to manage and report adverse effects that occur.
- Address any patient concerns about SCD and its management.
- Discuss the importance of medication adherence and lifestyle modifications to prevent complications of SCD.
- Determine if the patient has prescription coverage or whether recommended agents are included on the institution's formulary.
- Arrange for vaccination if the patient is not up to date with recommendations.

Follow-up: Montor and Evaluate:

- Follow-up at monthly intervals or more frequently to assess effectiveness and safety of therapy, avoid complications from SCD, and improve quality of life for the patient.
- Review medication history and physical examination findings, laboratory tests, and results of other diagnostic tests.
- Assess for adverse effects from medications that the patient is taking.
- Stress the importance of adherence with the therapeutic regimen. Adjust therapeutic regimens as needed based on patient response and adverse effects.

Abbreviations Introduced in This Chapter

ACS	Acute chest syndrome
CNS	Central nervous system
HbA	Adult hemoglobin
HbAS	One normal and one sickle hemoglobin gene
HbC	Hemoglobin C
HbF	Fetal hemoglobin
HbS	Sickle hemoglobin
HbSβ^0-thalassemia	One sickle hemoglobin and one β^0-thalassemia gene
HbSβ^+-thalassemia	One sickle hemoglobin and one β^+-thalassemia gene
HbSC	One sickle hemoglobin and one hemoglobin C gene
HbSS	Homozygous sickle hemoglobin
Hgb	Hemoglobin
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem-cell transplantation
ISC	Irreversibly sickled cell
MCV	Mean corpuscular volume
MenACWY	Quadrivalent meningococcal vaccine
NSAID	Nonsteroidal anti-inflammatory drug
PCA	Patient-controlled analgesia
PCV 13	13-Valent pneumococcal conjugate vaccine
PPV 23	23-Valent pneumococcal polysaccharide vaccine
SCA	Sickle cell anemia
SCD	Sickle cell disease
SCT	Sickle cell trait
STOP	Stroke Prevention Trial in Sickle Cell Anemia
VOC	Vasoocclusive crisis
WBC	White blood cell

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72

Patient Assessment, Antimicrobial Selection, and Stewardship

Angharad Ratliff and Catherine Oliphant

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe how antimicrobials differ from other drug classes in terms of their effects on individual patients as well as on society as a whole.
2. Recognize that antimicrobial resistance is an inevitable consequence of antimicrobial therapy.
3. Identify guiding principles to consider when treating patients with antimicrobials, and apply these principles in patient care.
4. Differentiate between microbial colonization and infection based on patient history, physical examination, and laboratory and culture results.
5. Evaluate and apply drug-specific considerations when selecting antimicrobial therapy.
6. Evaluate and apply patient-specific considerations when selecting antimicrobial therapy.
7. Identify and apply principles of patient education and monitoring response to antimicrobial therapy.
8. Discuss causes of patients failing to improve while on antimicrobials.
9. Define antimicrobial stewardship and describe the purpose of such a program.

INTRODUCTION

Antimicrobials are among the most commonly prescribed medications. Antimicrobial is a broad term referring to agents including antibiotics, antivirals, antiprotozoals, and antifungals. In this chapter, we will refer primarily to antimicrobials; however, when an example is specific to the antibiotic class or treatment of a bacterial infection, the term antibiotic will be used. KEY CONCEPT Antimicrobials are different from other classes of pharmaceuticals because they exert their action on microbes infecting the host as opposed to acting directly on the host. Today, there are many antimicrobials available for clinical use. However, in many cases, differences in mechanisms of action between antimicrobials are minor, and the microbiologic properties of the agents are similar. An estimated 50% of hospitalized patients will receive an antimicrobial and about 10% of ambulatory care visits are associated with an antibiotic prescription; however, antimicrobial use is not without risk.[1,2] KEY CONCEPT An inevitable consequence of exposing microbes to antimicrobials is that some organisms will develop resistance to the antimicrobial. The CDC's 2019 Antibiotic Resistance Threats in the United States estimates more than 2.8 million patients per year are infected with resistant pathogens resulting in approximately 35,000 deaths.[3] For several decades, infectious disease–related mortality in the United States has increased, in part owing to increases in antimicrobial resistance. Because antimicrobial use in one patient affects not only that patient but also other patients if they become infected with resistant bacteria, correct selection, use, and monitoring of clinical response are paramount. Antimicrobial stewardship programs promote the optimal use of antimicrobials and the concepts of these programs will be discussed in this chapter.

KEY CONCEPT There are two guiding principles to consider when treating patients with antimicrobials: (a) do no harm and (b) make the correct diagnosis! Patients with infections frequently present with signs and symptoms that are nonspecific and may be confused with other noninfectious diseases. Not only is it important to determine whether a disease process is of infectious origin, but it is also important to determine the specific causative pathogen of the infection. Antimicrobials vary in their spectrum of activity and their ability to inhibit or kill different species of bacteria. Antimicrobials that kill many different species of bacteria are called broad-spectrum antimicrobials, whereas antimicrobials that kill only a few species of bacteria are called narrow-spectrum antimicrobials. One might argue that treating everybody with broad-spectrum antimicrobials will increase the likelihood that a patient will get better even without knowing the bacteria causing infection. However, counter to this argument is the principle of "Do no harm!" Broad antimicrobial overage does increase the likelihood of empirically targeting the causative pathogen; unfortunately, this increases the risk of selecting for antimicrobial-resistant pathogens, which can lead to secondary infections. In addition, adverse events resulting from antibiotic therapy represent 16% of all emergency room visits for adverse drug events; this rate is similar to high-risk medications such as warfarin, digoxin, or insulin.[4] Antibiotics account for roughly one-third of all emergency department visits for adverse events due to systemically administered medications.[1] Therefore, the overall goal of antimicrobial therapy should be to cure the patient's infection; limit harm by minimizing patient risk for adverse events, including secondary infections; and limit societal risk from antimicrobial-resistant bacteria.

PATHOPHYSIOLOGY

Microbiome

Many areas of the human body are colonized with microbes—this is known as the microbiome. Knowing what organisms reside where can help guide empiric antimicrobial therapy (Figure 72–1 describes the microbiome by location). In addition, it is beneficial to know what anatomic sites are normally sterile. These include the cerebrospinal fluid, blood, and urine.

Determining Colonization Versus Infection

Infection refers to the presence of bacteria that are causing disease. Colonization refers to the presence of bacteria that are not causing disease. **KEY CONCEPT** It is important to differentiate infection from colonization because antimicrobial therapy targeting colonization is inappropriate and may lead to the emergence of resistant bacteria.

Endogenous Infection

Infections often arise from one's own microbiome, referred to as an **endogenous infection**. Endogenous infection may occur when there are disruptions of host defenses such as a break or entry in the skin or alterations in the microbiome due to recent antimicrobial use. Endogenous infections can also occur as a result of reactivation of a dormant infection such as tuberculosis or herpes virus infections.

Exogenously Acquired Bacterial Infections

Infections acquired from an external source are referred to as exogenous infections. These infections may occur as a result of human-to-human transmission, contact with exogenous bacterial populations in the environment, and animal contact. Obtaining a patient history is key to knowing what pathogens a patient is at risk for. A thorough patient history should include a review of the patient's recent travel and social history, antibiotic use and recent health care exposure. Clinical presentation should guide the aspects of patient history that are relevant to the infection. Treatment guidelines also recommend an assessment of a patient's risk factors for more resistant pathogens when selecting initial or empiric antimicrobial therapy. Resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* spp (VRE) may colonize hospitalized patients or patients who access the health care system frequently. It is important to know which patients have acquired these organisms because patients generally become colonized prior to developing infection, and colonized patients may be placed in isolation to minimize transmission.

CLINICAL PRESENTATION AND DIAGNOSIS

Physical Examination

Findings on physical examination such as rales, altered mental status, localized inflammation, erythema, warmth, edema, pain, and pus, along with the clinical presentation, can help identify the anatomic location of the infection. Once the anatomic site is identified, the most probable pathogens associated with disease can be determined based on likely endogenous or exogenous flora.

Fever often accompanies infection and is defined as a rise in body temperature above the normal 37°C (98.6°F). Fever can be a host response to bacterial pathogens. However, bacterial

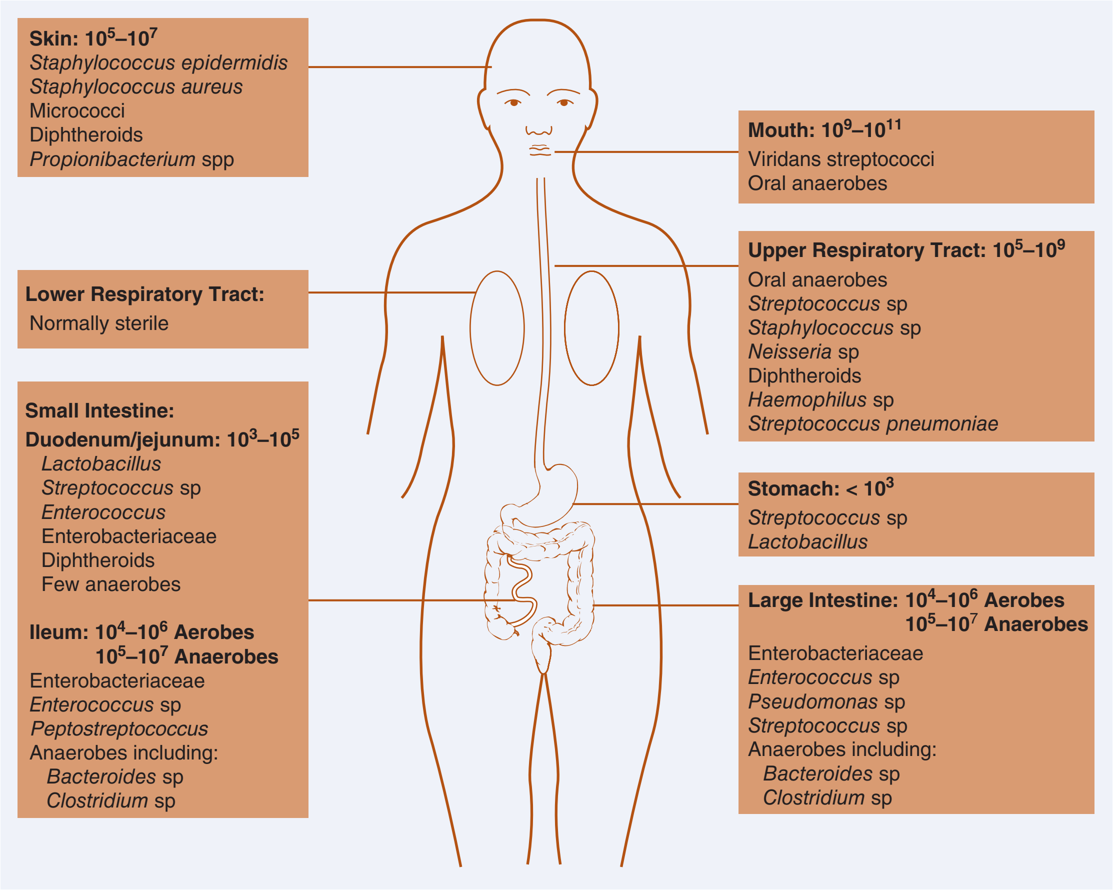
Skin: 10^5–10^7
Staphylococcus epidermidis
Staphylococcus aureus
Micrococci
Diphtheroids
Propionibacterium spp
Mouth: 10^9–10^{11}
Viridans streptococci
Oral anaerobes
Lower Respiratory Tract:
Normally sterile
Upper Respiratory Tract: 10^5–10^9
Oral anaerobes
Streptococcus sp
Staphylococcus sp
Neisseria sp
Diphtheroids
Haemophilus sp
Streptococcus pneumoniae
Small Intestine:
Duodenum/jejunum: 10^3–10^5
Lactobacillus
Streptococcus sp
Enterococcus
Enterobacteriaceae
Diphtheroids
Few anaerobes
Ileum: 10^4–10^6 Aerobes
10^5–10^7 Anaerobes
Enterobacteriaceae
Enterococcus sp
Peptostreptococcus
Anaerobes including:
Bacteroides sp
Clostridium sp
Stomach: < 10^3
Streptococcus sp
Lactobacillus
Large Intestine: 10^4–10^6 Aerobes
10^5–10^7 Anaerobes
Enterobacteriaceae
Enterococcus sp
Pseudomonas sp
Streptococcus sp
Anaerobes including:
Bacteroides sp
Clostridium sp

FIGURE 72–1. Microbiome.

Clinical Presentation

- Review of symptoms consistent with an infectious etiology.
- Signs and symptoms may be nonspecific (eg, fever) or specific.
- Signs and symptoms that are disease-state specific are reviewed in disease state–specific chapters.

Patient History

- History of present illness (HPI)
- Comorbidities
- Current medications
- Allergies
- Previous antibiotic exposure
- Previous hospitalization or health care utilization
- Travel history
- Social history
- Pet/animal exposure
- Occupational exposure
- Environmental exposure
- Dietary exposure

Physical Findings

- Vital signs
- Physical examination

Diagnostic Imaging

- X-rays
- CT scans
- MRI

Other Nonmicrobiological Laboratory Studies:

- White blood cell count (WBC) with differential
- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)
- Procalcitonin

Microbiologic Studies: (should be site-specific based on presumed source of infection)

- Gram stain
- Culture and susceptibility testing
    - Rapid diagnostic tests

infections are not the sole cause of fever. Fever also may be caused by fungal or viral infections, or noninfectious etiologies such as medications (eg, penicillins, cephalosporins, salicylates, and phenytoin), trauma, or other medical conditions (eg, autoimmune disease, malignancy, pulmonary embolism, and hyperthyroidism). Some patients with overwhelming infections may present with hypothermia. Certain patients may present as afebrile, including the elderly or those with localized infections, such as uncomplicated urinary tract infections (UTI).[5] For others, fever may be the only indication of infection. Fever may be the only finding in neutropenic patients who may not have the ability to mount a normal immune response to infection that can be identified through routine diagnostics.[6]

Imaging Studies

Imaging studies may help to identify the anatomic location of the infection. These studies are usually performed in conjunction with other tests to establish or rule out the presence of an infection. Chest x-rays are performed commonly to establish the diagnosis of pneumonia, as well as the severity of disease. Computed tomography (CT) or magnetic resonance imaging (MRI) may also be obtained when the source of infection is not easily identified by more cost-effective means such as an x-ray (Table 72–1). For more information regarding specific infections, review the chapters for individual infections.

Nonmicrobiological Laboratory Studies

Nonmicrobiological laboratory tests include the white blood cell count (WBC) and differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin levels (Table 72–1). In most cases, the WBC count is elevated (**leukocytosis**), in response to infection, but it may be decreased (**leukopenia**), owing to overwhelming or long-standing infection or diminished host response. The differential is the percentage of each type of WBC (Table 72–2). In response to physiologic stress, neutrophils leave the bloodstream and enter the tissue to "fight" against the offending pathogens resulting in leukocytosis. It is important to recognize that leukocytosis is nonspecific for infection and may temporarily occur in response to noninfectious conditions such as acute myocardial infarction or medications such as steroids. During an infection, bands or immature neutrophils are released at an increased rate to help fight infection, this leads to a "bandemia" or **"left shift."** The WBC count differential is key to determining whether an infection is present as some, particularly elderly, patients may present with a normal total WBC with a left shift. ESR and CRP are nonspecific markers of inflammation that increase as a result of the acute-phase reactant response, which is a response to inflammatory stimuli such as infection or tissue injury. These tests may be used as markers of clinical response because they are elevated when the

Table 72–1

Diagnostics Used in the Evaluation of Infectious Diseases

Vitals (normal value):
  Temperature (37°C /98.6°F)
  Blood pressure (≤ 120/80)
  Heart rate (60–100 beats per minute)
  Respiratory rate (12–20 beats per minute)
Laboratory (normal value):
  White blood cells/WBC (4500–11,000 cells/mm^3)
  C-reactive protein/CRP (< 10 mg/L)
  Erythrocyte sedimentation rate/ESR (< 20 males/< 30 females)
  Procalcitonin (< 0.15 ng/mL)
Imaging studies that may be used to identify an infection:
  X-rays
  CT
  MRI

Table 72–2

WBC and Differential

Type of Cell	Normal Value % (or Fraction)	Function	Abnormalities
Neutrophil	Segs 40–60 (0.40–0.60) Bands 3–5 (0.03–0.05)	Phagocytic	Leukocytosis • Bacterial infections • Fungal infections • Physiologic stress • Tissue injury (eg, myocardial infarction) • Medications (eg, corticosteroids) Leukopenia • Long-standing infection • Cancer • Medications (eg, chemotherapy)
Lymphocyte	20–40 (0.20–0.40)	T cells (cell-mediated immunity) B cells (humoral antibody response)	Lymphocytosis • Viral infections (eg, mononucleosis) • Tuberculosis • Fungal infections Lymphopenia • HIV
Monocyte	2–8 (0.02–0.08)	Phagocytic precursor to macrophage	Monocytosis • Tuberculosis • Protozoal infections • Leukemia
Eosinophil	1–4 (0.01–0.04)	Antigen-antibody reactions	Eosinophilia • Hypersensitivity reactions, including medications • Parasitic infections
Basophil	< 1 (0.01)		Hypersensitivity reactions

disease is acutely active and usually fall in response to successful treatment. This is particularly relevant in infections such as osteomyelitis and infective endocarditis where it is difficult to monitor response to therapy. These tests should not be used to diagnose infection because they may be elevated in noninfectious inflammatory conditions. Procalcitonin, a prohormone of calcitonin, is rapidly produced in response to bacterial infection. More recent data suggests that procalcitonin serum levels, in conjunction with clinical findings, may be a tool to assess when antibiotic therapy may be safely discontinued. American Thoracic Society/Infectious Disease Society of America guidelines on hospital/ventilator associated pneumonia suggest that procalcitonin levels may be used in addition to clinical criteria to guide antimicrobial discontinuation. Additionally, the Surviving Sepsis Guidelines recommend procalcitonin as an adjunctive tool for antibiotic discontinuation in patients without other indicators of infection.[7,8] However, procalcitonin should not be used as an indicator for antimicrobial therapy initiation. Community-acquired pneumonia (CAP) guidelines, also from the American Thoracic Society/Infectious Disease Society of America, recommend that the determination for antibiotic therapy be based off of clinically and radiologically confirmed CAP regardless of procalcitonin.[9]

Patient Encounter 1

HPI: BD is a 56-year-old woman with a 4-day history of an initial dry cough that is now productive, shortness of breath, fevers of 37.8°C to 38.7°C (100°F–101.7°F), malaise, and new right-sided chest pain. She also reports reduced oral intake due to feeling so poorly. She thought she had a cold but now feels significantly worse despite taking over-the-counter cough and cold medication and acetaminophen. Her past medical history includes diabetes, hypertension, hyperlipidemia, and hypothyroidism. She has a history of recurrent urinary tract infections and has received multiple antimicrobials in the previous 6 months including levofloxacin 3 weeks ago.

Allergies: NKDA

Meds:

Metformin 1000 mg ER PO twice daily

Sitagliptin 100 mg PO daily

Hydrochlorothiazide 25 mg PO daily

Lisinopril 10 mg PO daily

Atorvastatin 20 mg PO daily

Levothyroxine 100 mcg PO daily

Nyquil Cold & Flu Nighttime Relief (acetaminophen, dextromethorphan, and doxylamine)

Acetaminophen 500–1000 mg PO Q6–8 hours

What information in the history supports an infectious etiology?

Is this patient at risk for resistant pathogens? Why?

Microbiologic Studies

Microbiologic studies that allow for direct examination of a specimen may aid in a presumptive diagnosis and give an indication of the characteristics of the infecting organism. Specimens that may be collected for culture may include sputum, blood, or urine.

A Gram stain of collected specimens can give rapid information that can be applied immediately to patient care. A Gram stain may identify whether bacteria are present and determine bacterial morphologic characteristics (eg, gram-positive or gram-negative and shape—cocci, bacilli, coccobacilli). The presence of WBCs on a Gram stain indicates inflammation and suggests that the identified bacteria are pathogenic. The Gram stain may be useful in evaluating a sputum specimen's adequacy. For example, the presence of epithelial cells on sputum Gram stain suggests that the specimen is either poorly collected or contaminated. A poor specimen can give misleading information regarding the underlying pathogen and may result in inappropriate antimicrobial use. Certain bacterial specimens do not stain well or at all and must be identified by alternative staining techniques. Some examples of these specimens are *Mycoplasma* spp., *Legionella* spp., and *Mycobacterium* spp. Figure 72–2 identifies bacterial pathogens classified by Gram stain and morphologic characteristics.

Culture and susceptibility testing provide additional information to the clinician to select appropriate therapy. When a pathogen is identified, susceptibility tests can be performed to various antimicrobial agents. The minimum inhibitory concentration (MIC) is a standard susceptibility test. The MIC is the lowest concentration of antimicrobial that inhibits visible bacterial

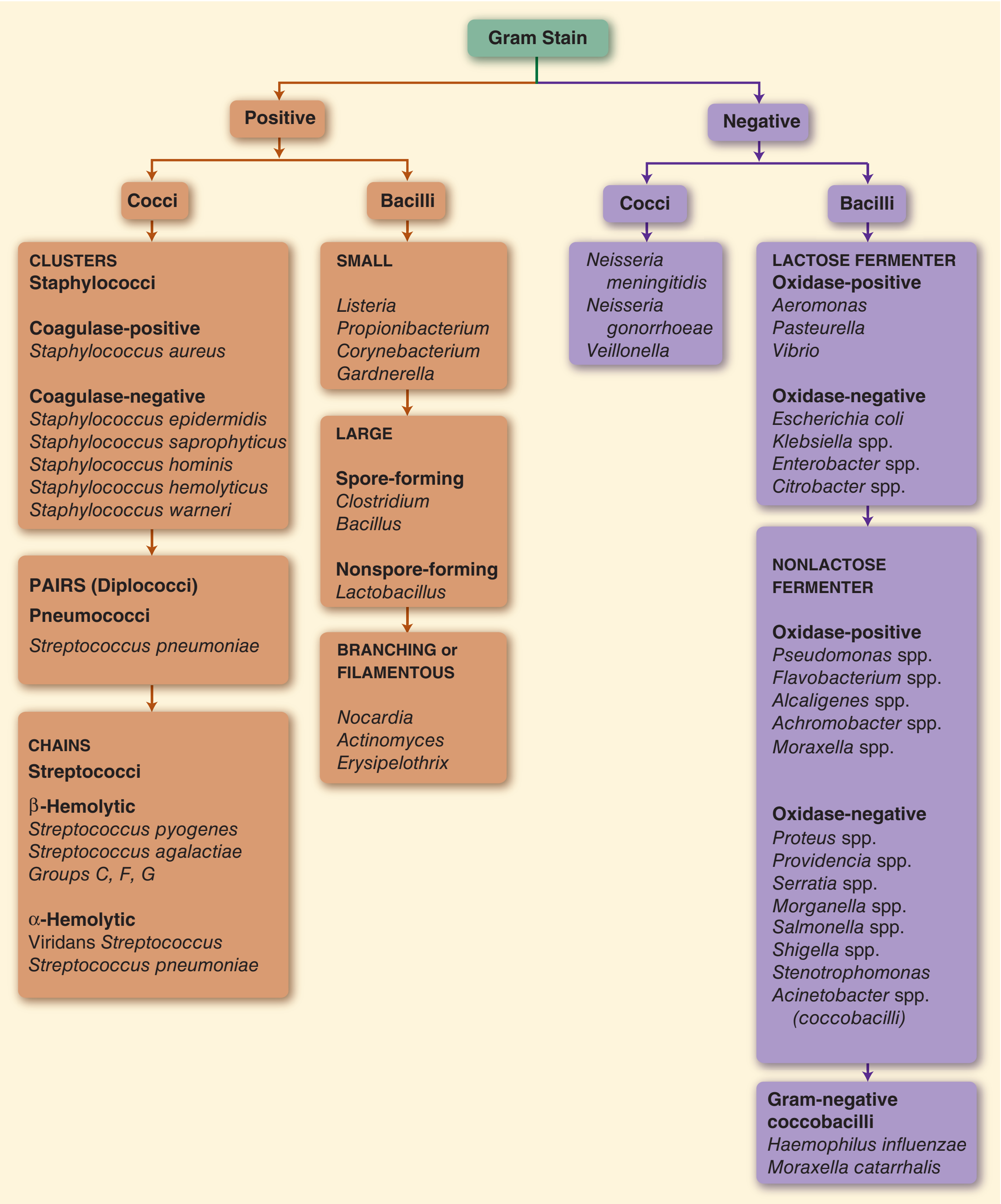
Gram Stain
Positive
Negative
Cocci
Bacilli
Cocci
Bacilli
CLUSTERS
Staphylococci
Coagulase-positive
Staphylococcus aureus
Coagulase-negative
Staphylococcus epidermidis
Staphylococcus saprophyticus
Staphylococcus hominis
Staphylococcus hemolyticus
Staphylococcus warneri
PAIRS (Diplococci)
Pneumococci
Streptococcus pneumoniae
CHAINS
Streptococci
β-Hemolytic
Streptococcus pyogenes
Streptococcus agalactiae
Groups C, F, G
α-Hemolytic
Viridans Streptococcus
Streptococcus pneumoniae
SMALL
Listeria
Propionibacterium
Corynebacterium
Gardnerella
LARGE
Spore-forming
Clostridium
Bacillus
Nonspore-forming
Lactobacillus
BRANCHING or FILAMENTOUS
Nocardia
Actinomyces
Erysipelothrix
Neisseria meningitidis
Neisseria gonorrhoeae
Veillonella
LACTOSE FERMENTER
Oxidase-positive
Aeromonas
Pasteurella
Vibrio
Oxidase-negative
Escherichia coli
Klebsiella spp.
Enterobacter spp.
Citrobacter spp.
NONLACTOSE FERMENTER
Oxidase-positive
Pseudomonas spp.
Flavobacterium spp.
Alcaligenes spp.
Achromobacter spp.
Moraxella spp.
Oxidase-negative
Proteus spp.
Providencia spp.
Serratia spp.
Morganella spp.
Salmonella spp.
Shigella spp.
Stenotrophomonas
Acinetobacter spp. (coccobacilli)
Gram-negative coccobacilli
Haemophilus influenzae
Moraxella catarrhalis

FIGURE 72–2. Important bacterial pathogens classified according to Gram stain and morphologic characteristics. (From Werth et al,. Laboratory tests to direct antimicrobial pharmacotherapy. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020.)

growth after approximately 24 hours. Breakpoint and MIC values determine whether the organism is susceptible (S), intermediate (I), or resistant (R) to an antimicrobial. If the MIC is below the breakpoint, the organism is considered to be susceptible to that agent. If the MIC is above the breakpoint, the organism is said to be intermediate or resistant. Reported culture and susceptibility results may not provide MIC values but generally report the S, I, and R results. When reviewing culture and susceptibility reports, it is important to also consider the other factors discussed in this chapter when selecting an antibiotic. Additionally, susceptibility reports generally only report one in a class of drugs and may not represent all available and appropriate treatment options.

KEY CONCEPT In general, bacterial cultures should be obtained prior to initiating antimicrobial therapy in patients with a systemic inflammatory response, risk factors for antimicrobial resistance, or infections where diagnosis or pathogen is uncertain. The decision to collect a specimen for culture depends on the physical and diagnostic findings, and whether or not the pathogens are readily predictable. For example, culture and susceptibility testing usually is not warranted in a young; otherwise, healthy woman who presents with signs and symptoms consistent with a UTI because the primary pathogen, *Escherichia coli*, is readily predictable. Conversely, cultures and susceptibility testing are routine for sterile-site specimens such as blood or spinal fluid in a patient with concerns for meningitis as well as for material from joints or abscesses that is presumed to be infected.

Rapid diagnostic tests are tools that can quickly identify pathogens and certain antimicrobial resistance patterns in minutes to hours. This can lead to the use of more effective and targeted antimicrobial therapy and reduce unnecessarily prolonged empiric antimicrobial therapy. These tests are best utilized in conjunction with an antimicrobial stewardship team who can properly interpret, assess, and apply to the patient. Studies have shown teamwork between the microbiology lab and antimicrobial stewardship can lead to improved clinical outcomes and reduction in unnecessary antimicrobial use.[10] Available rapid diagnostic tests include, but are not limited to, staphylococcus species, Group A *Streptococcus*, enterococcus, *Clostridioides difficile*, influenza, common respiratory viral pathogens, and extended-spectrum beta-lactamase or carbapenemase-producing Enterobacterales (formerly Enterobacteriaceae). For example, a rapid diagnostic test that can distinguish a coagulase negative staphylococcus from *Staphylococcus aureus* in blood cultures may allow for discontinuation of vancomycin if coagulase negative staphylococcus is deemed to be a contaminant rather than a true pathogen. With conventional cultures, this identification could take up to 2 to 4 days, during which the patient could be receiving suboptimal or inappropriate antimicrobial therapy.

TREATMENT

General Approach to Treatment, Including Nonantimicrobial Treatment

While antimicrobial therapy selection may be a major consideration in treating infectious diseases, it may not be the only therapeutic intervention. Other important therapies may include hydration, ventilatory support, supportive medications, and source control. Source control can be equally or more important than antimicrobials for the treatment of certain infectious diseases. Source control could involve drainage of an abscess or removal of infected tissue or prosthetic materials, such as catheters.

Antimicrobial Considerations in Selecting Therapy

When selecting antimicrobial therapy, it is important to recognize that there are many different antimicrobial regimens that will treat the infection. However, the optimal therapy will address both drug-specific and patient-specific factors to maximize therapeutic efficacy while minimizing potential adverse effects. The following therapy sections provide general factors to consider when selecting antimicrobial regimens. However, excellent and more in-depth resources for selecting specific antimicrobial regimens for a variety of infectious diseases are available through the guidelines developed by national or international organizations, such as the Infectious Diseases Society of America.[11]

KEY CONCEPT Drug-specific considerations in antimicrobial selection include spectrum of activity, collateral damage as it applies to effects on the microbiome, appropriate dose, pharmacokinetic and pharmacodynamic properties, adverse-effect and drug-interaction profile, and cost (Table 72–3).

Table 72–3

Considerations for Selecting Antimicrobial Regimens

Drug-Specific	Patient-Specific
Spectrum of activity and effects on microbiome	Anatomic location of infection
Dosing	Antimicrobial history
Pharmacokinetic properties	Drug allergy history
Pharmacodynamic properties	Renal and hepatic function
Adverse-effect potential	Concomitant medications
Drug-interaction potential	Pregnancy or lactation
Cost	Compliance potential

▶ *Spectrum of Activity*

Initial antimicrobial therapy should target the most likely pathogens based upon infection site as well as local resistance patterns based upon antibiograms. Because of the time required for cultures to identify a pathogen, most initial antimicrobial therapy is empiric. Prompt initiation of appropriate therapy is paramount in hospitalized patients with suspected infection, especially those who are critically ill. Patients who receive appropriate initial antimicrobial therapy survive at twice the rate of patients who receive inadequate therapy.[12] Empiric selection of antimicrobial spectrum of activity should be based on the pathogens most likely causing the infection as well as the severity of the illness. As acutely ill

Patient Encounter 2: Review of Symptoms, Physical Examination, and Laboratory Data

ROS: She has been experiencing a productive cough, shortness of breath, fevers, and chest pain. She denies urinary urgency or pain upon urination, nausea, or vomiting.

PE:

VS: BP 156/88 P110, RR 28, T 38.8°C, O_2 saturation on room air 86%, Ht 5 ft 2 in (157.5 cm), Wt 82 kg

Chest: Rhonchi with decreased breath sounds

CV: Tachycardic with regular rate and rhythm

Labs:

WBC $16.8 \times 10^3/\text{mm}^3$ (16.8×10^9/L), segs 76% (0.76), bands 17% (0.17), lymphs 7% (0.07)

SCr 1.6 mg/dL (142 μmol/L)

Glucose 297 mg/dL (16.5 mmol/L)

Procalcitonin 1.0 mcg/L

Sputum gram-stain: < 10 epis/lpf, > 25 WBCs/lpf, gram-positive cocci

Sputum culture: Pending

Chest radiography: right lower lobe infiltrate

What findings on physical examination are suggestive of an infectious process?

What laboratory findings and/or diagnostic studies have been performed to help establish the presence of an infection?

Are the findings of these laboratory and diagnostic studies suggestive of an infection?

What is your working diagnosis based on this patient encounter?

patients are at risk for more virulent pathogens, they generally require more broad-spectrum initial coverage.[7]

Collateral damage is defined as the alterations in a patient's microbiome as a result of antimicrobial therapy that can lead to secondary infections. *Clostridioides difficile* infection (CDI) is an example of a disease that occurs due to collateral damage. Antibiotics, especially high-risk agents such as fluoroquinolones, can increase the risk of CDI by suppressing intestinal microbiome, resulting in overgrowth of *C. difficile*.[13] If several different antimicrobials possess activity against a targeted pathogen, the antimicrobial that is least likely to be associated with collateral damage may be preferred.

▶ *Pharmacodynamic Properties*

Pharmacodynamics describes the relationship between drug exposure and pharmacologic effect. Antimicrobials are classified as either concentration-dependent or time-dependent based upon their activity. Concentration-dependent activity occurs where higher drug concentrations are associated with greater rates and extents of bacterial killing. Concentration-dependent antimicrobial activity is maximized when peak antimicrobial concentrations are high. Fluoroquinolones, aminoglycosides, and metronidazole are examples of antimicrobials that exhibit concentration-dependent activity. For concentration-dependent antimicrobials, such as aminoglycosides, dosing regimens can be optimized to address maximal concentration. One such example of this is extended interval dosing of aminoglycosides. This approach allows for less frequent dosing and thus decreased toxicity while still maintaining optimal efficacy. In contrast, time-dependent (or concentration-independent) activity refers to a minimal increase in the rate or extent of bacterial killing with an increase in antimicrobial dose. Time-dependent antimicrobial activity is maximized when these antimicrobials are dosed to maintain blood and/or tissue concentrations above the MIC in a time-dependent manner. β-Lactam and glycopeptide antimicrobials exhibit time-dependent activity. For time-dependent antimicrobials, such as β-lactams, dosing strategies such as extending the infusion time of the intravenous antimicrobial may be effective for maximizing efficacy.

▶ *Antimicrobial Dose Selection*

Clinicians should be aware that antimicrobial dosage regimens may differ depending on the site of infection as well as the severity of infection. Appropriately dosed regimens are designed for treatment of the diagnosed infection because they have demonstrated proven efficacy and are most likely to minimize harm. For example, ciprofloxacin, a fluoroquinolone, has various dosage regimens based upon the site of infection. The dosing for uncomplicated UTIs is 250 mg twice daily for 3 days. For pyelonephritis, the dose is 500 mg twice daily for 5 to 7 days. Severe complicated hospital-acquired pneumonia may require a dosage regimen of 750 mg twice daily for 7 days.

▶ *Adverse-Effect and Drug-Interaction Properties*

A major concern when selecting antimicrobial regimens should be the propensity for the regimen to cause adverse effects and the potential for drug interactions. When selecting an antimicrobial regimen, the potential for adverse effects should be weighed against perceived benefit. For example, multiple FDA Drug Safety Communications have been released regarding the safety of fluoroquinolones and recommend against the use of fluoroquinolones in uncomplicated infections due to increased risk of severe adverse effects.[14] Risk factors for adverse events may include the coadministration of other drugs that are associated with a similar type of adverse effect. For example, coadministration of the known nephrotoxin gentamicin with vancomycin increases the risk for nephrotoxicity compared with administration of either drug alone.[15] Other drug interactions may predispose the patient to dose-related toxicity through inhibition of drug metabolism. For example, macrolides have the potential to prolong cardiac QT intervals in a dose-dependent manner, potentially increasing the risk for sudden cardiac death. This risk is further increased when combined with other agents that prolong the QT interval such as citalopram, an antidepressant (see Table 72–4 and 72–5).[16]

▶ *Antimicrobial Cost*

A final consideration in selecting antimicrobial therapy relates to cost. When considering antimicrobial therapy, the least expensive antimicrobial is not necessarily the most cost-effective antimicrobial. Direct antimicrobial costs constitute a relatively small portion of the overall cost of care. If efficacy and potential toxicity is comparable between two antimicrobial regimens, the least expensive regimen should be considered. Another consideration related to cost is hospital or insurance formulary. This may dictate options that are available as well as cost to the patient.

Patient Considerations in Antimicrobial Selection

KEY CONCEPT Key patient-specific considerations in antimicrobial selection include recent antimicrobial exposures, identification of the site of infection, history of drug allergies, pregnancy or breast-feeding status, organ dysfunction that may affect drug clearance, immunosuppression, compliance, and the severity of illness (see Table 72–3).

▶ *Pharmacokinetic Properties*

Pharmacokinetics refers to a patient's drug exposure in vivo in terms of absorption, distribution, metabolism, and elimination. Absorption factors that may affect antimicrobial selection include bioavailability as well as route of administration of the antimicrobial. Bioavailability refers to the amount of a medication that reaches the site of action. Drug-related factors that may affect oral bioavailability include the formulation of the antimicrobial and stability of the drug in the gastrointestinal (GI) tract. In patients with systemic signs of infection such as hypotension, an intravenous route of administration should be used. This is because decreased blood flow to the GI tract could lead to decreased absorption of the antimicrobial. For example, in situations where agents are available both orally and intravenously, patients who have a functioning GI tract and are not hypotensive may be given antimicrobials orally. The use of oral antimicrobials with modest bioavailability may be restricted depending upon the severity of illness and anatomic location of the infection. Many agents in the β-lactam class fall into this category. In sequestered infections like meningitis, where higher systemic concentrations of antimicrobials are necessary to reach the infected source or for antimicrobials with poor bioavailability, intravenous (IV) formulations should be used.

Some antimicrobials are bound to proteins in serum. Only unbound drug is biologically active and will distribute freely between tissues. Protein binding is clinically relevant in highly protein-bound antimicrobials ($> 50\%$) as these agents may not be able to penetrate sequestered compartments, resulting in insufficient concentrations to eradicate bacteria. In addition, some drugs may not achieve sufficient concentrations in specific compartments based on distribution characteristics. Fluoroquinolones, such as levofloxacin, penetrate the prostate well and achieve high concentrations, thus they are preferred agents for the treatment of prostatitis.

Table 72–4

Antimicrobial Adverse Drug Reactions

Antimicrobial	Other Agent(s)	Mechanism of Action/Effect	Clinical Management
Aminoglycosides	Neuromuscular blocking agents	Additive adverse effects	Avoid
	Nephrotoxins (N) or ototoxins (O) (eg, amphotericin B [N], cisplatin [N/O], cyclosporine [N], furosemide [O], NSAIDs [N], radiocontrast [N], vancomycin [N])	Additive adverse effects	Monitor aminoglycoside SDC and renal function
Amphotericin B	Nephrotoxins (eg, aminoglycosides, cidofovir, cyclosporine, foscarnet, pentamidine)	Additive adverse effects	Monitor renal function
Azoles	See Ch 139 from Dipiro's 11e		
Chloramphenicol	Phenytoin, tolbutamide, ethanol	Decreased metabolism of other agents	Monitor phenytoin SDC, blood glucose
Foscarnet	Pentamidine IV	Increased risk of severe nephrotoxicity/hypocalcemia	Monitor renal function/serum calcium
Isoniazid	Carbamazepine, phenytoin	Decreased metabolism of other agents (nausea, vomiting, nystagmus, ataxia)	Monitor drug SDC
Macrolides/azalides	Digoxin	Decreased digoxin bioavailability and metabolism	Monitor digoxin SDC; avoid if possible
	Theophylline	Decreased metabolism of theophylline	Monitor theophylline SDC
Metronidazole	Ethanol (drugs containing ethanol)	Disulfiram-like reaction	Avoid
Penicillins and cephalosporins	Probenecid, aspirin	Blocked excretion of β-lactams	Use if prolonged high concentration of β-lactam desirable
Ciprofloxacin/norfloxacin	Theophylline	Decreased metabolism of theophylline	Monitor theophylline
Quinolones	Classes Ia and III antiarrhythmics	Increased Q-T interval	Avoid
	Multivalent cations (antacids, iron, sucralfate, zinc, vitamins, dairy, citric acid), didanosine	Decreased absorption of quinolone	Separate by 2 hours
Rifampin	Azoles, cyclosporine, methadone propranolol, PIs, oral contraceptives, tacrolimus, warfarin	Increased metabolism of other agent	Avoid if possible
Sulfonamides	Sulfonylureas, phenytoin, warfarin	Decreased metabolism of other agent	Monitor blood glucose, SDC, PT
Tetracyclines	Antacids, iron, calcium, sucralfate	Decreased absorption of tetracycline	Separate by 2 hours
	Digoxin	Decreased digoxin bioavailability	Monitor digoxin SDC; avoid if possible

PI, protease inhibitor; PT, prothrombin time; SDC, serum drug concentrations.

Azalides: azithromycin; azoles: fluconazole, itraconazole, ketoconazole, and voriconazole; macrolides: erythromycin and clarithromycin; protease inhibitors: amprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, and saquinavir; quinolones: ciprofloxacin, gemifloxacin, levofloxacin, and moxifloxacin.

Many antimicrobials undergo some degree of metabolism once ingested followed by elimination of active or inactive metabolites. Metabolism may occur via hepatic or other enzymatic processes including the cytochrome P450 system, and may play a role in antimicrobial selection as it relates to patient-specific comorbidities or concomitant drug interactions. The antimicrobial and/or its metabolites then undergo elimination. Route of elimination may be a factor in drug selection for specific infections. For example, sulfamethoxazole/trimethoprim has exclusive renal elimination and thus is an optimal antibiotic for cystitis.

▶ *Age*

Host factors can help to ensure selection of the most appropriate antimicrobial agent. Age can be an important factor in antimicrobial selection as it can affect renal and hepatic function. Populations with diminished renal function include neonates and the elderly. Similarly, hepatic function in the neonate is not fully developed, and drugs that are metabolized by this route may be ineffective or produce adverse effects. For example, sulfonamides and ceftriaxone may compete with bilirubin for binding sites and may result in hyperbilirubinemia and kernicterus. With regards to the elderly population, diminished renal function, increased comorbidities and concomitant medications elevate the risk for adverse effects and drug interactions as it relates to antimicrobial therapy and thus a higher level of vigilance is required when selecting antimicrobials.

▶ *Site of Infection*

Recognizing the presumed site of infection and most common pathogens associated with the infectious source should guide antimicrobial choice, dose, and route of administration. For example, community-acquired pneumonia is caused most commonly by *Streptococcus pneumoniae*, *E. coli* is the primary cause of uncomplicated UTIs, and staphylococci and streptococci are implicated most frequently in skin and skin-structure infections.

Table 72–5

Major Drug Interactions with Antimicrobials

Antimicrobial Class	Adverse Drug Reaction	Monitoring Parameters	Comments
Penicillins	Hypersensitivity reactions and rash, drug fever, diarrhea, emesis, abdominal pain, hepatitis, interstitial nephritis, leukopenia, thrombocytopenia, Coomb's positive-hemolytic anemia, *C. difficile* colitis, electrolyte abnormalities, seizures	Monitor for hypersensitivity reactions (eg, bronchospasm, anaphylaxis, angioneurotic edema, immediate urticaria). During prolonged therapy and/or high-dose regimens, periodically monitor renal function, hepatic function, and CBC	Most serious reaction is immediate IgEmediated anaphylaxis. Incidence is 0.05%, but 5%-10% can be fatal
Cephalosporins	Hypersensitivity reactions and rash, drug fever, diarrhea, interstitial nephritis, Coomb's positive-hemolytic anemia, leukopenia, thrombocytopenia, coagulopathy, hepatitis, *C. difficile* colitis	Monitor for hypersensitivity reactions (eg, bronchospasm, anaphylaxis, angioneurotic edema, immediate urticaria) and rash, renal function, hepatic function, and CBC	Patients with a history of IgE-mediated allergic reactions to penicillins should not receive a cephalosporin
Carbapenems	Hypersensitivity reactions and rash, headache, nausea, diarrhea, seizures, drug fever, eosinophilia, thrombocytopenia, hepatitis, *C. difficile* colitis	Monitor for hypersensitivity reactions (eg, bronchospasm, anaphylaxis, angioneurotic edema, immediate urticaria) and rash, renal function, hepatic function, and CBC	Skin test cross-sensitivity with penicillin reported to be up to 50%, but clinically significant cross-sensitivity reactions in penicillin-allergic patients reported to be as low as 1% Highest incidence of seizures with use of imipenem–cilastatin. More frequent in patients who are elderly, have history of seizure disorders and renal dysfunction
Monobactams	Rash, diarrhea, nausea, hepatitis, thrombocytopenia, *C. difficile* colitis	Monitor renal and hepatic function	May be used in patients with allergy to penicillins/cephalosporins
Aminoglycosides	Tubular necrosis and renal failure, vestibular and cochlear toxicity, neuromuscular blockade, vertigo, anemia, hypersensitivity	Monitor renal function, SDC, serum calcium, magnesium, sodium. Monitor for nausea, vomiting, nystagmus, and vertigo	Nephrotoxicity can be reversible. More frequent in patients with the following risk factors: elderly, history of renal dysfunction, concomitant administration of nephrotoxic drug (ie, cyclosporine, amphotericin B, radiocontrast, vancomycin), and duration of therapy Ototoxicities can be irreversible
Glycopeptides	Red man syndrome, phlebitis, renal dysfunction, neutropenia, leukopenia, eosinophilia, thrombocytopenia, drug fever	Monitor renal function, CBC, and SDC	Red man syndrome is associated with rapid infusion and nonspecific histamine release. May be prevented by prolonging infusions to over at least 60 minutes and pretreatment with antihistamines
Lipopeptides (daptomycin)	Hepatotoxicity, CPK elevation with or without myopathy, diarrhea, eosinophilic pneumonia, *C. difficile* colitis	Monitor LFTs, development of muscle pain/weakness, or neuropathy Obtain serum CPK levels at baseline and weekly (or more frequently in patients with prior or concomitant statin, renal dysfunction, or patients with elevations in CPK)	CPK elevation is dose-dependent. Obtain baseline and weekly CPK levels. Discontinue daptomycin if CPK exceeds 10 times normal level or if patient develops myopathy and CPK >1,000 IU/L (16.7 μkat/L). Consider stopping statin therapy during treatment with daptomycin
Oxazolidinones	Myelosuppression (thrombocytopenia, leukopenia, and anemia), peripheral neuropathy, optic neuropathy, blindness, lactic acidosis, diarrhea, nausea, serotonin syndrome, interstitial nephritis	Monitor for signs and symptoms of serotonin syndrome particularly in patients with prior or concomitant serotonergic agents, CBC with differential. For prolonged therapy, perform visual function tests, monitor visual acuity and visual field defect	Myelosuppression is reversible and associated with treatment duration >2 weeks

(*Continued*)

Table 72–5

Major Drug Interactions with Antimicrobials (*Continued*)

Antimicrobial Class	Adverse Drug Reaction	Monitoring Parameters	Comments
Tetracyclines	GI upset, nausea, vomiting, diarrhea, hepatotoxicity, esophageal ulcerations, photosensitivity, azotemia, visual disturbances, vertigo, hyperpigmentation, deposition on teeth, hemolytic anemia, pseudotumor cerebri, pancreatitis, *C. difficile* colitis	Monitor CBC with differential, LFTs, and renal function	Doxycycline preferred in patients with renal dysfunction Vestibular symptoms more frequent in women than in men Avoid use during pregnancy and in children
Chloramphenicol	Myelosuppression, aplastic anemia, "gray baby syndrome," optic neuritis, peripheral neuropathy, digital paresthesias, GI upset, *C. difficile* colitis, hypersensitivity	Obtain baseline CBC with differential and every 2 days during therapy. Monitor SDC (particularly in children and in patients with hepatic or renal insufficiency), liver and renal function	Bone marrow suppression associated with doses >4 g/day. Serum levels >50 mcg/ mL (mg/L; 155 μmol/L) are associated with increased risk for "gray baby syndrome"
Rifamycines	Discoloration of urine, tears, contact lens, sweat, hepatotoxicity, GI upset, flu-like syndrome, hypersensitivity, thrombocytopenia, leukopenia, drug fever, interstitial nephritis, thrombocytopenia	Monitor LFTs, bilirubin, renal function, CBC at baseline; continue to monitor every 2–4 weeks in patients with hepatic impairment or receiving concomitant hepatotoxic drugs	Increased potential for hepatitis with concomitant hepatotoxic drugs (ie, TB drugs)
Macrolides/azalide	GI intolerance, diarrhea, prolonged QTc, cholestatic hepatitis, reversible ototoxicity, torsade de pointes, rash, hypothermia, exacerbation of myasthenia gravis	Monitor LFTs and ECG in high-risk patients	
Clindamycin	Diarrhea, *C. difficile* colitis, nausea, vomiting, generalized rash, hypersensitivity	For prolonged therapy, monitor liver and renal function	
Fluoroquinolones	GI intolerance, headache, malaise, insomnia, dizziness, photosensitivity, QTc prolongation, tendon rupture, peripheral neuropathy, crystalluria, seizure, interstitial nephritis, Stevens-Johnson syndrome, allergic pneumonitis, *C. difficile* colitis	Monitor renal function, encephalopathic changes (eg, confusion, hallucinations, and tremor)	Tendon rupture more frequently seen in the elderly and kidney, heart, and lung transplant recipients, and with concurrent use of corticosteroids
Polymyxins	Nephrotoxicity, neurotoxicity (paresthesia, vertigo, ataxia, blurred vision, slurred speech), neuromuscular blockade, bronchospasm (administered via inhalation)	Obtain baseline renal function tests and regularly during therapy. Monitor for signs of neuromuscular blockade (eg, respiratory depression, apnea, muscle weakness)	Nephrotoxicity is dose-dependent
Sulfonamides and trimethoprim	GI intolerance, rash, hyperkalemia, bone marrow suppression (anemia with folate deficiency, thrombocytopenia, and leukopenia), serum sickness, hepatitis, photosensitivity, crystalluria with azotemia, urolithiasis, methemoglobinemia, Stevens-Johnson syndrome, toxic epidermal necrolysis, aseptic meningitis, pancreatitis, interstitial nephritis, Sweet syndrome, neurologic toxicity	Monitor for hypersensitivity reactions and rash, CBC, renal and hepatic function, serum potassium, serum glucose	HIV-infected patients are at increased risk for developing adverse drug reactions Methemoglobinemia due to severe G6PD deficiency
Metronidazole	GI intolerance, headache, metallic taste, dark urine, peripheral neuropathy, disulfiram reactions with alcohol, insomnia, stomatitis, aseptic meningitis, dysarthria	Monitor hepatic function, mental/ neurologic status	Peripheral neuropathy is reversible and associated with prolonged treatment

CBC, complete blood count; CPK, creatine phosphokinase; LFT, liver function test; SDC, serum drug concentrations; TB, tuberculosis.

► *Recent Antimicrobial Use and Risk Factors for Resistant Organisms*

Patients with a history of recent antimicrobial use may have an altered microbiome or harbor resistant organisms (see Table 72–6). If a patient develops a new infection while on therapy or fails therapy, it is reasonable to prescribe either a different class of antimicrobial or alternative agent directed at the most likely pathogens. When selecting an antimicrobial for recurrence of a previously treated infection, review of patient history may reveal a need for broader spectrum coverage or identification of pathogen-specific resistance patterns. Factors associated with the acquisition of nosocomial pathogens include previous hospitalization or recent health care utilization through residing in a nursing home, hemodialysis, and outpatient antimicrobial therapy. Nosocomial pathogens are often resistant organisms.[8,9,17-26]

Table 72–6

Risk Factors for Drug-Resistant Organisms

Pathogen	Risk Factors
Methicillin-resistant *Staphylococcus aureus* (MRSA)	• Hospitalization (current/recent within previous 90 days) • ICU admission • MRSA colonization/prior MRSA infection • Recent antimicrobial agent use within previous 90 days • Residence in nursing home/long-term care facility • Invasive indwelling device (urinary catheter, central venous catheter/intravenous catheter) • Open wounds • Hemodialysis • Intravenous drug user (IVDU) • Sharing towels or athletic equipment • Participation in contact sports
Pseudomonas aeruginosa	• Hospitalization during past 90 days • ICU admission • Pseudomonas infection or colonization in past year • Recent antimicrobial agent use in previous 90 days (increased risk with fluoroquinolones, cephalosporins, carbapenems, β-lactams) • Residence in nursing home/long-term care facility • Severe lung disease (prior tracheostomy, bronchiectasis, very severe COPD) • Corticosteroid exposure • Malignancy • Hemiplegia
Extended Spectrum Beta-Lactamase producing Gram-Negative organisms (ESBLs)	• Hospitalization (recent or > 5 days) • ICU admission • Prior infection or colonization with an ESBL-producing organism • Recent antimicrobial agent use • Invasive procedure (urinary catheter, central venous catheter/intravenous catheter, other surgical procedures) • Residence in nursing home/long-term care facility • Age ≥ 65 • Male sex
Carbapenem-Resistant Enterobacterales[a] (CRE)	• Hospitalization • ICU admission • Prior infection or colonization with another multi-drug-resistant organism • Mechanical ventilation • Recent antimicrobial agent use (increased risk with fluoroquinolones, cephalosporins, carbapenems, aminoglycosides) • Residence in nursing home/long-term care facility • Invasive indwelling device (urinary catheter, central venous catheter/intravenous catheter) • Invasive procedure with a scope (endoscopic retrograde cholangiopancreatography [ERCP], duodenal endoscope)
Fluoroquinolone-resistant organisms	• Hospitalization • Prior use of fluoroquinolone in previous 6 months • Residence in nursing home/long-term care facility • Outpatient procedure in previous 30 days • Diabetes • Hepatic cirrhosis • Chronic respir/aableory disease • Urinary catheter • Recurrent urinary tract infections • Male

[a] Enterobacterales is the order of gram-negative bacteria among which Enterobacteriaceae is included. This terminology is newly proposed, and the two terms are often used interchangeably in the literature.

Patient Encounter 3: Empiric Selection of Antibiotics

Based on the information presented, select an empiric antimicrobial regimen for this patient. Your plan should include:

(a) A tentative infectious diagnosis or source, including likely pathogens or resistant organisms.

(b) A specific antimicrobial regimen, including drug(s), dose, and route of administration.

(c) Description of any ancillary treatments.

(d) A rationale for your empiric antimicrobial selection based on drug- and patient-specific considerations.

Drug Allergies

Antimicrobial allergies are some of the most common drug-related allergies reported and have significant potential to cause adverse events.[27] In particular, reported penicillin-related allergy is common and can be problematic as this contributes to the unnecessary or inappropriate use of other antimicrobial agents. Cephalosporins are preferred therapy for surgical prophylaxis in most cases. Recent data highlights that patients who receive a second-choice antimicrobial as a result of a documented penicillin allergy are more likely to experience adverse effects including surgical site infections.[28] A patient's medical history should be reviewed to determine the offending β-lactam and nature of the allergic reaction. Patients with mild or certain nonimmunologic reactions to penicillins may receive a β-lactam antimicrobial. Non-IgE- mediated findings, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or interstitial nephritis, should not be rechallenged with the offending agent, desensitized to penicillin, or undergo penicillin allergy skin testing. Previously, it was thought that patients with a history of findings consistent with IgE-mediated reactions (type I) such as anaphylaxis, urticaria, or bronchospasm should not be administered any type of β-lactam antimicrobial. However, newer data suggests that β-lactam antimicrobials may be safely administered. Data demonstrate that the actual cross-reactivity between penicillins and cephalosporins is likely less than 1% and slightly lower with carbapenems. Penicillins, cephalosporins, and carbapenems have the β-lactam ring in common; however, it is more likely that the cross-reactivity between penicillins and cephalosporins is secondary to side chain groups (R1 and R2). Therefore, in the majority of patients with a penicillin allergy, cephalosporins with dissimilar side chains, carbapenems, and monobactams may be safely administered.[29,30] Structural side chain similarities among β-lactam agents may be found in the literature.[29] Antimicrobial stewardship programs have worked extensively to improve antibiotic prescribing by delabeling penicillin allergies using various methods, including penicillin skin testing, direct oral challenges, and desensitization.[31]

Renal/Hepatic Function

Renal and/or hepatic function should be considered prior to initiation of antimicrobial therapy. Most antimicrobials undergo renal elimination and dosing adjustments are frequently necessary. Recommendations for dosing adjustments are available in the literature or tertiary databases.[32] Failure to adjust the antimicrobial dose or interval may result in drug accumulation and adverse effects.

Concomitant Medications

Concomitant administration of other medications may influence the selection of the antimicrobial, dose, and monitoring. Medications that commonly interact with antibiotics include, but are not limited to, warfarin, oral contraceptives, phenytoin, digoxin, multivalent cations (eg, calcium, magnesium, and zinc), and sucralfate. Drug interactions between antimicrobials and other medications may occur via the cytochrome P-450 system, protein-binding displacement, and alteration of vitamin K–producing bacteria. Interactions may result in increased or decreased concentrations of one or both agents, increasing the risk of adverse effects or additive toxicity.

Pregnancy/Lactation

Antimicrobial agents must be used with caution in pregnant and nursing women. Fluoroquinolones, tetracyclines, and sulfonamides pose potential threats to the fetus or infant and avoidance during a specific trimester or the entire pregnancy is warranted. For example, avoidance of trimethoprim/sulfamethoxazole in the first and late third trimester is recommended. Pharmacokinetic variables are also altered during pregnancy. Both the clearance and volume of distribution are increased during pregnancy. As a result, increased dosages and/or more frequent administration of certain drugs may be required to achieve adequate concentrations.[33]

Adherence is essential to ensure efficacy. Patients may stop taking their antibiotics once the symptoms subside and save them for a "future" infection. Self-medication with saved antibiotics may be harmful and contribute to antibiotic resistance. Poor adherence may be due to adverse effects, tolerability, cost, complexity of the regimen, and lack of patient education.

Key considerations in selecting antimicrobial regimens start with obtaining a good patient medical and medication history, recognizing drug-specific adverse-event characteristics, and anticipating potential problems proactively. If it is necessary to use an antimicrobial with a relatively high frequency of adverse effects, informing patients of the risks and benefits of therapy, as well as what to do if an adverse effect occurs, may improve patient adherence and safety.

OUTCOME EVALUATION

Figure 72–3 provides an overview of patient- and antimicrobial agent—specific factors to consider when selecting an antimicrobial regimen. It further delineates monitoring of therapy and actions to take depending on the response to therapy.

After selection and initiation of an antimicrobial regimen, there are additional patient care and monitoring considerations that should be addressed to improve the likelihood of a successful outcome. **KEY CONCEPT** Patient education, de-escalation of antimicrobial therapy based on culture results, monitoring for clinical response as well as adverse effects, and appropriate duration of therapy are important.

Modifying Empiric Therapy Based on Cultures and Clinical Response

If culture results are available, therapy should be de-escalated. Antimicrobial de-escalation generally refers to the discontinuation of antimicrobials that provide a spectrum of activity greater than necessary to treat the infection. De-escalation of empiric therapy may also include discontinuing antibiotics based on clinical criteria and negative culture results, such as the absence of antibiotic-resistant pathogens.[34] The purpose of de-escalating

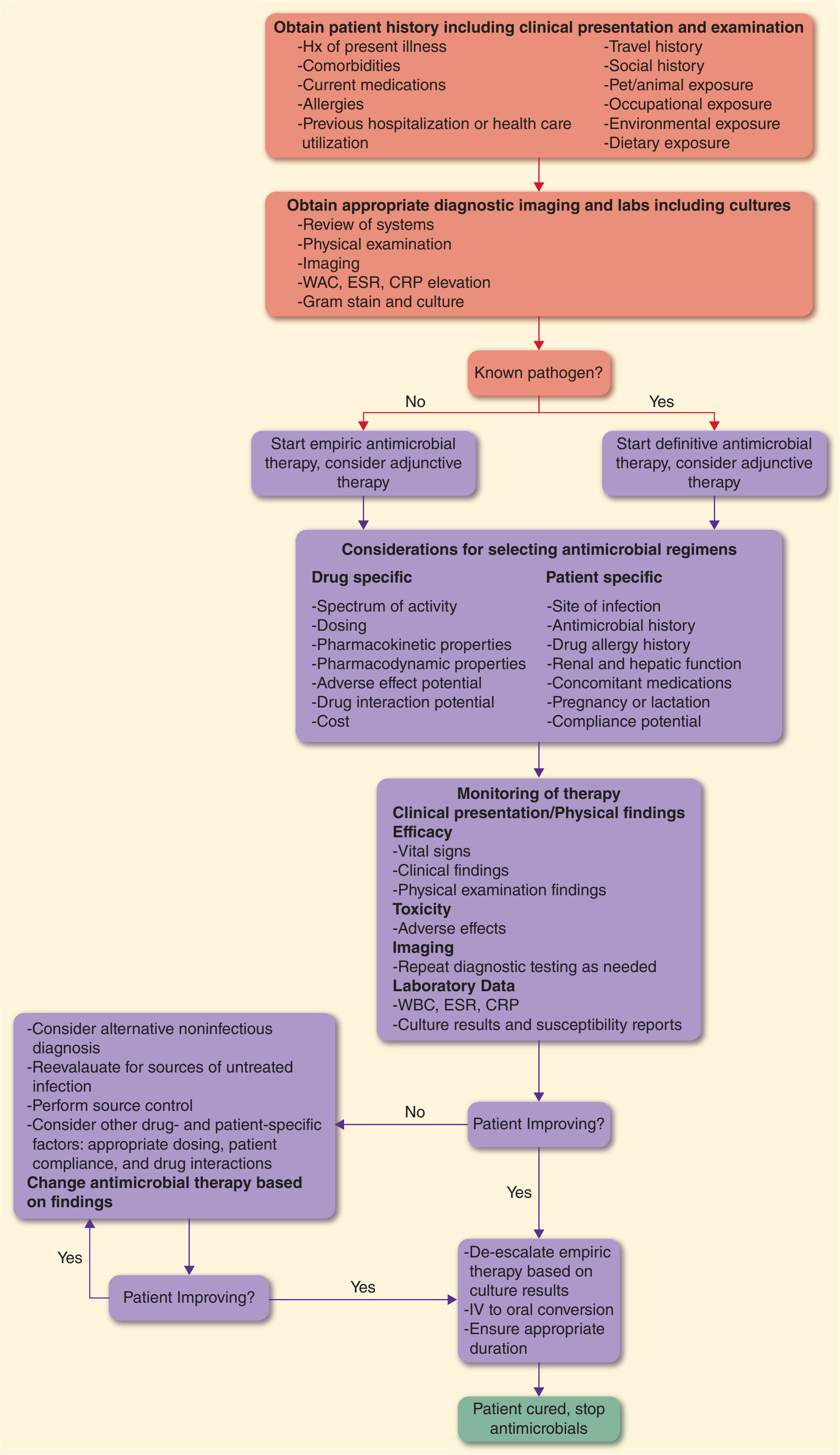
Obtain patient history including clinical presentation and examination
-Hx of present illness
-Comorbidities
-Current medications
-Allergies
-Previous hospitalization or health care utilization
-Travel history
-Social history
-Pet/animal exposure
-Occupational exposure
-Environmental exposure
-Dietary exposure
Obtain appropriate diagnostic imaging and labs including cultures
-Review of systems
-Physical examination
-Imaging
-WAC, ESR, CRP elevation
-Gram stain and culture
Known pathogen?
No
Yes
Start empiric antimicrobial therapy, consider adjunctive therapy
Start definitive antimicrobial therapy, consider adjunctive therapy
Considerations for selecting antimicrobial regimens
Drug specific
-Spectrum of activity
-Dosing
-Pharmacokinetic properties
-Pharmacodynamic properties
-Adverse effect potential
-Drug interaction potential
-Cost
Patient specific
-Site of infection
-Antimicrobial history
-Drug allergy history
-Renal and hepatic function
-Concomitant medications
-Pregnancy or lactation
-Compliance potential
Monitoring of therapy
Clinical presentation/Physical findings
Efficacy
-Vital signs
-Clinical findings
-Physical examination findings
Toxicity
-Adverse effects
Imaging
-Repeat diagnostic testing as needed
Laboratory Data
-WBC, ESR, CRP
-Culture results and susceptibility reports
Patient Improving?
No
-Consider alternative noninfectious diagnosis
-Reevalauate for sources of untreated infection
-Perform source control
-Consider other drug- and patient-specific factors: appropriate dosing, patient compliance, and drug interactions
Change antimicrobial therapy based on findings
Yes
Patient Improving?
Yes
Yes
-De-escalate empiric therapy based on culture results
-IV to oral conversion
-Ensure appropriate duration
Patient cured, stop antimicrobials

FIGURE 72–3. Approach to selection of antimicrobial therapy.

therapy is to prevent the occurrence of adverse events, minimize the risk of *C. difficile* infections and the development of resistance. In cases in which a specific organism is recovered that has a known preferred antimicrobial treatment of choice, therapy might be changed to that specific agent. For example, antistaphylococcal penicillins and first-generation cephalosporins are considered to be the agents of choice for methicillin-susceptible *S. aureus* owing to their bactericidal and narrow-spectrum activity, lower risk for the adverse events, and improved clinical outcomes compared with vancomycin.[35] In other cases, empiric coverage might be discontinued if a specific suspected pathogen is not identified by culture or an alternative, noninfectious diagnosis is established. In addition, IV antimicrobials are associated with an increased risk of adverse events as compared to oral antimicrobials. Therefore, for less severe infections and when patients are clinically stable, it is desirable to convert to oral antimicrobials with a comparable antimicrobial spectrum.[36]

Duration of Therapy

Once the appropriate antimicrobial has been identified, duration of therapy should be considered. Patient clinical response as well as site of infection will help determine the appropriate duration. Studies of several infectious processes have suggested that shorter durations of therapy can result in similar clinical outcomes as longer durations of therapy, frequently with fewer complications or secondary infections.[8,9] In this period of extensive antimicrobial resistance, clinicians should keep abreast of changing recommendations and guidelines emphasizing shorter durations of therapy.

Patient Encounter 4: Patient Care and Monitoring

Update: Ceftriaxone and azithromycin were initiated.

After 48 hours of therapy, the following parameters are obtained:

PE:

VS: BP 132/72, P 70, RR 22, T 37.2°C (98.9°F), O2 saturation on room air of 94%

Labs:

WBC $9.2 \times 10^3/\text{mm}^3$ (9.2×10^9/L)/ differential 85% segs, 10% lymphs, 5% monos

SCr 1.1 mg/dL (97.2 μmol/L)

Glucose 126 mg/dL (6.9 mmol/L)

Sputum culture: *Streptococcus pneumoniae*

Susceptibility Report:

Penicillin MIC 0.25 mcg/mL (breakpoint < 2 mcg/mL)

Ceftriaxone MIC 0.25 mcg/mL (breakpoint < 1 mcg/mL)

Erythromycin MIC 1 mcg/mL (breakpoint 0.25 mcg/mL)

What information suggests improvement in the patient's condition?

Do any of the antimicrobial doses need to be adjusted for changes in organ function?

Should antimicrobial therapy be modified based on the culture results?

Can the antimicrobial therapy be converted from IV to oral therapy?

How long should the duration of antimicrobial therapy be?

Failure of Antimicrobial Therapy

While many infections respond readily to antimicrobials, some infections do not. However, it is important to remember that antimicrobial therapy comprises only a portion of the overall disease treatment, and there may be many factors that contribute to a lack of improvement. Drug- and patient-specific factors such as appropriate dosing, patient compliance, and drug interactions can be associated with therapeutic failure and should be considered. **KEY CONCEPT** In addition, inadequate diagnosis resulting in inappropriate empiric antimicrobial selection, poor source control, or the development of a secondary infection are causes of antimicrobial failure. Failure to improve should warrant broadening the differential diagnosis to include noninfectious causes. Another common cause of failure is poor source control. A diagnostic search for unknown sources of infection, removal of indwelling devices in the infected environment or surgical drainage of abscesses should be undertaken if the patient's condition is not improving. With secondary infections, the patient generally improves, but then relapses and develops a new infection caused by a new pathogen. When a patient fails to respond to initial antibiotic therapy, consideration should be taken to involve an infectious disease physician as studies have shown that specialist involvement improves patient outcomes.[37]

ANTIMICROBIAL STEWARDSHIP

KEY CONCEPT Antimicrobial stewardship promotes the optimal use of antimicrobial agents to reduce the emergence of resistant pathogens, improve the quality of patient care, and reduce costs. Antimicrobial stewardship programs have been implemented in a variety of settings including hospitals, long-term care facilities, and ambulatory care. To reflect the importance of antimicrobial stewardship, a component of Joint Commission accreditation involves creating a program that adheres to the Core Elements of an Antibiotic Stewardship Program. See Table 72–7.

Program leaders are often a physician and a pharmacist trained in infectious diseases. Other key personnel/support include clinicians, infection prevention, quality improvement, microbiology laboratory, information technology, and nursing. However, any clinician can utilize the practices mentioned in this chapter to become an antimicrobial steward. The goal is to support and track optimal antimicrobial use through various interventions and measures. It is imperative that clinicians educate themselves on appropriate use of antimicrobials and become involved in the effort to improve prescribing practices.[34]

Table 72–7

CDC Core Elements of Antibiotic Stewardship Programs

Leadership commitment
Accountability
Drug expertise
Key support groups
Action (implement policies/interventions to improve patient care)
Tracking/reporting antimicrobial use and outcomes
Education

Patient Care Process

Collect Information:

- Review patient symptoms to indicate source of infection.
- Review pertinent patient medical history including significant comorbid conditions.
- Determine patient allergy histories (including reactions and timing).
- Determine and document recent antimicrobial exposure

Assess the Information:

- Review patient labs, including labs obtained for specific infectious syndromes and vital signs.
- Determine if patient has any hardware, prosthetic material or other foreign bodies (eg, central venous catheter, urinary catheter, endotracheal tube).
- Assess the severity of illness.
- Assess patient-specific risk factors based on infection type to aid in determining appropriate empirical therapy.
- Review local antimicrobial susceptibility patterns including antibiograms.

Develop a Care Plan:

- Based on proposed infectious diagnosis combined with above data assessed, select empirical antimicrobial regimen.
- Consider additional diagnostics and culture and susceptibility reports.

Implement the Care Plan:

- Timely antimicrobials are required, especially in those with sepsis.
- Provide patient education regarding importance of adherence to therapy and adverse effects.

Follow-up: Monitor and Evaluate:

- Follow-up on culture and susceptibility reports to determine opportunities to streamline antimicrobial therapy.
- Some antimicrobials may require therapeutic drug monitoring (eg, vancomycin) to evaluate for safety and effectiveness.
- Duration of therapy should be determined based on several factors including but not limited to infection type, culture results, host immune status, and source control (eg, removal of a central venous catheter).

Abbreviations Introduced in This Chapter

CDC	Centers for Disease Control and Prevention
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
HPI	History of present illness
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
PMH	Past medical history
UTI	Urinary tract infection
VRE	Vancomycin-resistant *Enterococcus*
WBC	White blood cell count

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Central Nervous System Infections

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Discuss the pathophysiology of central nervous system (CNS) infections and the impact on antimicrobial treatment regimens (including antimicrobial dosing and CNS penetration).
2. Describe the signs, symptoms, and clinical presentation of CNS infections.
3. List the most common pathogens causing CNS infections and identify risk factors for infection with each pathogen.
4. State the goals of therapy for CNS infections.
5. Outline the initial management strategies for CNS infections.
6. Design appropriate empirical antimicrobial regimens for patients suspected of having CNS infections (taking age, vaccine history, and other patient-specific information into account) caused by each of the following pathogens, and analyze the impact of antimicrobial resistance on both empirical and definitive therapy: *Neisseria meningitidis* meningitis, *Haemophilus influenzae* meningitis, *Listeria monocytogenes* meningitis, group B *Streptococcus* meningitis, gram-negative bacillary meningitis, postneurosurgical infection, CNS shunt infection, herpes simplex encephalitis.
7. Modify empirical antimicrobial regimens based on laboratory data and other diagnostic criteria.
8. Discuss the management of close contacts of patients diagnosed with CNS infections.
9. Identify candidates for vaccines and other prophylactic therapies to prevent CNS infections.
10. Describe the role of adjunctive agents (eg, dexamethasone) in the management of CNS infections.

INTRODUCTION

The term *central nervous system (CNS) infections* describes a variety of infections involving the brain and spinal cord and associated tissues, fluids, and membranes, including meningitis, encephalitis, brain abscess, cerebrospinal fluid (CSF) shunt infections, and postoperative infections. **KEY CONCEPT** CNS infections, such as meningitis, are considered neurologic emergencies that require prompt recognition, diagnosis, and management to prevent death and residual neurologic deficits. Improperly treated CNS infections are associated with high rates of morbidity and mortality. Despite advances in care, the overall mortality of bacterial meningitis in the United States remains at approximately 15%, and at least 10% to 30% of survivors are afflicted with neurologic impairment, including hearing loss, hemiparesis, and learning disabilities.[1,2] Antimicrobial therapy and preventive vaccines have revolutionized management and improved outcomes of bacterial meningitis and other CNS infections dramatically.

EPIDEMIOLOGY AND ETIOLOGY

CNS infections are uncommon and declining in incidence, with a rate of 0.8 per 100,000 persons between 1997 and 2010.[3] However, the severity of these infections demands prompt medical intervention and treatment. CNS infections can be caused by bacteria, fungi, mycobacteria, viruses, parasites, and spirochetes.

Bacterial meningitis is the most common cause of CNS infections. While vaccination has reduced the incidence of disease by many common pathogens, *Streptococcus pneumoniae* (pneumococcus) remains the most common pathogen for bacterial meningitis (0.306 cases per 100,000), followed by *Neisseria meningitidis* (meningococcus, 0.123 cases per 100,000).[3] Staphylococcal species and gram-negative bacteria account for 0.114 and 0.127 cases per 100,000 persons, respectively in the United States.[3] Group B *Streptococcus* (GBS) and *Listeria monocytogenes* remain important causes, but current data on their incidence are lacking.[2] Vaccines directed against bacteria causing meningitis and related infections (eg, pneumonia and ear infections) have reduced the risk of infections due to *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* type B (Hib) dramatically.[2,3] Prior to the availability of Hib conjugate vaccines, Hib meningitis or other invasive disease was documented in one in 200 children by the age of 5 years and due to widespread use, its incidence has decreased such that it is no longer a leading pathogen.[3] Historically, a 7-valent conjugate pneumococcal vaccine (PCV7) was administered, but despite use of the PCV7, *S. pneumoniae* remained the most common pathogen for pediatric bacterial meningitis. In 2010, a 13-valent conjugate pneumococcal vaccine was licensed for use in the United States; however, its impact on the epidemiology of disease in the United States is still unknown. In France, the 13-valent vaccine reduced the incidence of pneumococcal meningitis by 27.4%

and similar reductions were seen in Canada with strains found in the vaccine.[4,5]

Encephalitis may result from viral, bacterial, parasitic, or other noninfectious causes. Herpes simplex virus (HSV) is the most common cause of encephalitis in the United States, accounting for 10% of all cases.[6] The annual incidence of viral encephalitis is 3.5 to 7.4 infections per 100,000 persons.[6] Other pathogens including common bacterial meningitis causes, *Rickettsia* species, enteroviruses, arboviruses, varicella-zoster virus, rotavirus, coronavirus, influenza viruses A and B, West Nile virus, and Epstein-Barr virus may be associated with a meningoencephalopathic presentation.[7] Approximately 20,000 hospitalizations each year are secondary to encephalitis, accounting for $650 million in healthcare costs.[8] Over the past 10 to 20 years, mortality secondary to encephalitis has remained constant, correlating with the increased number of people living with human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS).

Neurosurgical procedures may place patients at risk for meningitis due to bacteria acquired at the time of surgery or in the postoperative period, including *Staphylococcus aureus*, coagulase-negative staphylococci, and gram-negative bacilli. In addition to bacteria, other pathogens may cause meningitis in at-risk patients. Immunocompromised patients, such as solid-organ transplant patients and patients living with HIV infection, are at risk for fungal meningitis with *Cryptococcus neoformans* and encephalitis secondary to *Toxoplasma gondii* and JC virus. Tuberculosis can spread from pulmonary sites to cause clinical disease in the CNS. Life-threatening viral encephalitis and meningitis can occur in otherwise healthy, young individuals, as well as in patients immunocompromised by age or other factors.

Risk factors for CNS infections can be classified as follows:

- *Environmental:* Recent exposures (eg, close contacts with meningitis or respiratory tract infection, contaminated foods), active or passive exposure to cigarette smoke, close living conditions.
- *Recent infection in the patient:* Respiratory infection, otitis media, sinusitis, mastoiditis.
- *Immunosuppression:* Anatomic or functional asplenia, sickle cell disease, alcoholism, cirrhosis, immunoglobulin or complement deficiency, cancer, HIV/AIDS, uncontrolled diabetes mellitus, debilitated state of health.
- *Surgery, trauma:* Neurosurgery, head trauma, CSF shunt, cochlear implant.
- Noninfectious causes of meningitis include malignancy, medications (eg, sulfonamides, nonsteroidal anti-inflammatory drugs [NSAIDs], IV immunoglobulin), autoimmune disease (eg, lupus), and trauma.[6,7]
- The most common pathogens causing bacterial meningitis, by age group and other risk factors, are found in Table 73–1.

Patient Encounter 1, Part 1

NB is a 10-year-old, 35 kg boy without a significant past medical history. He is active in sports and recently returned from a baseball tournament where he lived in shared housing with his teammates. He now presents to the emergency department with a 2-day history of headache, fever, and confusion. Physical findings and laboratory values include temperature of 38.9°C (102°F) and WBC of 18.7×10^3/mm^3 (18.7×10^9/L), with 73% (0.73) polymorphonuclear cells (PMNs). Examination reveals nuchal rigidity and altered mental status. He is up to date on his vaccinations.

What signs and symptoms consistent with meningitis are present in NB?

What causative pathogens should be suspected in NB?

What empiric antimicrobials should be started?

PATHOPHYSIOLOGY

Meningitis is an inflammation of the membranes of the brain and spinal cord (**meninges**) and the CSF in contact with these membranes, whereas encephalitis is an inflammation of the brain tissue. CSF produced in the brain ventricles flows through the subarachnoid space and downward through the spinal cord, insulating and protecting delicate CNS tissue.

To initiate a CNS infection, pathogens must gain entry into the CNS by **contiguous** spread, **hematogenous** seeding, direct inoculation, or reactivation of latent infection. Contiguous spread occurs when infections in adjacent structures (eg, sinus cavities or the middle ear) invade directly through the blood–brain barrier. Hematogenous seeding occurs when a remote infection causes bacteremia that seeds the CSF, such as pneumococcal pneumonia. Reactivation of latent infection results from dormant viral, fungal, or mycobacterial pathogens in the spine, brain, or nerve tracts. Direct inoculation of bacteria into the CNS is the result of trauma, congenital malformations, or complications of neurosurgery.

Once through the blood–brain barrier, pathogens replicate due to limited host defenses in the CNS. Figure 73–1 depicts the pathophysiologic changes associated with meningitis. Neurologic tissue damage is the result of the host's immune reaction to bacterial cellular components, which trigger cytokine production, particularly tumor necrosis factor alpha (TNF-α) and interleukin 1 (IL-1), and other inflammatory mediators.[9] Bacteriolysis resulting from antibiotic therapy further contributes to the inflammatory process. Cytokines increase permeability of the blood–brain barrier, allowing influx of neutrophils and other host defense cells that contribute to the development of cerebral edema and increased intracranial pressure characteristic of meningitis.[10] The increase in intracranial pressure is responsible for the hallmark clinical signs and symptoms of meningitis: headache, neck stiffness, altered mental status, photophobia, and seizures. Untreated, these pathophysiologic changes may result in cerebral ischemia, herniation, and death.

The CNS response to infection is cellular and chemical changes in the CSF. KEY CONCEPT Ideally, lumbar puncture (LP) to obtain CSF for direct examination and laboratory analysis, as well as blood cultures and other relevant cultures, should be obtained before initiation of antimicrobial therapy. However, initiation of antimicrobial therapy should not be delayed if a pretreatment LP cannot be performed.

Normal CSF has a characteristic composition in terms of protein and glucose content, as well as cell count. Table 73–2 lists CSF findings normally observed and in the setting of meningitis.

CLINICAL PRESENTATION AND DIAGNOSIS

A high index of suspicion should be maintained for patients at risk for CNS infections. Prompt recognition and diagnosis are essential so that antimicrobial therapy can be initiated as quickly as possible. A medical history (including risk factors for infection and history of possible recent exposures) and physical

Table 73–1

Most Likely Pathogens and Recommended Empirical Therapy, by Risk Factor, for Bacterial Meningitis[2,24,25]

Predisposing Factor	Most Likely Pathogens	Recommended Empirical Antibiotic Therapy
Age		
Less than 3 months	Group B *Streptococcus* *Escherichia coli* *Klebsiella pneumoniae* *Listeria monocytogenes*	Ampicillin *plus* cefotaxime *or* aminoglycoside
3 months to less than 18 years	*Streptococcus pneumoniae* *Neisseria meningitidis*	Cefotaxime *or* ceftriaxone *plus* vancomycin
18 years to less than 60 years	*S. pneumoniae* *N. meningitidis*	Cefotaxime *or* ceftriaxone *plus* vancomycin
60 years *or* older	*S. pneumoniae* Gram-negative bacilli *L. monocytogenes*	Cefotaxime *or* ceftriaxone *plus* vancomycin *plus* ampicillin
Immunocompromised	*S. pneumoniae* *N. meningitidis* *L. monocytogenes* Gram-negative bacilli (including *Pseudomonas aeruginosa*)	Cefotaxime *or* ceftriaxone *plus* vancomycin *plus* ampicillin (include agents against *Pseudomonas spp.* if suspected with a consideration for double coverage)
Surgery, Trauma		
Postneurosurgical infection	*S. aureus* (including MRSA) Coagulase-negative *Staphylococcus* (including MRSE) Gram-negative bacilli (including *P. aeruginosa*)	
Penetrating head trauma	*S. aureus* (including MRSA) coagulase-negative *Staphylococcus* Gram-negative bacilli (including *P. aeruginosa*)	Vancomycin *or* linezolid *plus* cefepime or ceftazidime *or* meropenem (consider empiric use of two active antibiotics against *Pseudomonas* spp. if suspected)
CSF shunt	Coagulase-negative *Staphylococcus* (including MRSE) *S. aureus* (including MRSA) Gram-negative bacilli (including *P. aeruginosa*)	

MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*.

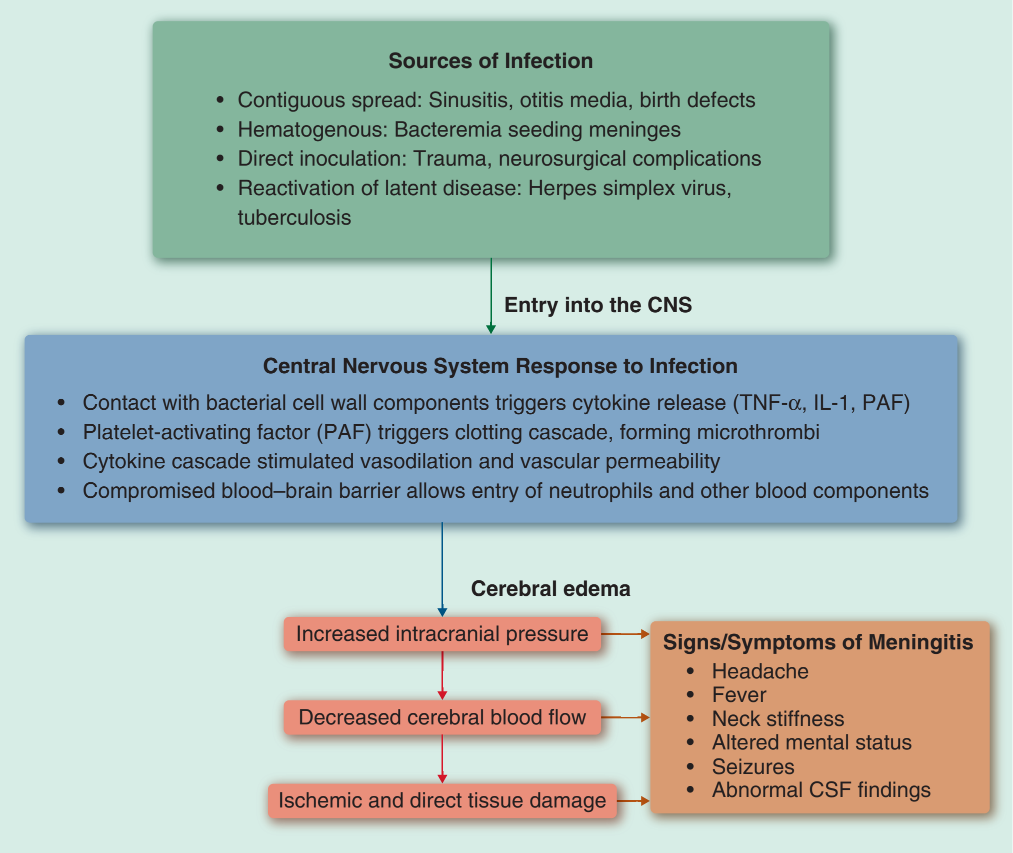
Sources of Infection
• Contiguous spread: Sinusitis, otitis media, birth defects
• Hematogenous: Bacteremia seeding meninges
• Direct inoculation: Trauma, neurosurgical complications
• Reactivation of latent disease: Herpes simplex virus, tuberculosis
Entry into the CNS
Central Nervous System Response to Infection
• Contact with bacterial cell wall components triggers cytokine release (TNF-α, IL-1, PAF)
• Platelet-activating factor (PAF) triggers clotting cascade, forming microthrombi
• Cytokine cascade stimulated vasodilation and vascular permeability
• Compromised blood–brain barrier allows entry of neutrophils and other blood components
Cerebral edema
Increased intracranial pressure
Decreased cerebral blood flow
Ischemic and direct tissue damage
Signs/Symptoms of Meningitis
• Headache
• Fever
• Neck stiffness
• Altered mental status
• Seizures
• Abnormal CSF findings

FIGURE 73–1. Pathophysiology of bacterial meningitis.

Table 73–2

CNS Response to Infection (CSF Findings)

	Normal CSF	Bacterial Infection	Viral Infection	Fungal Infection	Tuberculosis
WBC ($\times 10^3/\text{mm}^3$ *or* $\times 10^9/\text{L}$)	< 0.005	1.0–greater than 5.0	0.1–1	0.1–0.4	50–500
WBC differential (% or fraction in brackets, predominant cell type)	> 85% (0.85) monocytes	At least 80% (0.80) PMNs	50% (0.50) lymphocytes (PMN early)	> 50% (0.50) lymphocytes	> 80% (0.80) lymphocytes (PMNs early)
Protein (mg/dL, mg/L)	20–45 (200–450)	> 100 (> 1000)	50–100 (500–1000)	100–200 (1000–2000)	40–150 (400–1500)
Glucose (mg/dL, mmol/L)	45–80 (2.5–4.4)	5–40 (0.3–2.2)	30–70 (1. 7–3. 9)	< 30–70 (< 1. 7–3. 9)	< 30–70 (< 1. 7–3. 9)
CSF: serum glucose ratio	At least 0.6 serum glucose	< 0.4 serum glucose	At least 0.6 serum glucose	< 0.4 serum glucose	< 0.4 serum glucose
CSF stain	Negative	Positive Gram stain (60%–90%)	Negative	Positive India ink stain (Cryptococcus)	Positive acid-fast bacilli stain
Opening pressure	< 20 mm Hg	> 20 mm Hg	< 20 mm Hg	> 20 mm Hg	> 20 mm Hg

CSF, cerebrospinal fluid; PMNs, polymorphonuclear neutrophils.

From Refs. 5 and 11.

Clinical Presentation and Diagnosis of CNS Infections

General

- Evaluate patient risk factors and recent exposures.
- Evaluate other possible causes: space-occupying lesion (which may *or* may not be malignant), drug-induced CNS pathology autoimmune disease, and trauma.[12,13]

Signs and Symptoms[2]

- Ninety-five percent of patients with bacterial meningitis have two of the following: headache, fever, neck stiffness, and altered mental status.
- Headache (87%)
- Nuchal rigidity (stiff neck) (83%)
- Fever (77%)
- Nausea (74%)
- Altered mental status (ie, confusion, lethargy, and obtundation) (69%)
- Focal neurologic defects (including positive Brudzinski sign and Kernig sign) (33%)
- Seizures
- Malaise, restlessness
- Photophobia
- Skin lesions (diffuse petechial rash observed in 50% of patients with meningococcal meningitis)
- Signs and symptoms in neonates, infants, and young children: nonspecific findings, such as altered feeding and sleep patterns, vomiting, irritability, lethargy, bulging fontanel, seizures, respiratory distress, and petechial/purpuric rash[17]
- Predictors of an unfavorable outcome: seizures, focal neurologic findings, altered mental status, papilledema, hypotension, septic shock, and pneumococcal meningitis[4]

Laboratory Tests[5,18,44]

- CSF examination via lumbar puncture (LP, spinal tap); contraindicated in patients with cardiorespiratory compromise, increased intracranial pressure and papilledema, focal neurologic signs, seizures, bleeding disorders, abnormal level of consciousness, and possible brain herniation (a CT scan should be performed before LP if there is a question of a CNS mass to avoid potential for brain herniation) (see Table 73–2 for specific CSF findings)
- Elevated opening pressure (may be decreased in neonates, infants, and children)
- Cloudy CSF
- Decreased glucose
- Elevated protein
- Elevated WBC (differential provides clues to offending pathogen)
- Gram stain (adequate for diagnosis in 60%–90% of patients with bacterial meningitis)
- Culture and sensitivity (positive in 70%–85% without prior antibiotic therapy, likelihood of positivity reduced by 20% in those who have had prior therapy)
- If CSF Gram stain and/or culture is negative, rapid diagnostic tests (such as latex agglutination) may be useful; these tests are positive even if bacteria are dead
- Polymerase chain reaction (PCR; DNA amplification of the most common bacterial meningitis pathogens) may be useful to help exclude bacterial meningitis
- Elevated CSF lactate and C-reactive protein
- Blood cultures (at least two cultures, one set; positive in 66%)
- Scraping of skin lesions (eg, rash) for direct microscopic examination and culture
- Other cultures should be obtained as clinically indicated (eg, sputum)
- WBC with differential
- Fungal meningitis: CSF culture, CSF and serum cryptococcal antigen titers, microscopic examination of CSF specimens
- Tuberculous meningitis: CSF culture, PCR evaluation (preferred), and acid-fast stain

examination yield important information to help guide the diagnosis and treatment of meningitis. Common signs and symptoms include fever, headache, nuchal rigidity, and photophobia. Infants present with nonspecific signs and symptoms, including excessive irritability or crying, vomiting or diarrhea, tachypnea, altered sleep pattern, and poor eating. Depending on involved pathogens and disease severity, patients may also present with altered mental status, stupor, and seizures.

TREATMENT

Goals of Therapy

Prior to antibiotic therapy and vaccination bacterial meningitis was almost universally fatal, with survivors suffering from debilitating residual neurologic deficits, such as permanent hearing loss.[1,2] Although significant improvements have been made, the fatality rate of meningitis remains above 15% in adults, likely due to its occurrence in debilitated patient populations.[2]

KEY CONCEPT The treatment goals for CNS infections are to prevent death and residual neurologic deficits, eradicate or control causative micro-organisms, ameliorate clinical signs and symptoms, and implement vaccination and suppressive measures to prevent future infections. Surgical debridement should be employed, if appropriate (as in postneurosurgical infections and brain abscess). Supportive care, consisting of hydration, electrolyte replacement, antipyretics, antiemetics, analgesics, antiepileptic drugs, and wound care (for surgical wounds), is an important adjunct to antimicrobial therapy, particularly early in the treatment course.

Treatment Principles

KEY CONCEPT Prompt initiation of IV high-dose bactericidal antimicrobial therapy directed at the most likely pathogen(s) is essential due to the high morbidity and mortality associated with CNS infections. Although there are no prospective studies that relate timing of antibiotic administration to clinical outcome in bacterial meningitis, a longer duration of symptoms and more advanced disease before treatment initiation increase the risk of a poor outcome.[2,11] Initiation of antibiotic therapy as soon as possible after bacterial meningitis is suspected or proven (even before hospitalization) reduces mortality and neurologic sequelae.[11-13]

Patient Encounter 1, Part 2

NB, the 10-year-old patient with signs and symptoms of meningitis underwent lumbar puncture. Initial results from CSF studies are WBC $2 \times 10^3/\text{mm}^3$ ($2 \times 10^9/\text{L}$) with 85% (0.85) PMNs and 39% (0.39) monocytes, protein 182 mg/dL (1820 mg/L), glucose 18 mg/dL (1.0 mmol/L). Gram stain shows gram-positive cocci. Vital signs remain stable in the ED. First doses of antimicrobial therapy are initiated in the ED, and NB is admitted to a pediatric medicine ward for continued treatment and confirmation of final diagnosis. Culture results confirm *Streptococcus pneumoniae* with a penicillin MIC of 1 mg/L and ceftriaxone/cefotaxime susceptibility. Antimicrobials are streamlined and continued for the full duration.

What clues in the CSF results are suggestive of bacterial meningitis?

Would adjunctive steroids offer additional benefit in this patient?

How can his antibiotic regimen be streamlined at this time?

Patient Encounter 1, Part 3

NB has clinically improved on hospital day 3 and would like to be discharged home to continue therapy, but would prefer oral therapy if available. As his teammate's parents learn of his illness, they are concerned about the possibility of their children getting sick and begin to follow up with their own primary care providers. They wonder about medications and vaccinations to prevent the disease.

How long should therapy be continued in NB?

What oral options are viable options for continuation as an outpatient in this case?

Who should receive antimicrobial prophylaxis for Streptococcus pneumoniae?

High-dose parenteral bactericidal antibiotic therapy is required to achieve CSF antibiotic concentrations adequate to rapidly sterilize the CSF and reduce the risk of complications. Data from animal studies and patients demonstrate better outcomes when bactericidal antibiotic therapy (vs bacteriostatic therapy) is used to sterilize the CSF.[14] However, successful treatment of meningitis has been reported with bacteriostatic agents. The presence of infection in the CSF reduces the activity of some classes of antibiotics. For example, the decreased pH of CSF associated with meningitis significantly reduces the activity of aminoglycoside antibiotics.[15]

Antimicrobial pharmacokinetics and pharmacodynamics must be considered when designing treatment regimens for CNS infections. The key of treatment success is the ability of antibiotics to reach and achieve effective concentrations at the infection site. In experimental models of meningitis, maximum bactericidal activity is achieved when CSF concentrations exceed the minimum bactericidal concentration (MBC) of the infecting pathogen by 10- to 30-fold.[16] In general, low-molecular-weight lipophilic antibiotics that are nonionized at physiologic pH and not highly protein bound penetrate best into CSF and other body tissues and fluids.[15,17] In addition to drug characteristics, integrity of the blood–brain barrier determines antibiotic penetration into CSF. The CSF penetration of most, but not all, antibiotics is enhanced by the presence of infection and inflammation. Sulfonamides, trimethoprim, chloramphenicol, rifampin, and most antitubercular drugs achieve therapeutic CSF levels even without meningeal inflammation.[7] Most β-lactams and related antibiotics (ie, carbapenems and monobactams), vancomycin, quinolones, acyclovir, linezolid, daptomycin, and colistin achieve therapeutic CSF levels in the presence of meningeal inflammation.[7] Aminoglycosides, first-generation cephalosporins, second-generation cephalosporins (except cefuroxime), clindamycin, and amphotericin do not achieve therapeutic CSF levels, even with inflammation, but clindamycin does achieve therapeutic brain tissue levels.[7]

An adequate duration of therapy is required to treat meningitis successfully (Table 73–3). **KEY CONCEPT** Parenteral (IV) therapy is administered for the full course of therapy for CNS infections to ensure adequate CSF penetration throughout the course of treatment. Antibiotic treatment (and dexamethasone, if used as a treatment adjunct) reduces the inflammation associated with meningitis, which, in turn, reduces the penetration of some antibiotics into the CSF, and parenteral therapy must be used

Table 73–3

Pathogen-Based Definitive Treatment for CNS Infections[11,24]

Pathogen	Recommended and Alternative Antimicrobial Therapy (Adult Doses)	Adverse Effects/ Safety Monitoring	Renal and Hepatic Dose Adjustment	Duration (Days)
Neisseria meningitidis[a]	*Standard Therapy*			
Penicillin MIC < 0.1 mg/L	Penicillin G 4 million units IV every 4 hours or	Hypersensitivity (rash, anaphylaxis), diarrhea	*Renal*: CrCl < 50 mL/min (0.83 mL/s): 3 million units IV every 4 hours; CrCl < 10 mL/min (0.17 mL/s): 2 million units IV every 4 hours *Hepatic*: No dose adjustment	7
	Ampicillin 2 g IV every 4 hours	Hypersensitivity (rash, anaphylaxis), diarrhea	*Renal*: CrCl < 50 mL/min (0.83 mL/s): 2 g IV every 8 hours; CrCl < 30 mL/min (0.50 mL/s): 2 g IV every 12 hours; CrCl < 10 mL/min (0.17 mL/s): 2 g IV every 24 hours *Hepatic*: No dose adjustment	
	Alternative Therapies			
	Ceftriaxone 2 g IV every 12 hours or	LFT elevation, cholecystitis	*Renal*: No dose adjustment *Hepatic:* Caution in severe hepatic impairment	
	Cefotaxime 2 g IV every 4 hours	Pseudocholelithiasis	*Renal*: CrCl < 80 mL/min (1.34 mL/s): 2 g IV every 6–8 hours; CrCl < 50 mL/min (0.83 mL/s): 2 g IV every 8–12 hours; CrCl < 30 mL/min (0.50 mL/s): 2 g IV every 12 hours; CrCl < 10 mL/min (0.17 mL/s): 2 g IV every 24 hours *Hepatic:* No dose adjustment	
Penicillin MIC 0.1–1 mg/L	*Standard Therapy*			
	Ceftriaxone *or* cefotaxime			
	Alternative Therapies			
	Moxifloxacin 400 mg IV every 24 hours *or*	Nausea/vomiting/diarrhea, dizziness, headache, QT prolongation	*Renal*: No dose adjustment *Hepatic*: Caution in severe hepatic impairment	
	Meropenem 2 g IV every 8 hours *or*	Rash, hypersensitivity, diarrhea, decreased seizure threshold	*Renal*: CrCl < 50 mL/min (0.83 mL/s): 2 g IV every 12 hours; CrCl < 30 mL/min (0.50 mL/s): 500 mg to 1 g IV every 12 hours; CrCl < 10 mL/min (0.17 mL/s): 500 mg to 1 g IV every 24 hours *Hepatic*: No dose adjustment	
	Chloramphenicol 1–1.5 g IV every 6 hours	Rash, diarrhea, seizures, anemia, gray baby syndrome, hypersensitivity, neurotoxicity (last choice due to toxicities)	*Renal*: No dose adjustment *Hepatic*: Reduce dose in moderate to severe impairment; consider serum drug monitoring	
Streptococcus pneumoniae				
Penicillin MIC < 0.1 mg/L	*Standard Therapy*			10–14
	Penicillin G *or* ampicillin			
	Alternative Therapies			
	Ceftriaxone *or* cefotaxime *or* chloramphenicol			
Penicillin MIC 0.1–1 mg/L (ceftriaxone/cefotaxime-sensitive strains)	*Standard Therapy*			
	Ceftriaxone *or* cefotaxime			
	Alternative Therapies			
	Cefepime 2 g IV every 8 hours *or* meropenem	Hypersensitivity (rash, anaphylaxis), decreased seizure threshold	*Renal:* CrCl < 50 mL/min (0.83 mL/s): 2 g IV every 12–24 hours; CrCl < 30 mL/min (0.50 mL/s): 1–2 g IV every 24 hours *Hepatic*: No dose adjustment	

(*Continued*)

Table 73–3

Pathogen-Based Definitive Treatment for CNS Infections[11,24] (*Continued*)

Pathogen	Recommended and Alternative Antimicrobial Therapy (Adult Doses)	Adverse Effects/ Safety Monitoring	Renal and Hepatic Dose Adjustment	Duration (Days)
Penicillin MIC 2 mg/L *or* greater	*Standard Therapy* Vancomycin 15 mg/kg IV every 8–12 hours (with dosing based on serum levels) plus ceftriaxone *or* cefotaxime *Alternative Therapies* Moxifloxacin	Vancomycin: rash, red man syndrome (if infused too quickly) nephrotoxicity, thrombocytopenia	*Renal:* CrCl < 50 mL/min (0.83 mL/s): dosing every 24 hours; CrCl < 20 mL/min (0.33 mL/s): dosing based on serum concentrations; all dose adjustments should be made based on serum concentrations *Hepatic:* No dose adjustment	
Cefotaxime/ ceftriaxone MIC at least 1 mg/L	*Standard Therapy* Vancomycin *plus* ceftriaxone *or* cefotaxime *Alternative Therapies* Moxifloxacin			
H. influenzae β-Lactamase-negative	*Standard Therapy* Ampicillin *Alternative Therapies* Ceftriaxone *or* cefotaxime *or* cefepime *or* moxifloxacin *or* chloramphenicol			7
β-Lactamase-positive	*Standard Therapy* Ceftriaxone *or* cefotaxime *Alternative Therapies* Cefepime *or* moxifloxacin *or* chloramphenicol			
Listeria monocytogenes	*Standard Therapy* Ampicillin *or* penicillin G *plus* gentamicin (5 mg/kg/day, dosing based on serum concentrations)	Gentamicin: nephrotoxicity, ototoxicity	*Renal:* CrCl < 60 mL/min (1.00 mL/s): Use of traditional pharmacokinetic dosing; dose adjustments per serum concentrations *Hepatic:* No dose adjustment	21
	Alternative Therapies Trimethoprim-sulfamethoxazole (10–20 mg/kg trimethoprim) IV per day in divided doses every 6–8 hours *or* meropenem	Trimethoprim-sulfamethoxazole: rash, SJS, bone marrow suppression, hepatotoxicity, elevated serum creatinine, hyperkalemia	*Renal*: CrCl < 50 mL/min (0.83 mL/s): 10–15 mg/kg trimethoprim IV per day divided every 8 hours; CrCl < 10 mL/min (0.17 mL/s): 7–10 mg/kg trimethoprim IV per day divided every 8–12 hours *Hepatic:* No dose adjustment	
Streptococcus agalactiae (group B. *Streptococcus*)	*Standard Therapy* Ampicillin *or* penicillin G *Alternative Therapies* Ceftriaxone *or* cefotaxime			14–21
Enterobacteriaceae	*Standard Therapy* Ceftriaxone *or* cefotaxime *Alternative Therapies* Aztreonam 2 g IV every 6–8 hours	Phlebitis, fever, rash, headache, confusion, seizures	*Renal*: CrCl < 50 mL/min (0.83 mL/s): 2 g IV every 8 hours; CrCl < 30 mL/min (0.50 mL/s): 2 g IV every 12 hours; CrCl < 10 mL/min (0.17 mL/s): 1 g IV every 12 hours *Hepatic:* No dose adjustment	
	Moxifloxacin *or* meropenem *or* trimethoprim-sulfamethoxazole *or* ampicillin			

(*Continued*)

Table 73–3

Pathogen-Based Definitive Treatment for CNS Infections[11,24] (*Continued*)

Pathogen	Recommended and Alternative Antimicrobial Therapy (Adult Doses)	Adverse Effects/ Safety Monitoring	Renal and Hepatic Dose Adjustment	Duration (Days)
Pseudomonas aeruginosa	*Standard Therapy* cefepime *or* ceftazidime 2 g IV every 8 hours *or* meropenem (addition of aminoglycoside should be considered)	Hypersensitivity, rash, anemia, neutropenia, eosinophilia, LFT elevation	*Renal*: CrCl < 50 mL/min (0.83 mL/s): 1–2 g IV every 12 hours; CrCl < 30 mL/min (0.50 mL/s): 1–2 g IV every 24 hours; CrCl < 10 mL/min (0.17 mL/s): 1 g IV every 24 hours *Hepatic*: No dose adjustment	
	Alternative Therapies Aztreonam *or* ciprofloxacin 400 mg IV every 8–12 hours (addition of aminoglycoside should be considered)	Nausea/vomiting/diarrhea, dizziness, headache, rash, confusion, seizures	Ciprofloxacin: *Renal*: CrCl < 30 mL/min (0.50 mL/s): 400 mg IV every 24 hours *or* 200 mg IV every 12 hours *Hepatic*: No dose adjustment	
Staphylococcus aureus	*Standard Therapy*			
Methicillin-susceptible	Nafcillin *or* oxacillin 2 g IV every 4 hours	Rash, nausea/vomiting/ diarrhea, acute interstitial nephritis	*Renal*: No dose adjustment *Hepatic*: No dose adjustment (combined renal and hepatic impairment may require dose adjustment)	
	Alternative Therapies Vancomycin *or* meropenem	Rifampin: Hepatotoxicity, red-orange discoloration of body fluids, skin rash, hepatic enzyme induction		
Methicillin-resistant	*Standard Therapy* Vancomycin *plus* Rifampin 600 mg po *or* IV daily if shunt involved		*Renal*: No dose adjustment *Hepatic*: Caution in moderate/severe hepatic impairment	
	Alternative Therapies Linezolid 600 mg IV every 12 hours *or* trimethoprim-sulfamethoxazole	Linezolid: blood dyscrasias, myalgias, arthralgias, neuropathy	*Renal*: No dose adjustment *Hepatic*: No dose adjustment	
Staphylococcus epidermidis	*Standard Therapy* Vancomycin *plus* rifampin 600 mg po *or* IV daily if shunt involved			
	Alternative Therapies Linezolid			
Herpes simplex virus	*Standard Therapy* Acyclovir 10 mg/kg IV every 8 hours (adults); 20 mg/kg IV every 8 hours (neonates)	Nephrotoxicity, crystalluria, nausea/ vomiting, neurotoxicity, phlebitis	*Renal*: CrCl < 50 mL/min (0.83 mL/s): 10 mg/kg IV every 12 hours; CrCl < 30 mL/min (0.50 mL/s): 10 mg/kg IV every 24 hours; CrCl < 10 mL/min (0.17 mL/s): 5 mg/kg IV every 24 hours *Hepatic*: No dose adjustment	
	Alternative Therapy Foscarnet 120–200 mg/kg IV per day in divided doses every 8–12 hours	Nephrotoxicity, electrolyte imbalances, nausea/ vomiting, headache, penile ulceration, thrombophlebitis, seizures	*Renal*: CrCl: 1.0–1.4 mL/min/kg (0.017–0.023 mL/s/kg): 70 mg/kg IV every 12 hours; CrCl: 0.8–1.0 mL/min/kg (0.013–0.017 mL/s/kg): 50 mg/kg IV every 12 hours; CrCl: 0.6–0.8 mL/min/kg (0.010–0.013 mL/s/kg): 80 mg/kg IV every 24 hours; CrCl: 0.5–0.6 mL/min/kg (0.008–0.010 mL/s/kg): 60 mg/kg IV every 24 hours; CrCl: 0.4–0.5 mL/min/kg (0.007–0.008 mL/s/kg): 50 mg/kg IV every 24 hours; CrCl < 0.4 mL/min/kg (0.007 mL/s/kg) *or* < 20 mL/min (0.33 mL/s) not recommended *Hepatic*: No dose adjustment	

(*Continued*)

Table 73–3

Pathogen-Based Definitive Treatment for CNS Infections[11,24]

Pathogen	Recommended and Alternative Antimicrobial Therapy (Adult Doses)	Adverse Effects/ Safety Monitoring	Renal and Hepatic Dose Adjustment	Duration (Days)
Cryptococcus neoformans	Amphotericin B 0.7mg/kg IV daily *plus* flucytosine 100–150 mg/kg/day in divided doses every 6 hours (induction) Fluconazole 400–800 mg (maintenance) Fluconazole 200 mg (secondary prophylaxis)	Amphotericin: nephrotoxicity, electrolyte imbalances Flucytosine: bone marrow suppression, rash Fluconazole: transaminitis; QTc prolongation	*Renal*: Caution in severe renal dysfunction; consider alternative dosing strategy or change to lipid formulation *Hepatic*: No dose adjustment Flucytosine: *Renal*: CrCl 25–50 mL/min (0.42–0.83 mL/s): every 12 hours; CrCl 10–25 mL/min (0.17–0.42 mL/s) every 24 hours; CrCl < 10 mL/min (0.17 mL/s) 12.5 mg/kg every 24 hours *Hepatic*: No dose adjustment Fluconazole *Renal*: CrCl < 50 mL/min (0.83 mL/s) decrease dose by 50% *Hepatic*: Consider 50% reduction in mild-moderate hepatic insufficiency; risk-benefit in severe hepatic dysfunction	
Toxoplasmosis gondii	Pyrimethamine 200 mg po × 1, then 50 mg (< 60 kg) to 75 mg (≥ 60 kg) daily *plus* sulfadiazine 1000 mg (< 60 kg) to 1500 mg (≥ 60 kg) po every 6 hours plus leucovorin 10–25 mg po daily	Pyrimethamine: bone marrow suppression, high-risk for anemia Sulfadiazine: nephrotoxicity, bone marrow suppression, rash, SJS	*Renal*: No dose adjustment *Hepatic*: No dose adjustment *Renal*: CrCl 25–50 mL/min (0.42–0.83 mL/s): every 12 hours; CrCl 10–25 mL/min (0.17–0.42 mL/s) every 24 hours; CrCl less than 10 mL/min (< 0.17 mL/s) caution use due to high risk of crystalluria *Hepatic*: No dose adjustment	

[a] Empiric therapy with a third-generation cephalosporin should be used until in vitro susceptibility data are known.

LFTs, liver function tests; MIC, minimum inhibitory concentration; SJS, Stevens-Johnson syndrome.

throughout the entire treatment course to ensure adequate concentrations. Carefully selected patients who have close medical monitoring and follow-up may be able to receive a portion of their parenteral meningitis treatment on an outpatient basis.[11,18] A management algorithm for adults with suspected bacterial meningitis, as recommended by the Infectious Diseases Society of America (IDSA), is summarized in Figure 73–2.

Empirical Antimicrobial Therapy

After diagnosis, prompt and aggressive antimicrobial therapy with an appropriate empirical treatment is of the utmost importance in patients with suspected CNS infections. In most patients, a diagnostic LP will be performed before beginning antibiotics, but this should never delay initiation of antimicrobials. Antibiotic pretreatment may alter the CSF profile and complicate interpretation. **KEY CONCEPT** Empirical therapy should be directed at the most likely pathogen(s) for a specific patient, taking into account age, risk factors for infection (including underlying disease and immune dysfunction, vaccine history, and recent exposures), CSF Gram stain results, CSF antibiotic penetration, and local antimicrobial resistance patterns. Results of the CSF Gram stain may be used to help narrow empirical therapy for bacterial meningitis. In the absence of a positive Gram stain, empirical therapy should be continued for at least 48 to 72 hours, when meningitis may, in most cases, be ruled out by CSF findings inconsistent with bacterial meningitis, negative CSF culture, and negative polymerase chain reaction (PCR) evaluations. A repeat LP may be useful in the absence of other findings. Table 73–1 outlines recommendations for empirical antibiotic therapy for bacterial meningitis by most likely pathogen(s) and patient risk factors.

Impact of Antimicrobial Resistance on Treatment Regimens for Meningitis

Development of resistance to β-lactam antibiotics, including penicillins and cephalosporins, has significantly impacted the management of bacterial meningitis with one-fifth of CSF isolates resistant to penicillin and 3.5% of isolates resistant to cephalosporins.[19] The Clinical and Laboratory Standards Institute (CLSI) has set a lower ceftriaxone susceptibility breakpoint for pneumococcal CSF isolates (1 mg/L) than for isolates from non-CNS sites (2 mg/L). Empirical treatment regimens now include the combination of a third-generation cephalosporin plus vancomycin. Recognition of relative and high-level resistance to *N. meningitidis* in the laboratory, as well as in clinical treatment failures, has led to greater use of third-generation cephalosporins for empirical therapy of meningococcal meningitis.[3,11] Treatment of suspected or proven β-lactamase-mediated Hib meningitis also requires a third-generation cephalosporin. Increasing rates of methicillin-resistant *S. aureus* (about one-third of staphylococcal CSF isolates) and coagulase-negative staphylococci require the

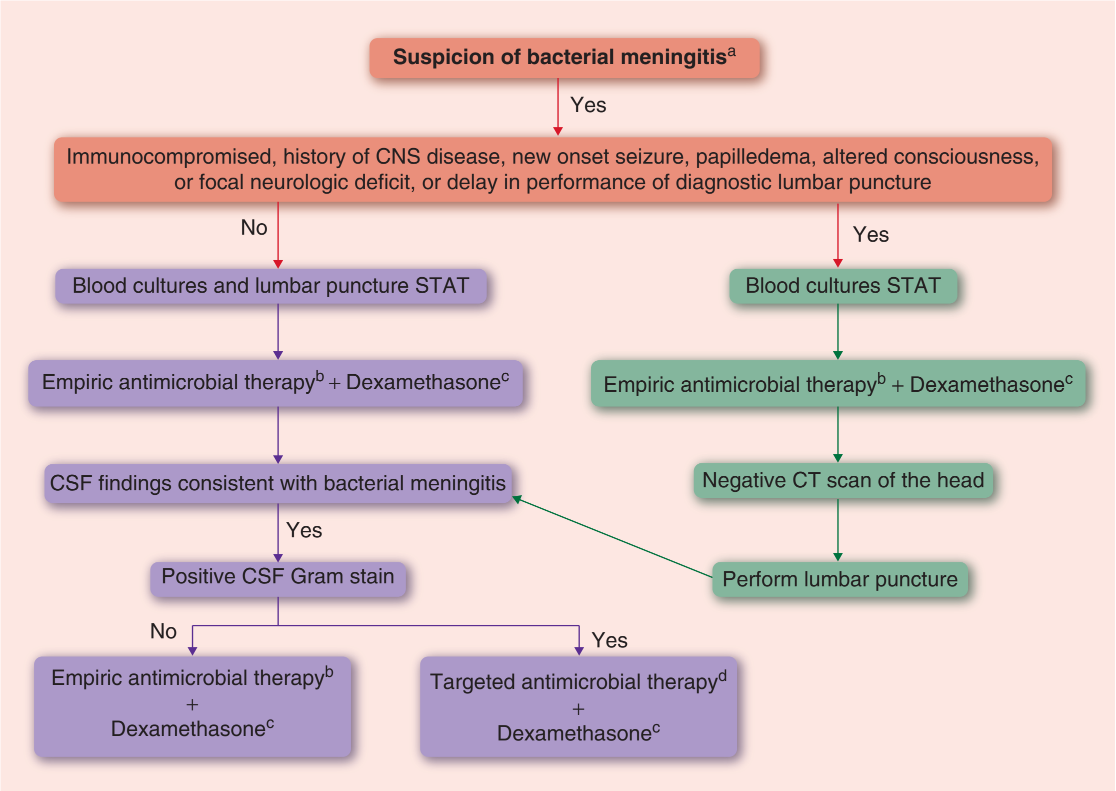
Suspicion of bacterial meningitis[a]
Yes
Immunocompromised, history of CNS disease, new onset seizure, papilledema, altered consciousness, or focal neurologic deficit, or delay in performance of diagnostic lumbar puncture
No
Yes
Blood cultures and lumbar puncture STAT
Blood cultures STAT
Empiric antimicrobial therapy[b] + Dexamethasone[c]
Empiric antimicrobial therapy[b] + Dexamethasone[c]
CSF findings consistent with bacterial meningitis
Negative CT scan of the head
Yes
Perform lumbar puncture
Positive CSF Gram stain
No
Yes
Empiric antimicrobial therapy[b] + Dexamethasone[c]
Targeted antimicrobial therapy[d] + Dexamethasone[c]

FIGURE 73–2. Management algorithm for adults with suspected bacterial meningitis. [a]Management algorithm is similar for infants and children with suspected bacterial meningitis. [b]See Table 73–1 for empirical treatment recommendations. [c]See text for specific recommendations for use of adjunctive dexamethasone in adults with bacterial meningitis. [d]See Table 73–3 for pathogen-based definitive treatment recommendations. (Adapted, with permission, from Moris G, Garcia-Monco JC. The challenge of drug-induced aseptic meningitis. Arch Intern Med. 1999;159:1185–1194.)

use of vancomycin for empirical therapy when these staphylococcal pathogens are suspected.[11,18]

The emergence and continued rise of multidrug-resistant strains of gram-negative organisms such as *Pseudomonas aeruginosa*, *Acinetobacter* species, AmpC, and extended-spectrum β-lactamase (ESBL) producing strains of Enterobacteriaceae have become a recognized threat nationally, and broad-spectrum therapy taking into account local resistance patterns should be used.

Pathogen-Directed Antimicrobial Therapy

KEY CONCEPT Empirical antimicrobial therapy should be modified on the basis of laboratory data and clinical response. If cultures, CSF Gram stain, or antigen/antibody testing indicate a specific pathogen, therapy should be adjusted quickly as needed to ensure adequate coverage for the offending pathogen(s). Table 73–3 outlines recommended definitive pathogen-directed treatment regimens, recommended treatment duration, and key adverse effects that should be monitored during antibiotic therapy for meningitis. Table 73–4 provides pediatric doses of selected agents used in bacterial meningitis treatment.

▶ *Neisseria meningitidis* Meningitis

N. meningitidis CNS infections are decreasing in incidence with 0.1 cases per 100,000 population in the United States in 2018.[20] They most commonly occur in children and young adults. From 10% to 20% of survivors of meningococcal meningitis experience long-term sequelae, including hearing loss, limb loss, and neurologic deficits.[20] Nearly all meningococcal disease is caused by five serogroups: A, B, C, Y, and W-135. In the United States, serotypes B, C, and Y each are responsible for approximately 30% of cases.[3,4]

Meningococcal meningitis is observed most commonly in individuals living in close quarters (eg, college students, military personnel). Infants younger than 1 year are at the highest risk, possibly because pneumococcal vaccination reduces bactericidal antibodies.[21] Children, adolescents, and young adults are also at high risk.[20,22] *N. meningitidis* colonizes the nasopharynx and usually is transmitted via inhaled respiratory droplets from patients or asymptomatic carriers. A subclinical bacteremia typically ensues, seeding the meninges. Meningococcal disease is often (approximately 50%) associated with a diffuse petechial rash, and patients may experience behavioral changes. Patients may develop fulminant meningococcal sepsis, characterized by shock, disseminated intravascular coagulation (DIC), and multiorgan failure.[23] Meningococcal sepsis has a poor prognosis and carries a mortality rate of up to 80%, whereas the mortality rate with meningococcal meningitis alone is 13%.[23,24] Patients with suspected meningococcal infection should be kept on respiratory isolation for the first 24 hours of treatment.[20]

Increasing penicillin resistance requires that third-generation cephalosporins now be used for empirical treatment until *in vitro* susceptibilities are known.[11,15] Patients with a history of type I penicillin allergy or cephalosporin allergy may be treated with vancomycin. Treatment should be continued for 7 days, after which no further treatment is necessary.

Prevention of meningococcal disease by vaccination is a key to reducing the incidence of meningococcal meningitis.

Table 73–4

Pediatric Doses of Selected Agents Used in Bacterial Meningitis Treatment

	Neonates, 0–7 Days	Neonates, 8–28 Days	Infants and Children
Ampicillin	150 mg/kg IV per day in divided doses every 8 hours	200 mg/kg IV per day in divided doses every 6–8 hours	300 mg/kg IV per day in divided doses every 8 hours
Cefepime	—	—	150 mg/kg/day in divided doses every 8 hours
Cefotaxime	100–150 mg/kg IV per day in divided doses every 8–12 hours	150–200 mg/kg IV per day in divided doses every 6–8 hours	225–300 mg/kg/day in divided doses every 6–8 hours
Ceftriaxone	—	—	80–100 mg/kg IV per day in divided doses every 12 hours
Gentamicin	5 mg/kg IV per day in divided doses every 12 hours (with dosing based on serum levels)	7.5 mg/kg IV per day in divided doses every 8 hours with dosing based on serum levels	7.5 mg/kg IV per day in divided doses every 8 hours based on serum levels
Meropenem	—	—	120 mg/kg IV per day in divided doses every 8 hours
Nafcillin/oxacillin	75 mg/kg IV per day in divided doses every 8–12 hours	Nafcillin: 100–150 mg/kg IV per day in divided doses every 6–8 hours; Oxacillin: 150–200 mg/kg IV per day in divided doses every 6–8 hours	200 mg/kg IV per day in divided doses every 6 hours max, 2 g pediatrics > 3 months of age
Penicillin G	0.15 million units/kg IV per day in divided doses 8–12 hours	0.2 million units/kg IV per day in divided doses every 6–8 hours	0.3 million units/kg IV per day in divided doses every 4–6 hours
Vancomycin	20–30 mg/kg IV per day in divided doses every 8–12 hours	30–45 mg/kg IV per day in divided doses every 6–8 hours	60 mg/kg IV per day in divided doses every 6 hours

LFTs, liver function tests; MIC, minimum inhibitory concentration.

Adapted, with permission, from Scheld WM, Koedel U, Nathan B, Pfister HW. Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury. J Infect Dis 2002;186(Suppl 2):S225–S233.

The quadrivalent conjugate meningococcal vaccine protects against four of the five serotypes causing invasive disease (A, C, Y, and W-135). A separate vaccine product confers protection against serogroup B. Meningococcal vaccines can be used in outbreak situations, with protective antibodies measurable within 7 to 10 days. Routine vaccination should be administered between ages 11 and 12 years with a booster dose at age 16 with quadrivalent vaccine that provides protection against serogroups A, C, Y, and W.[20] Additional vaccination against serogroup B can be considered in all patients for short-term disease protection in a shared-decision-making process and is recommended in those with immunocompromising conditions. In addition, individuals aged 2 through 54 years who are immunocompromised (including those with complement deficiencies, who have HIV, or who have asplenia) or those with recent disease exposure during community outbreaks should receive the quadrivalent vaccine and the vaccine against Serogroup B is also recommended for immunocompromised individuals and during outbreaks.[20] Additionally, children less than 2 years may also need quadrivalent vaccine and serogroup B vaccine, depending on risk factors. **KEY CONCEPT** Close contacts of patients with meningococcal infections should be evaluated for antimicrobial prophylaxis. Close contacts include members of the same household, individuals who share sleeping quarters, daycare contacts, and individuals exposed to oral secretions of meningitis patients. After consultation with the local health department, close contacts should receive prophylactic antibiotics to eradicate nasopharyngeal carriage of the organism. Household contacts of patients with meningococcal meningitis have a 400- to 800-fold increased risk of developing meningitis.[23] Prophylactic antibiotics should be started as soon as possible, preferably within 24 hours of exposure and within 14 days. Recommended regimens, all of which are 90% to 95% effective, for adults include rifampin 600 mg orally every 12 hours for 2 days, ciprofloxacin 500 mg orally for one dose, or ceftriaxone 250 mg intramuscularly for one dose. Regimens for children include rifampin 5 mg/kg orally every 12 hours for 2 days (< 1 month of age), rifampin 10 mg/kg orally every 12 hours for 2 days (> 1 month of age), or ceftriaxone 125 mg intramuscularly for one dose (< 12 years of age).[11,23] It is not known whether close contacts who have been vaccinated will benefit from prophylaxis. Patients with meningococcal meningitis who are treated with antibiotics other than third-generation cephalosporins also should be considered for prophylaxis to eradicate the nasopharyngeal carrier state.[22]

▶ *Streptococcus pneumoniae Meningitis*

S. pneumoniae is the most common cause of meningitis in adults and in children younger than 2 years of age. Pneumococcus is associated with the highest mortality observed with bacterial

Patient Encounter 2, Part 1

BB is an 18-year-old college freshman who is brought to the ED with a 1-day history of extreme fatigue and fever. Her roommate brought her to ED because of confusion and vomiting. Vital signs and laboratory values include a rectal temperature of 38.6°C (101.5°F), respirations 24 per minute, heart rate 119 beats/min, and peripheral WBC of $22.1 \times 10^3/mm^3$ ($22.1 \times 10^9/L$), with 72% (0.72) PMNs. Physical examination reveals an unresponsive patient with nuchal rigidity.

What signs and symptoms consistent with meningitis are present in BB?

What clues to causative pathogen are present in BB?

What empiric antimicrobial regimen should be started?

meningitis in adults (14%–18%), and coma and seizures are more common in pneumococcal meningitis.[1-3] Patients at high risk for pneumococcal meningitis include the elderly, alcoholics, post-splenectomy patients, patients with sickle cell disease, and patients with cochlear implants. At least 50% of pneumococcal meningitis cases are due to a primary infection of the ears, sinuses, or lungs.

Due to increases in pneumococcal resistance to high-dose -penicillin G, the preferred empirical treatment now includes a third-generation cephalosporin in combination with vancomycin.[11] All CSF isolates should be tested for penicillin and cephalosporin resistance by methods endorsed by the CLSI. Once *in vitro* sensitivity results are known, therapy may be tailored (see Table 73–3). Patients with a history of type I penicillin or cephalosporin allergy may be treated with vancomycin. Treatment should be continued for 10 to 14 days, after which no further maintenance therapy is required. Antimicrobial prophylaxis is not indicated for close contacts.

Administration of vaccines to high-risk individuals is a key strategy to reduce the risk of invasive pneumococcal disease. Routine use of the 13-valent pneumococcal vaccine (PCV13) has led to sharp declines in pneumococcal disease for adults and children.[25] The 23-valent pneumococcal vaccine targets serotypes that account for more than 90% of invasive disease in high-risk patients. However, the 23-valent vaccine does not produce a reliable immunologic response in children younger than 2 years, nor does it reduce pneumococcal carriage. The 7-valent pneumococcal protein-polysaccharide conjugate vaccine used between 2000 and 2010 targeted the seven most common serotypes in children and provided protection (94% reduction) against invasive pneumococcal disease (such as sepsis and meningitis) in children younger than 5 years.[4,26,27] PCV13, a 13-valent vaccine introduced in 2010, confers protection against additional serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. Due to observed declines in disease with PCV13, it is now recommended that PCV13 be used for children younger than 18 years.[25] For adults aged ≥ 65 years, the 23-valent vaccine should be routinely administered as a single dose. PCV13 vaccination should be considered in immunocompromised adults.[25] Additionally, immunization schedules provided by Centers for Disease Control and Prevention (CDC) are updated at least annually and should be consulted for more details.

▸ *Haemophilus influenzae Meningitis*

Prior to the introduction of the Hib conjugate vaccine, *H. influenzae* type B was the most common cause of bacterial meningitis in the United States.[3,4] Routine inoculation of pediatric patients against Hib has significantly reduced the incidence of Hib meningitis between 1998 and 2007.[3,4] The Hib vaccine is also recommended for patients undergoing splenectomy. Hib meningeal disease is often associated with a parameningeal focus such as a sinus or middle ear infection. Due to β-lactamase–mediated resistance, the empirical treatment of choice is third-generation cephalosporins (eg, ceftriaxone and cefotaxime). Treatment should be continued for 7 days, after which no further maintenance therapy is required.

KEY CONCEPT Close contacts of patients with H. influenzae type B meningitis should be evaluated for antimicrobial prophylaxis. The risk of Hib meningitis in close contacts may be up to 200- to 1000-fold higher than in the general population.[7] Invasive Hib disease, including meningitis, should be reported to the local health department and the CDC. Prophylaxis to eliminate nasal and oropharyngeal carriage of Hib in exposed individuals should be initiated after consultation with local health officials. Rifampin (600 mg/day for adults; 20 mg/kg/day for children, maximum of 600 mg/day) is administered for 4 days.[11,16] Rifampin prophylaxis is not necessary for individuals who have received the full Hib vaccine series. Exposed, unvaccinated children between 12 and 48 months of age should receive one dose of vaccine, and unvaccinated children 2 to 11 months of age should receive three doses of vaccine, as well as rifampin prophylaxis.[11,16]

Patient Encounter 2, Part 2

BB underwent lumbar puncture. Initial results from CSF studies are WBC $1.82 \times 10^3/\text{mm}^3$ ($1.82 \times 10^9/\text{L}$) with 76% (0.76) PMNs, protein 255 mg/dL (2550 mg/L), glucose 30 mg/dL (1.7 mmol/L), with a concurrent serum glucose of 110 mg/dL (6.1 mmol/L). Gram stain shows gram-positive diplococci and culture results identify *Neisseria* infection with a penicillin MIC of 1 mg/L. The patient is admitted to an acute care unit and remains clinically stable.

What complications is BB at risk for acutely? What potential long-term complications may result?

How can her antibiotic regimen be streamlined at this time?

How long should the antibiotics be continued?

▸ *Listeria monocytogenes Meningitis*

L. monocytogenes is an intracellular gram-positive bacillus that contaminates foods, such as soft cheese, unpasteurized milk, raw meats and fish, processed meats, and raw vegetables. Bacteria from contaminated foods colonize the GI tract, pass into the bloodstream, and overcome natural cellular immune responses to cause infection. *L. monocytogenes* meningitis, usually observed in patients at extremes of age and in immunocompromised patients with depressed cellular immunity (including patients with leukemia, solid-organ transplants, and HIV/AIDS) has an overall mortality rate of up to 30% and is associated with miscarriage when infection occurs during pregnancy.[28,29]

Only a limited number of antibiotics show bactericidal activity against *L. monocytogenes*. The combination of high-dose ampicillin or penicillin G and an aminoglycoside is synergistic and bactericidal against *L. monocytogenes*. A total treatment course of at least 3 weeks is required. Because of concerns about the risk of nephrotoxicity with an extended treatment course of aminoglycosides, patients are treated with combination therapy for 10 days and may finish out the remainder of their treatment with ampicillin or penicillin alone.[29] In penicillin-allergic patients, trimethoprim-sulfamethoxazole is the agent of choice due to documented *in vitro* bactericidal activity against *L. monocytogenes*, as well as good CNS penetration. Vancomycin and cephalosporins are not effective treatments for *L. monocytogenes* meningitis. Prophylaxis is not needed for close contacts, nor is suppressive therapy indicated. Patients with severe depression of cell-mediated immunity should be advised to avoid foods that may be contaminated with *L. monocytogenes.*

▸ *Group B Streptococcus Meningitis*

Infection with GBS (eg, *S. agalactiae*) is the most common cause of neonatal sepsis and meningitis. Around 15% to 35%

of pregnant women are a carrier of GBS in the vagina or rectum. Group B streptococci can be acquired during childbirth after exposure to infected secretions from the mother's birth canal or rectum. Neonates born to women who are carriers are at very high risk (1 of every 100–200 babies) of developing invasive group B streptococcal disease.[30] Neonatal meningitis is associated with significant morbidity and mortality. Synergistic treatment with penicillin or ampicillin, plus gentamicin, for 14 to 21 days is recommended for group B streptococcal meningitis.[11]

To reduce the risk of clinical group B streptococcal disease in neonates, pregnant women should be screened at 35 to 37 weeks' gestation to determine whether they are carriers of group B streptococci.[30] Intrapartum antibiotics (eg, penicillin or ampicillin) are recommended for pregnant women with the following characteristics: group B streptococcal carrier state detected at screening, history of group B streptococcal bacteriuria at any time during pregnancy, and history of delivery of infant with invasive group B streptococcal disease.[30]

▶ *Gram-Negative Bacillary Meningitis*

Meningitis caused by enteric gram-negative bacilli is an important cause of morbidity and mortality in populations at risk, including those with diabetes, malignancy, cirrhosis, immunosuppression, advanced age, parameningeal infection, and/or a defect allowing communication from skin to CNS (eg, neurosurgery, congenital defects, cranial trauma).[7]

The optimal treatment for gram-negative bacillary meningitis is not well defined. The introduction of extended-spectrum cephalosporins has improved patient outcomes significantly. Although the third-generation cephalosporins ceftriaxone and cefotaxime provide good coverage for most Enterobacteriaceae, these antibiotics are not active against *P. aeruginosa*. Ceftazidime, cefepime, and carbapenems are effective in pseudomonal meningitis.[15,17] Addition of an aminoglycoside may improve treatment results; however, CNS penetration of aminoglycosides is extremely poor, even in the setting of inflamed meninges. Intrathecal or intraventricular administration of aminoglycosides may be useful, but intraventricular antibiotics have been associated with increased mortality in neonates.[15,31] Intrathecal therapy is accomplished by administering the antibiotic into the CSF via LP, whereas intraventricular therapy is usually administered in the ventricles of the brain.

Initial therapy of suspected or documented pseudomonal meningitis should include an antipseudomonal β-lactam (eg, cefepime, meropenem) plus an aminoglycoside (eg, tobramycin, amikacin). Although the carbapenem imipenem-cilastatin has similar activity to these β-lactams, its use is not recommended in meningitis because of the risk of seizures. Aztreonam, high-dose ciprofloxacin, and colistin are alternative treatments for pseudomonal meningitis, although local susceptibility rates should be considered before initiating alternative therapy. Local therapy (ie, intrathecal or intraventricular therapy) may be indicated in patients with multidrug-resistant gram-negative bacillary meningitis or in patients who fail to improve on IV antibiotics alone. In cases of multidrug-resistant pathogens, alternative pharmacodynamic dosing strategies such as continuous or extended infusion of β-lactam antimicrobials may be considered to optimize target attainment (time greater than minimum inhibitory concentration [MIC]). Given the differences in local hospital resistance patterns, administration of pathogen-directed treatment is very important after microbiology results become available. Therapy for gram-negative bacillary meningitis should be continued for at least 21 days.

▶ *Healthcare-Associated Meningitis and Ventriculitis*

Patients who undergo neurosurgical procedures or have invasive or implanted foreign devices including CSF shunts, intraspinal pumps or catheters, or epidural catheters are at risk for CNS infections. Key pathogens in postneurosurgical infections include coagulase-negative staphylococci, *S. aureus*, streptococci, propionibacteria, and gram-negative bacilli, including *E. Coli*, Enterobacter species, Citrobacter species, and *P. aeruginosa*.[32] Clinical signs and symptoms may be similar to those of other CNS infections, and there also may be evidence of malfunction of implanted hardware or visible signs of a postoperative wound infection. Diagnosis of these infections includes analysis of CSF fluid, obtained either via lumbar puncture or the implanted device. Additionally, device removal is usually necessary for adequate infection treatment and microbiologic identification from removed devices may be helpful.[32]

Empirical therapy for postoperative infections in neurosurgical patients (including patients with CSF shunts) should include vancomycin in combination with either cefepime, ceftazidime, or meropenem. In patients who cannot receive vancomycin either due to contraindications or resistance, linezolid, daptomycin, or trimethoprim-sulfamethoxazole may be used to treat *Staphylococcal* infection. Evidence with these agents is limited and selection should be based on susceptibility testing.[32] The addition of rifampin is recommended for treatment of intracranial or intraspinal hardware infections including shunts or drains. Removal of infected devices is desirable; aggressive antibiotic therapy (including high-dose IV antibiotic therapy plus intraventricular vancomycin and/or tobramycin) may be effective for patients in whom hardware removal is not possible.[33] The duration of treatment for these infections is 10 to 14 days. The use of prophylactic antibiotics against meningitis post-device placement beyond procedural prophylaxis remains controversial.[34,35] Peri-Procedural antimicrobials are recommended prior to device placement, but prolonged prophylaxis while devices are in place is not recommended.[32]

Brain abscesses are localized collections of pus within the cranium. These infections are difficult to treat due to the presence of walled-off infections in the brain tissue reducing antibiotic penetration. In addition to appropriate antimicrobial therapy (a discussion of which is beyond the scope of this chapter), surgical debridement is often required as an adjunctive measure. Surgical debridement may also be required in the management of neurosurgical postoperative infections.

▶ *Viral Encephalitis and Meningitis*

Viral encephalitis and meningitis may mimic bacterial meningitis on clinical presentation but often can be differentiated by CSF findings (see Table 73–2). The most common viral pathogens are enteroviruses, which cause approximately 85% of cases of viral CNS infections.[7] Other viruses that may cause CNS infections include arboviruses, HSV, cytomegalovirus, varicella-zoster virus, rotavirus, coronavirus, influenza viruses A and B, West Nile virus, and Epstein-Barr virus. Viral CNS infections are acquired through hematogenous or neuronal spread.[7] Most cases of enteroviral meningitis or encephalitis are self-limiting with supportive treatment.[36] However, arbovirus, West Nile virus, and Eastern equine virus infections are associated with a less favorable prognosis.

In contrast to other viral encephalitides, HSV type 1 and 2 encephalitis are treatable. Although rare (one case per 250,000 population per year in the United States), HSV encephalitis is a serious, life-threatening infection.[37] More than 90% of HSV encephalitis in adults is due to HSV type 1, whereas HSV type 2 predominates in neonatal HSV encephalitis (> 70%).[38] HSV encephalitis is the result of reactivation of a latent infection (two-thirds of cases) or a severe case of primary infection (one-third). Without effective treatment, the mortality rate may be as high as 85%, and survivors often have significant residual neurologic deficits. In accordance with 2008 IDSA guidelines, high-dose IV acyclovir is the drug of choice, given for 2 to 3 weeks at a dose of 10 mg/kg IV every 8 hours in adults, based on ideal body weight, and for 3 weeks at a dose of 20 mg/kg IV every 8 hours in neonates.[39] Patients receiving acyclovir should maintain adequate hydration (consider continuous IV hydration) to help prevent acute kidney injury secondary to crystal nephropathy.[41] Foscarnet 120 to 200 mg/kg/day divided every 8 to 12 hours for 2 to 3 weeks is the treatment of choice for acyclovir-resistant HSV.[39]

▶ *Opportunistic CNS Infections*

Cerebral Toxoplasmosis Across the globe, cerebral toxoplasmosis represents the most common focal brain infection in HIV-infected patients. Infection rates in the United States vary but are reported to be approximately 15% among patients with AIDS.[40] The majority of cases occur in patients with $CD4^+$ cell counts less than 100 cells/mm^3 (100×10^6/L). Potent antiretroviral therapy and primary prophylaxis (first-line option is sulfamethoxazole-trimethoprim) in IgG-positive patients have greatly reduced the disease burden.[41] First-line therapy in toxoplasmosis encephalitis is pyrimethamine plus sulfadiazine, given concomitantly with leucovorin to prevent severe hematologic adverse effects secondary to pyrimethamine (see tables for dosing).[41] Clindamycin may be substituted for sulfadiazine in cases of contraindications to sulfa-based therapy. Sulfamethoxazole-trimethoprim may also be an option, specifically in patients unable to take oral therapy. Adjunctive corticosteroids and anticonvulsant therapy should be considered to reduce sequelae from the inflammatory process and control active seizures, respectively.[41]

Cryptococcal Meningitis CNS disease secondary to *Cryptococcus neoformans* is primarily observed in severely immunocompromised hosts, such as those with HIV infection. Potent antiretroviral therapy has significantly reduced the disease burden from preantiretroviral therapy rates of 5% to 8% in developed countries. The majority of disease occurs in patients with $CD4^+$ cell counts less than 50 cells/mm^3 (50×10^6/L). First-line therapy is considered amphotericin B deoxycholate 0.7 mg/kg IV daily plus flucytosine 100 mg/kg/day orally in four divided doses for a minimum of 2 weeks.[41] Therapeutic drug monitoring may be considered for flucytosine to help reduce the risk of adverse effects. Development of renal dysfunction as a result of disease and/or drug toxicity should be closely monitored and may prompt dose reduction or possible switch to alternative lipid formulations of amphotericin, which may be less nephrotoxic. High-dose fluconazole is considered an alternative first-line therapy, especially in resource-limited areas. Secondary prophylaxis with fluconazole for an indefinite period is recommended following the completion of at least 2 weeks of induction therapy and 8 weeks of maintenance therapy with fluconazole.[41]

▶ *Adjunctive Dexamethasone Therapy*

The adjunctive agent dexamethasone improves outcomes in selected patient populations with bacterial meningitis. Dexamethasone inhibits the release of proinflammatory cytokines and limits the CNS inflammatory response stimulated by infection and antibiotic therapy.

Clinical benefit in reducing neurologic deficits (primarily by reducing hearing loss) has been observed in infants and children, if dexamethasone is initiated prior to antibiotic therapy.[1,42] The American Academy of Pediatrics recommends dexamethasone (0.15 mg/kg IV every 6 hours for 2 to 4 days) for infants and children at least 6 weeks of age with Hib meningitis and consideration of dexamethasone in pneumococcal meningitis.[11,43] In contrast to this recommendation, a large multicenter cohort study failed to show any mortality benefit of adjunctive dexamethasone therapy regardless of age or responsible pathogen (*S. pneumoniae* or *N. meningitidis*).[44] Dexamethasone should be initiated 10 to 20 minutes before or no later than the time of initiation of antibiotic therapy; it is not recommended for infants and children who have already received antibiotic therapy because it is unlikely to improve treatment outcome in these patients. There are insufficient data to make a recommendation regarding the use of adjunctive dexamethasone therapy in neonatal meningitis.

In adults, a significant benefit was observed with dexamethasone in reducing meningitis complications, including death, particularly in patients with pneumococcal meningitis.[45] The IDSA recommends dexamethasone 0.15 mg/kg IV every 6 hours for 2 to 4 days (with the first dose administered 10–20 minutes before or with the first dose of antibiotics) in adults with suspected or proven pneumococcal meningitis.[11] Dexamethasone is not recommended for adults who have already received antibiotic therapy. Some clinicians would administer dexamethasone to all adults with meningitis pending results of laboratory tests. Benefit of dexamethasone in bacterial meningitis in an HIV-positive population has not been clearly established.[46]

There is controversy regarding the administration of dexamethasone to patients requiring vancomycin for pneumococcal meningitis. Animal models indicate that concurrent steroid use reduces vancomycin penetration into the CSF by 42% to 77% and delays CSF sterilization.[15] A prospective evaluation in patients with pneumococcal meningitis receiving vancomycin and adjunctive dexamethasone demonstrated that adequate concentrations of vancomycin (nearly 30% of serum concentrations) were achievable in the CSF, provided appropriate vancomycin dosage was utilized.[47] Treatment failures have been reported in adults with resistant pneumococcal meningitis who were treated with dexamethasone, but the risk–benefit of using dexamethasone in these patients cannot be defined at this time. Animal models indicate a benefit of adding rifampin in patients with resistant pneumococcal meningitis whenever dexamethasone is used.[15,17]

Patient Encounter 2, Part 3

Upon review of her records, BB did not receive vaccination against *Neisseria meningitis* prior to college. In addition, her roommates are concerned about getting sick and inquire about measures to help prevent disease.

Who should receive antimicrobial prophylaxis for Neisseria?

Who should receive vaccination against meningococcal disease?

Patient Care Process

Collect Information:

- Obtain a complete patient allergy history, including details on the severity of reactions, and obtain a medication history.
- Determine if patient has received recent antibiotics that may influence LP results or treatment decisions.
- Review laboratory values, past medical history, and vaccination history.

Assess the Information:

- Analyze CSF findings to determine the likely etiology of meningitis.
- Assess the patient history for possible risk factors for specific etiologies of meningitis.
- Determine from a medication history if any medicines may be associated with drug-induced aseptic meningitis.

Develop a Care Plan:

- Based on patient-specific factors and local susceptibility patterns, determine appropriate empirical antimicrobial treatment plan.
- Assess LP results, results of antigenic testing, and culture and susceptibility for additional data to help streamline therapy.

Implement the Care Plan:

- Collaborate with treatment team to ensure timely administration of antibiotic in relation to performing LP and obtaining blood cultures.
- Collaborate with treatment team to determine appropriate administration of adjunctive corticosteroid therapy.

Follow-up: Monitor and Evaluate:

- Monitor patient for any antimicrobial-related adverse events. Provide recommendations for necessary prophylaxis based on causative pathogen and exposure history.
- Determine appropriate length of therapy for diagnosed CNS infection.
- Provide recommendations for outpatient parenteral therapy as needed upon discharge from acute care facility.

OUTCOME EVALUATION

Monitor patients with CNS infections continuously throughout their treatment course to evaluate their progress toward achieving treatment goals, including relief of symptoms, eradication of infection, and reduction of inflammation to prevent death and the development of neurologic deficits. These treatment goals are best achieved by appropriate parenteral antimicrobial therapy, including empirical therapy to cover the most likely pathogens, followed by directed therapy after culture and sensitivity results are known. **KEY CONCEPT** Components of a monitoring plan to assess efficacy and safety of antimicrobial therapy of CNS infections include clinical signs and symptoms and laboratory data (eg, CSF findings, culture, sensitivity data).

During the patient's treatment course, monitor clinical signs and symptoms at least 3 times daily. Trends are more important than one-time assessments. Expect fever, headache, nausea and vomiting, and malaise to begin to improve within 24 to 48 hours of initiation of antimicrobial therapy and supportive care. Evaluate the patient for resolution of neurologic signs and symptoms, such as altered mental status and nuchal rigidity, as the infection is eradicated and inflammation is reduced within the CNS. Expect improvement and subsequent resolution of signs and symptoms as the treatment course continues. At the time of hospital discharge, arrange outpatient follow-up for several weeks to months depending on the causative pathogen, clinical treatment course, and patient's underlying comorbidities.

Monitoring of laboratory tests is important in patients receiving treatment for CNS infections. Monitor CSF and blood cultures so that antimicrobial therapy can be tailored to the etiologic organisms. Follow-up cultures may be obtained to prove eradication of the organism(s) or treatment failure. Although repeat LP generally is not performed, consider repeat LP for patients who do not respond clinically after 48 hours of appropriate antimicrobial therapy, especially those with resistant pneumococcus who receive dexamethasone.[11] Other candidates for repeat LP include those with infection with gram-negative bacilli, prolonged fever, and recurrent meningitis. Repeat the LP in neonates to determine the duration of therapy. Repeat LP also may be performed to relieve elevated intracranial pressure. Expect repeat blood cultures to become negative quickly during therapy and the serum WBC count to improve and normalize with appropriate antimicrobial therapy.

Evaluate antimicrobial dosing regimens to ensure efficacy of the treatment regimen. Trough vancomycin concentrations of 15 to 20 mg/L (10–14 μmol/L) are recommended for the treatment of CNS infections. Some clinicians have shifted to an AUC-based monitoring of vancomycin, however there are limited data for target concentrations in CNS infections at this time.[42] Monitor patients for drug adverse effects, drug allergies, and drug interactions. The specific safety monitoring plan will depend on the antibiotic(s) used (Table 73–3). Pay close attention to concomitant medications in patients on rifampin for treatment or prophylaxis. Rifampin is a potent inducer of hepatic metabolism and may reduce the efficacy of other drugs metabolized by the cytochrome P-450 enzyme pathway.

Abbreviations Introduced in This Chapter

CDC	Centers for Disease Control and Prevention
CLSI	Clinical and Laboratory Standards Institute
CNS	Central nervous system
CSF	Cerebrospinal fluid
DIC	Disseminated intravascular coagulation
ESBL	Extended spectrum β-lactamase
GBS	Group B *Streptococcus*
Hib	*Haemophilus influenzae* type B
HSV	Herpes simplex virus
IDSA	Infectious Diseases Society of America
IL-1	Interleukin 1
LP	Lumbar puncture
MBC	Minimum bactericidal concentration

MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSE	Methicillin-resistant *Staphylococcus epidermidis*
NSAIDs	Nonsteroidal anti-inflammatory drugs
PCR	Polymerase chain reaction
PMN	Polymorphonuclear cell
SJS	Stevens-Johnson Syndrome
TNF-α	Tumor necrosis factor-alpha

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Lower Respiratory Tract Infections

Diane M. Cappelletty

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. List the common pathogens that cause community-acquired pneumonia (CAP), ventilator-associated pneumonia (VAP), and hospital-acquired pneumonia (HAP).
2. Explain the pathophysiology of pneumonia and associated host defenses.
3. List the signs and symptoms associated with CAP, HAP, and VAP.
4. Identify patient and organism factors required to guide the selection of a specific antimicrobial regimen for an individual patient.
5. Design an appropriate empirical antimicrobial regimen based on patient-specific data for an individual with CAP, HAP, and VAP.
6. Design an appropriate antimicrobial regimen based on both patient- and organism-specific data.
7. Develop a monitoring plan based on patient-specific information for a patient with one of the three categories of pneumonia.
8. Apply the complete Patient Care Process to caring for patients with any type of pneumonia.
9. Formulate appropriate educational information to be provided to a patient with pneumonia.
10. Explain prevention of pneumonia via immunization and include who the appropriate patient groups are for receiving the various vaccines.

INTRODUCTION

Pneumonia is inflammation of the lung with consolidation. The cause of the inflammation is infection, which can be caused by a wide range of organisms. **KEY CONCEPT** There are three classifications of pneumonia: community-acquired, hospital-acquired, and ventilator-associated. Patients who develop pneumonia in the outpatient setting and have not been in any healthcare facilities, which include wound care and hemodialysis clinics, have community-acquired pneumonia (CAP). Aspiration was once considered a category of pneumonia, now it should be considered a patient factor for possible anaerobic organism involvement. In addition, healthcare-associated pneumonia was once a category of pneumonia but not any longer. It was defined as pneumonia that develops inside or outside the hospital in the presence of risk factors for multidrug-resistant (MDR) pathogens. Now recommendations are for hospitals to generate antibiograms to guide healthcare professionals on the most appropriate empiric therapy for patients who acquire this type of pneumonia and individually assess risk factors for MDR pathogens. Hospital-acquired pneumonia (HAP) is defined as pneumonia that occurs 48 hours or more after admission.[1] Ventilator-associated pneumonia (VAP) requires endotracheal intubation for at least 48 hours before the onset of pneumonia.[1]

EPIDEMIOLOGY AND ETIOLOGY

Etiology and Mortality Rates

KEY CONCEPT The etiology of bacterial pneumonia varies in accordance with the type of pneumonia. Table 74–1 lists the more common pathogens associated with the various types or classifications of pneumonia. *Streptococcus pneumoniae* colonizes the nasopharyngeal flora in up to 50% of healthy adults and may colonize the lower airways in individuals with chronic bronchitis.[2,3] It possesses many virulence factors, enhancing its ability to cause infection in the respiratory tract.

KEY CONCEPT Therefore, it is not surprising that *S. pneumoniae* is the predominant bacterial pathogen associated with CAP. The second-most common pathogen is one of the atypical organisms, *Mycoplasma pneumoniae*. Nontypeable *Haemophilus influenzae* intermittently colonizes about 80% of the population, and the incidence of permanent colonization increases in chronic obstructive pulmonary disease (COPD) patients and those with cystic fibrosis. Therefore, the likelihood of nontypeable *H. influenzae* causing pneumonia increases in COPD patients. *Moraxella catarrhalis* is a more common cause of pneumonia in the very young and the very old. *Chlamydophila pneumoniae* and *Legionella pneumophila* are less frequent causes than the other bacterial and atypical organisms. Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is associated with necrotizing and severe pneumonia in healthy children and young adults. Less than 2% of all CA-MRSA infections are pneumonia (most are skin and soft tissue).[4,5]

Viruses are a common cause of CAP in children (about 65%) and in adults ranging from 12% to 29%.[5-7] Mixed infections of viruses and bacteria have been increasingly identified in 11% to 56% of cases.[5-8] Viruses most often associated with pneumonia in adults include influenza A and B and rhinoviruses but can be

Table 74–1

Common Pathogens by Type of Pneumonia

Type of Pneumonia	Common Pathogens
Community	Aerobic bacteria: *Streptococcus pneumoniae, Haemophilus influenzae*, MSSA, *Moraxella catarrhalis* Atypical: *Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella pneumophila* Viruses: rhinoviruses and influenza most common, coronaviruses may be increasing in prevalence
Hospital	*S. pneumoniae*, MSSA, *Escherichia coli, Klebsiella pneumoniae* (*M. pneumoniae, C. pneumoniae* are rare) (MDR pathogen risk factors present; MRSA, *Pseudomonas aeruginosa*, extended-spectrum β-lactamase-producing Gram-negative bacilli, carbapenemase-producing Gram-negative bacilli)
Ventilator	MRSA, extended-spectrum β-lactamase-producing Gram-negative bacilli, *P. aeruginosa, Acinetobacter* spp., carbapenemase-producing Gram-negative bacilli

MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus.*

caused by adenoviruses, enteroviruses, cytomegalovirus, varicella-zoster virus, herpes simplex virus, and others. In children, viral pneumonia is more commonly caused by respiratory syncytial virus, influenza A, and parainfluenza, and less commonly by those listed previously for adults. Influenza is associated with seasonal local outbreaks (epidemics) and global outbreaks (pandemics). Influenza viruses are characterized and named for the hemagglutinin (H) and neuraminidase (N) proteins on the surface of the viruses. There are 16 hemagglutinin and 9 neuraminidase subtypes of influenza A, and H1 to H3 and N1 and N2 are the principal antigenic types found in humans.[9] Coronaviruses are emerging as important pathogens associated with pneumonia in predominantly adults and to a lesser extent in pediatric patients. While most coronaviruses are associated with mild respiratory disease, a few strains have been responsible for epidemics such as severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV) in the early-to-mid-2000s and a pandemic by SARS-CoV-2 in 2019 to 2021.[10]

Mortality associated with CAP is dependent on the severity of the illness and the age of the patient. Elderly patients admitted to the hospital with severe pneumonia have mortality rates up to 40%.[11-14] In the outpatient setting (mild-to-moderate disease), the mortality rate is less than 5%.[15] Mortality among case reports of CA-MRSA necrotizing pneumonia is 42%.[4] Pneumonia owing to aspiration of oral contents is caused by a variety of anaerobes (*Bacteroides* spp., *Fusobacterium* spp., *Prevotella* spp., and anaerobic Gram-positive cocci) as well as *Streptococcus* spp. *M. catarrhalis*, and *Eikenella corrodens* may be involved but much less frequently.[15,17] When gastric contents are aspirated, enteric Gram-negative bacilli and *S. aureus* are more commonly the pathogens.[17]

HAP and VAP may be caused by a wide spectrum of organisms. HAP and VAP pathogens are influenced by risk factors for MDR bacteria. These factors include: intravenous antibiotic use within the past 90 days (HAP and VAP) and for VAP septic shock at the time of VAP, acute respiratory distress syndrome (ARDS) preceding VAP, 5 or more days of hospitalization, and acute renal replacement therapy.[1] MDR organisms include extended spectrum β-lactamase and/or carbapenemase-producing enteric Gram-negative bacilli, *Pseudomonas aeruginosa*, *Acinetobacter* spp., or MRSA. The number of infections caused by MDR bacteria is increasing significantly in hospitalized patients.[1,5,14,18-20]

PATHOPHYSIOLOGY

Local Host Defenses

Local host defenses of both the upper and lower respiratory tract along with the anatomy of the airways are important in preventing infection. Upper respiratory defenses include the mucociliary apparatus of the nasopharynx, nasal hair, normal bacterial flora, IgA, and complement. Local host defenses of the lower respiratory tract include cough, mucociliary apparatus of the trachea and bronchi, antibodies (IgA, IgM, and IgG), complement, and alveolar macrophages. Mucous lines the cells of the respiratory tract, forming a protective barrier for the cells. This minimizes the ability of organisms to attach to the cells and initiate the infectious process. The squamous epithelial cells of the upper respiratory tract are not ciliated, but those of the columnar epithelial cells of the lower tract are. The cilia beat in a uniform fashion upward, moving particles up and out of the lower respiratory tract.

Particles greater than 10 μm are efficiently trapped by mechanisms of the upper airway and are removed from the nasopharynx either by swallowing or by expulsion. The mucociliary apparatus of the trachea and bronchi along with the sharp angles of the bronchi often are effective at trapping and eliminating particles that are 2 to 10 μm in size. Particles in the range of 0.5 to 1 μm may consistently reach the alveolar sacs of the lung. Microorganisms fall within this size range, and if they reach the alveolar sacs, then infection may result if alveolar macrophages and other defenses cannot contain the organisms.

Aspiration

Aspiration is a fairly common occurrence in adults during sleep.[1] Aspiration of the oropharyngeal or gastric contents may lead to aspiration pneumonia or chemical (acid) pneumonitis. Risk factors for aspiration include dysphagia, change in oropharyngeal

Patient Encounter 1, Part 1

A 72-year-old African American woman presents to your ED with difficulty breathing, coughing, confusion, and shortness of breath. Her son brought her to the ED. Her physical examination reveals that she is easily confused and oriented to name and place (×2), has decreased breath sounds on the right side, and has rales and crackles in the right lower lobe. Her temperature is 38.7°C (101.6°F), respiratory rate is 24 breaths/min, oxygen saturation 88% on room air, and blood pressure is 110/70 mm Hg. She is coughing up greenish sputum.

What are her signs and symptoms of pneumonia?

What are the most common two bacterial organisms that could be causing the pneumonia?

What is the most common atypical organism, as well as the most common two viruses that could be causing the pneumonia?

Patient Encounter 2, Part 1

A 66-year-old man was admitted to the hospital for abdominal aortic aneurysm surgery. He developed complications postoperatively and was intubated 7 days ago. The nurses note an increase in the amount and purulence of his sputum. Attempts yesterday and today to wean him off the ventilator have failed. He is sedated but does respond to commands. His temperature is 38.9°C (102°F), blood pressure is 115/74 mm Hg, and white blood cell (WBC) $22.6 \times 10^3/\text{mm}^3$ (22.6×10^9/L) with a cell differential of 75% (0.75) neutrophils, 8% (0.08) bands, 14% (0.14) lymphocytes, and 3% (0.03) monocytes. The chest X-ray revealed left middle lobe infiltrates.

What are his signs and symptoms of pneumonia?

What are the most common three bacterial organisms that could be causing the pneumonia?

colonization, gastroesophageal reflux (GER), and decreased host defenses.

Dysphagia can be caused by stroke or other neurologic disorders, seizures, alcoholism, and aging.[15] Oropharyngeal colonization may be altered by oral/dental disease, poor oral hygiene, tube feedings, or medications. This could result in a higher number of anaerobic organisms in the oral cavity or colonization with enteric Gram-negative bacilli.[16] Acid suppression is an important factor in the treatment of GER disease, which may allow enteric Gram-negative bacilli to colonize the gastric contents. Finally, impaired mucous production or cilia function, decreased immunoglobulin in secretions, and an altered cough reflex may increase the likelihood of infection following an aspiration. The infection can result in a necrotizing pneumonia or lung abscess.

Inflammatory Response

Once breakdown of the local host defenses occurs and organisms invade the lung tissue, an inflammatory response is generated either by the organisms causing tissue damage or by the immune response to the presence of the organisms. This inflammatory response either can remain localized in the infected tissue or can become systemic. The role of the alveolar macrophages is twofold. First, to engulf the organisms to contain the infection, and second, to process the antigens for presentation in regional lymph nodes in order to generate a specific immune response by either the cell-mediated or humoral system, or both. The macrophages release cytokines in the area of the infection, which result in increased mucous production, constricting the local vasculature and lymphatic vessels and attraction of other immune cells to the site. The increase in mucus is associated with symptoms such as cough and sputum production. If tumor necrosis factor alpha (TNF-α) and interleukins (ILs)-1 and -6 are released systemically, then the symptoms become more severe and can include hypotension, organ dysfunction, and/or a septic or septic-shock clinical presentation.

CLINICAL PRESENTATION AND DIAGNOSIS

Several scoring systems are available for assessing the severity of the pneumonia: the pneumonia severity index (PSI); confusion, uremia, respiratory rate, blood pressure (CURB); CURB-65 (for those ≥ 65 years of age), and systolic BP, oxygenation, age, and respiratory rate (SOAR).[11,14] These models are used to help determine the severity of illness, prognosis (mortality risk), and the need for hospitalization.[11,14,15] PSI has a higher discriminative power in predicting mortality over CURB and is preferred by the CAP guidelines for assessing severity of illness.

TREATMENT

KEY CONCEPT The goal of antibiotic therapy is to eliminate the patient's symptoms, minimize or prevent complications, and decrease mortality. Potential complications secondary to pneumonia include further decline in pulmonary function in patients with underlying pulmonary disease, prolonged mechanical ventilation, bacteremia/sepsis/septic shock, and death. The use of an antimicrobial agent with the narrowest spectrum of activity that covers the suspected pathogen(s) without having activity against organisms not involved in the infection is preferred to minimize the development of resistance and secondary infections such as *Clostridioides difficile* diarrhea/colitis.

General Approach to Treatment

Designing a therapeutic regimen for any patient with any type of pneumonia begins with three general categories of consideration:

1. Patient-specific factors that will impact therapy.
2. The most common two to three organisms likely causing the infection and resistance issues associated with each organism.
3. The antimicrobials that will cover these organisms. Local resistance patterns, which can be obtained from hospital or clinic antibiograms, will influence the choice of antimicrobial. The spectrum should not be too broad or narrow; they should penetrate the site of infection and be the most cost effective.

Patient factors that need to be considered include age, renal function, drug allergies and/or drug intolerances, immune status (diabetes, neutropenia, or immunocompromised host), cardiovascular (cardiomyopathy, pulmonary hypertension, congenital heart disease, heart failure, or coronary artery disease), pulmonary disease (COPD, cancer, cystic fibrosis, pulmonary fibrosis, moderate-to-severe asthma, smoking, and vaping), pregnancy, medical insurance and prescription coverage, exposure to resistant organisms, and prior antibiotic exposure(s). Patients with these comorbid conditions are at increased risk of severe pneumonia from any organism but markedly important for coronavirus.

- The most common pathogens vary with the type of pneumonia and are listed in Table 74–1. *M. pneumoniae* lack a cell wall; therefore, β-lactam drugs have no activity against this organism. The atypical organisms have not changed in recent years with respect to antibiotic resistance. β-Lactamase production in *H. influenzae* has remained relatively steady over the last 5 to 10 years, and the rate is approximately 25%.[21] *S. pneumoniae* has developed resistance mechanisms against many classes of antimicrobials, and the mechanisms include the following:
- Alteration of the penicillin-binding proteins (PBPs), inactivating β-lactams
- Efflux or methylation of the ribosome-inactivating macrolides
- Ribosome protection (tetM gene) inactivating tetracyclines
- Alteration of DNA gyrase or topoisomerase IV inactivating fluoroquinolones

S. pneumoniae resistance to commonly prescribed antimicrobials such as the penicillins and macrolides/azalides dramatically increased in the late 1980s through the mid-to-late 1990s and has

Clinical Presentation of CAP or Aspiration Pneumonia

General

Patients may experience nonrespiratory symptoms in addition to respiratory symptoms. With increasing age, both respiratory and nonrespiratory symptoms decrease in frequency.

KEY CONCEPT Symptoms

- Respiratory—cough (productive or nonproductive), shortness of breath, and difficulty breathing
- Nonrespiratory—fever, fatigue, sweats, headache, myalgias, mental status changes

KEY CONCEPT Signs

- Temperature may increase or decrease from baseline, but most often it is elevated. The temperature may be sustained or intermittent.
- Respiratory rate is often increased. Cyanosis, increased respiratory rate, and use of accessory muscles of respiration are suggestive of severe respiratory compromise.
- Breath sounds may be diminished. Rales or rhonchi may be heard.
- Confusion, lethargy, and disorientation are relatively common in elderly patients.

Diagnostic Tests

- Chest X-ray should reveal single or multiple infiltrates.
- Oxygen saturation on room air should be more than 90% (0.90), as determined by pulse oximetry.
- Arterial blood gases are beneficial primarily in patients with severe pneumonia.

Laboratory Tests

- The WBC may or may not be elevated. In elderly patients, a drop in WBCs also can be a sign of infection. The differential should show a predominance of neutrophils if a bacterial infection is present. The presence of bands also could be an indicator of bacterial infection. Elevated lymphocytes are an indication of viral infection.
- Blood urea nitrogen (BUN) and serum creatinine are needed to dose antibiotics appropriately and to minimize or prevent drug toxicity (especially in the elderly patient).

Microbiology Tests

- Sputum Gram stain should demonstrate the presence of WBCs and the absence of squamous epithelial cells. It may or may not show a predominance of one type of organism.
- Sputum culture and susceptibility are not obtained in the outpatient setting. The value of culturing is debated owing to the rapidity in which *S. pneumoniae* dies in transport media and the inability to reliably or routinely culture atypical organisms.
- Bronchoscopy may be performed to improve the ability to diagnose pneumonia. Tracheal secretions often are better specimens than sputum owing to the lack of oral contamination.
- Serology (IgM and IgG) is useful in determining the presence of atypical organisms such as *Mycoplasma* and *Chlamydophila*.
- Urinary *Legionella* antigen is used to diagnose *L. pneumophila*.
- Polymerase chain reaction (PCR) is being used more frequently to detect the DNA of respiratory pathogens.
- Blood cultures should be obtained in all patients admitted to the ICU with pneumonia. Positive blood cultures are present in about 1% to 20% of patients with CAP.

Clinical Presentation of Severe CAP

General

In approximately 10% of patients, CAP will be severe enough to require intensive care or mechanical ventilation.

KEY CONCEPT Symptoms

Respiratory—cough (productive or nonproductive), shortness of breath, difficulty breathing

- Nonrespiratory—fever, fatigue, sweats, headache, myalgias, mental status changes

Signs

- Temperature may increase or decrease from baseline, but most often it is elevated. The temperature may be sustained or intermittent.
- Respiratory rate is greater than 30 breaths/min, cyanosis and use of accessory muscles of respiration are suggestive of severe respiratory compromise.
- Hypotension (systolic blood pressure < 90 mm Hg or diastolic blood pressure < 60 mm Hg).
- Requirement for vasopressors.
- Breath sounds may be diminished. Rales or rhonchi may be heard.
- Urine output less than 20 mL/hour or less than 80 mL over 4 hours.
- Confusion, lethargy, and disorientation are relatively common in elderly patients.

Diagnostic Tests

As stated in the clinical presentation of community-acquired pneumonia. Nasal swab MRSA PCR testing has a strong negative predictive value for MRSA pneumonia.

Laboratory Tests

As stated in the clinical presentation of community-acquired pneumonia.

Microbiology Tests

As stated in the clinical presentation of community-acquired pneumonia.

Diagnosis of VAP

Clinical Strategy

- Chest X-ray should reveal a new infiltrate *plus* two of the following:
- Temperature greater than 38.0°C (100.4°F)
- Leukocytosis or leukopenia
- Purulent secretions
- Semiquantitative cultures obtained identify the pathogen(s).
- Tracheal aspirates grow more organisms than invasive quantitative cultures and often result in the overuse of antibiotics.

remained relatively flat in the 2000s. Resistance information collected nationally along with susceptibility testing for new antimicrobials demonstrates that average national rates of resistance to penicillin and macrolides were approximately 13% and 38%, respectively.[22,23] Resistance to trimethoprim/sulfamethoxazole is approximately 25%, and fluoroquinolone resistance remains less than 0.5%.[23]

For HAP, and VAP, the risk of infection from an MDR pathogen is relatively high. The number and type of organisms that are MDR vary from hospital to hospital, making it more difficult to generate guidelines for treatment. Therefore, the treatment recommendations may be too broad or too narrow for any given institution and local antibiogram data should influence the choice of therapeutic regimens. Risk factors for developing infection caused by a resistant pathogen are as follows:

- intravenous antibiotic use within the past 90 days
- septic shock at the time of HAP or VAP
- ARDS preceding VAP
- 5 or more days of hospitalization
- acute renal replacement therapy

The patient- and drug-related categories are common to all types of pneumonia, but the organisms vary with the type of pneumonia. Guidelines have been generated by experts in the field for all types of pneumonia. These guidelines were generated to provide practitioners with evidence-based therapeutic options for the management of patients with pneumonia.

Pharmacologic Therapy for CAP

KEY CONCEPT Treatment of CAP is predominantly empiric, that is, treatment is started without knowing the causative pathogen. The most recent guidelines are the result of collaboration between the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS).[24] The approach to patient care is based on the classification of patients into two broad categories, outpatient and inpatient, and then further dividing the groups by comorbid conditions and location in the hospital, respectively. These guidelines use patient-specific data along with predominant pathogen information to design appropriate empirical antimicrobial regimens. Table 74–2 summarizes these therapeutic options.

▶ *Adult Outpatient Previously Healthy*

First-line therapeutic options for treating previously healthy adults without risk factors for MRSA or *P. aeruginosa* include the use of amoxicillin or doxycycline, a macrolide (erythromycin, clarithromycin) or an azalide (azithromycin) only if local pneumococcal resistance rates are less than 25%.[24] If a patient has failed therapy with a first-line agent, one has to consider why the patient failed. The most common reasons are either medication adherence issues or the presence of resistant organisms. If a resistant organism is suspected, then the use of one of the respiratory

Patient Encounter 1, Part 2: Medical History, Physical Examination, and Diagnostic Tests

A 72-year-old African American woman presents to your ED with difficulty breathing, coughing, confusion, and shortness of breath.

PMH: Hypertension for 38 years, noninsulin dependent diabetes for 15 years, currently controlled

FH: Father died of lung cancer at the age of 68 years; mother died of natural causes

SH: Denies alcohol, smokes 1/2 pack per day. Lives alone and has two children. She is 5′3″ (160 cm) and weighs 250 lb (113.6 kg).

Allergies: sulfa—hives, red-burning skin, doxycycline—rash

Meds: Lisinopril/hydrochlorothiazide 20/25 mg orally once daily; metformin 1000 mg orally twice daily

ROS: (+) difficulty breathing and shortness of breath; (–) chest pain, N/V/D, change in appetite

PE:

VS: BP 110/70 mm Hg, P 88 beats/min, RR 24 breaths/min, T 38.7°C (101.6°F)

CV: RRR, normal S1, S2; no murmurs, rubs, or gallops

Lungs: Decreased breath sounds on the right side, and has rales and crackles in the right lower lobe, greenish sputum production

Abd: Soft, nontender, nondistended; (+) bowel sounds, no hepatosplenomegaly, heme (–) stool

Neuro: Oriented to name and place, easily confused

Diagnostic Tests: Chest X-ray: right lower lobe infiltrate; oxygen saturation 88% (0.88) on room air

Labs: WBCs 22.4 × $10^3/\text{mm}^3$ (22.4 × 10^9/L) with a cell differential of 70% (0.70) neutrophils, 2% (0.02) bands, 20% (0.20) lymphocytes, and 8% (0.08) monocytes; BUN 10 mg/dL (3.57 mmol/L), SCr 0.8 mg/dL (70.74 μmol/L), fasting glucose 110 mg/dL (6.1 mmol/L); sputum Gram stain: moderate Gram-positive diplococci, few Gram-negative bacilli, rare squamous epithelial cells, many WBCs; sputum culture is pending.

Given this additional information, what is your assessment of the patient's condition?

Identify your treatment goals for the patient.

What organisms should you include in your list of potential pathogens?

What pharmacologic agents are available for treating this patient?

Table 74–2

Summary of CAP Treatment

Adult outpatient otherwise healthy	*Monotherapy*
Empirical coverage against *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, (Mycoplasma pneumoniae, Chlamydophila pneumoniae* much less common)	Amoxicillin 1 g three times daily, or doxycycline 100 mg twice daily (or azithromycin 500 mg × 1 then 250 mg once daily, clarithromycin 500 mg twice daily or clarithromycin ER 1000 mg once daily, only if local pneumococcal resistance rates are < 25%)
Adult outpatient comorbidities	*Combination therapy*
Empirical coverage against *S. pneumoniae, H. influenzae, S. aureus*, (*M. pneumoniae, C. pneumoniae* much less common)	Amoxicillin-clavulanate 500/125 mg three times daily or 875/125 mg twice daily or 2000/125 mg twice daily or cefpodoxime 200 mg twice daily, or cefuroxime 500 mg twice daily, *plus* azithromycin, or clarithromycin or, doxycycline (see dosing above)
	Monotherapy
	Gemifloxacin 320 mg once daily, levofloxacin 750 mg once daily, moxifloxacin 400 mg once daily
Adult inpatient (non-ICU)	*Combination therapy*
Empirical coverage against *S. pneumoniae, H. influenzae, S. aureus*, (*M. pneumoniae, C. pneumoniae* much less common)	Cefotaxime 1–2 g q8h, or ceftriaxone 1–2 g q24h, or ampicillin-sulbactam 1.5–3 g q6h, or ertapenem 1 g q24h *plus* azithromycin, or clarithromycin, or doxycycline (see dosing above)
	Monotherapy
	Levofloxacin, moxifloxacin (see dosing above)
Adult inpatient ICU (no Pseudomonas)	*Combination therapy*
Empirical coverage against *S. pneumoniae, Legionella pneumophila, H. influenzae,* enteric GNB, and *S. aureus*	Cefotaxime or ceftriaxone *plus* azithromycin, or levofloxacin, or moxifloxacin (see dosing above)
Adult inpatient ICU (Pseudomonas is a concern)	*Combination therapy*
Empirical coverage against *Pseudomonas aeruginosa, S. pneumoniae, L. pneumophila, H. influenzae,* enteric GNB, and *S. aureus*	Cefepime, or ceftazidime, or piperacillin–tazobactam, or imipenem, or meropenem *plus* or ciprofloxacin or levofloxacin or an aminoglycoside (see Table 74–4 for dosing) If an aminoglycoside is chosen, then add azithromycin or levofloxacin or moxifloxacin
Adult inpatient non-ICU or ICU (MRSA is a concern)	
Empirical coverage against *S. pneumoniae, L. pneumophila, H. influenzae,* enteric GNB, and *S. aureus* (*Pseudomonas* if ICU)	Add vancomycin or linezolid to the regimens listed above (see Table 74–4 for dosing)
Pediatric outpatient	*Monotherapy*
Empirical coverage against *S. pneumoniae, M. pneumoniae,* and *C. pneumoniae*	High-dose amoxicillin, or high-dose amoxicillin-clavulanate, or intramuscular ceftriaxone, or azithromycin, or clarithromycin
Pediatric inpatient (non-ICU)	*Monotherapy*
Empirical coverage against *S. pneumoniae*	Fully immunized child—ampicillin or penicillin G Partially immunized child—ceftriaxone or cefotaxime
	Combination therapy
Empirical coverage against *S. pneumoniae, H. influenzae, M. pneumoniae,* and *C. pneumoniae*	IV cefuroxime, or cefotaxime, or ceftriaxone, or ampicillin-sulbactam plus azithromycin, or clarithromycin
Pediatric inpatient ICU	*Combination therapy*
Empirical coverage against *S. pneumoniae, L. pneumophila, H. influenzae,* enteric GNB, and *S. aureus*	Cefotaxime, or ceftriaxone plus azithromycin, or clarithromycin

CA-MRSA, community-acquired methicillin-resistant *S. aureus*; GNB, Gram-negative bacteria; ICU, intensive care unit.

fluoroquinolones active against *S. pneumoniae* (gemifloxacin, levofloxacin, or moxifloxacin) is warranted.

▶ *Adult Outpatient With Comorbid Conditions*

The comorbid conditions that can impact therapy and outcomes in patients with CAP include diabetes mellitus, chronic heart, liver, lung, or renal disease, alcoholism, malignancy, or asplenia.[24] If the patient did not receive antibiotics in the last 3 months, then either a respiratory fluoroquinolone alone or a combination of amoxicillin-clavulanate or oral cephalosporin agent plus a macrolide/azalide or doxycycline is recommended. If the patient received an antibiotic in the last 3 months, the recommendation is to use an agent from a different class.

▶ *Adult Inpatient Not in the ICU*

For patients admitted to the hospital with CAP, the severity of illness is generally increased (caused either by the organism itself or underlying comorbidities in the patient), and the pathogens are essentially the same as in the outpatient setting. Recommendations for patients without risk factors for MRSA or *P. aeruginosa* are to use either a respiratory fluoroquinolone alone or a combination of an IV β-lactam antimicrobial agent plus an advanced macrolide/azalide (clarithromycin/azithromycin) or doxycycline. Macrolides are preferred over doxycycline in combination with the β-lactam antimicrobial agent. Recommended β-lactams include cefotaxime, ceftriaxone, or ampicillin-sulbactam.[24] Omadacycline, a tetracycline, and lefamulin, a pleuromutilin, are new agents that have demonstrated efficacy for treating CAP. The guidelines do not recommend their use at this time and suggest further studies establishing safety and efficacy are needed. The first antibiotic dose should be administered within the first 24 hours of admission. Conversion to oral therapy should occur when the patient is hemodynamically stable, improving clinically, and able to take oral medications, which often is within 48 to 72 hours for most patients. Discharge from the hospital should be as soon as the patient is stable and without other medical

Patient Encounter 2, Part 2: Medical History, Physical Examination, and Diagnostic Tests

A 66-year-old man was admitted to the hospital for abdominal aortic aneurysm surgery. He developed complications postoperatively and was intubated 7 days ago. The nurses note an increase in the amount and purulence of his sputum. Attempts yesterday and today to wean him off the ventilator have failed.

PMH: Hypertension for 15 years, currently controlled.

FH: Father and mother deceased from natural causes. Both had hypertension, mother had hypothyroidism.

SH: Smoked a pack per day for 22 years quit 10 years ago, social alcohol two to three beers or liquor per week. He lives with his wife; he is a plumber. He is 5′10″ (177.8 cm) and weighs 96.4 kg (212 lb).

Allergies: Amoxicillin—hives, difficulty breathing

Meds: Losartan 50 mg orally once daily, atorvastatin 40 mg orally once daily

PE:

VS: BP 105/70 mm Hg, P 80 beats/min, T 38.8°C (101.9°F).

CV: RRR, normal S_1, S_2; no murmurs, rubs, or gallops.

Abd: Soft, nontender, nondistended; (+) bowel sounds, no hepatosplenomegaly.

Diagnostic Tests: Chest X-ray: left middle and lower lobe infiltrates; oxygen saturation 98% (0.98) on ventilator.

Labs: WBC is 25.4×10^3/mm^3 (25.4×10^9/L) with a cell differential of 70% (0.70) neutrophils, 9% (0.09) bands, 15% (0.15) lymphocytes, and 6% (0.06) monocytes; BUN 10 mg/dL (3.6 mmol/L), SCr 0.9 mg/dL (80 μmol/L); sputum Gram stain: many Gram-negative bacilli, many WBCs; culture is pending.

Given this additional information, what is your assessment of the patient's condition?

Identify your treatment goals for the patient.

What pharmacologic agents are available for treating this patient?

complications. The need to observe the patient in the hospital on their oral antibiotic is not necessary.[24]

▶ *Adult Inpatient in the ICU*

Patients admitted to the ICU have severe pneumonia, and the likely etiology includes *S. pneumoniae* and *H. influenzae* as in the other pneumonia categories; however, the incidence of *L. pneumophila* increases in this setting and should be considered a potential pathogen. In addition, enteric Gram-negative bacilli and *S. aureus* are more frequently the cause of the pneumonia in these patients. The recommendations for treating patients with no risk factors for MRSA or *P. aeruginosa* are to treat with an IV β-lactam plus either azithromycin or a respiratory fluoroquinolone. These combination therapies minimize the risk of treatment failure due to a resistant pathogen as well as provide broad coverage.[24] The β-lactams are the same as for inpatient non-ICU treatment. If the patient is allergic to β-lactams, then aztreonam can be substituted for the β-lactam.

If *P. aeruginosa* is suspected, then the antimicrobial treatment must be broadened to cover *Pseudomonas* as well as the organisms listed previously. Owing to the high resistance rates observed with *Pseudomonas*, regimens empirically double covering the *Pseudomonas* to ensure at least one of the antibiotics is active against it can be employed. The regimens include the use of an antipneumococcal, antipseudomonal β-lactam (cefepime, ceftazidime, piperacillin/tazobactam, imipenem, or meropenem),[24] plus either ciprofloxacin or levofloxacin or an aminoglycoside. If the aminoglycoside is chosen, then either IV azithromycin or a respiratory fluoroquinolone should be added to cover the atypical bacterial organisms.

Patient Encounter 1, Part 3: Creating a Care Plan

A 72-year-old African American woman presents to your ED with difficulty breathing, coughing, confusion, and shortness of breath.

Based on the information presented, create a care plan for this patient's pneumonia. Your plan should include: (a) a statement of drug-related needs and/or problems; (b) a patient-specific detailed therapeutic plan; and (c) monitoring parameters to assess efficacy and safety.

If MRSA is suspected in the patient, then vancomycin or linezolid should be considered. Daptomycin cannot be used because surfactant in the lung inactivates the drug, thus rendering it ineffective for pneumonia. CA-MRSA can cause a necrotizing pneumonia, and the cause is believed to be due to its many virulence factors, including the Panton-Valentine leukocidin toxin.[4] In these patients the use of an agent that decreases toxin production may be beneficial. Linezolid decreases toxin production; the other recommended agents to decrease toxin production and added to vancomycin therapy are clindamycin or a respiratory fluoroquinolone.[24]

▶ *Aspiration in the Inpatient Setting*

Empirical coverage for anaerobes is not recommended if a patient aspirates unless there is a lung abscess or empyema.[24] The rationale for this recommendation is that aspiration commonly occurs in adults while sleeping and the difficulty in separating aspiration pneumonia from other types of pneumonia. Aspiration of gastrointestinal contents often results in chemical pneumonitis and not infection although alteration of gastric pH due to use of proton pump inhibitors might influence this.

▶ *Influenza*

Influenza viruses A and B can cause pneumonia in pediatric and adult patients. Amantadine and rimantadine were available oral agents with activity against influenza virus type A. If started within 48 hours of the onset of the first symptoms, they reduce the duration of the illness by about 1.3 days. However, resistance to the adamantanes is over 90%.[25] Oseltamivir and zanamivir are oral agents active against both type A and B influenza that reduce the duration of the illness by about 1.3 days if initiated within 40 to 48 hours of the first symptoms.[26] Baloxavir marboxil is an oral agent and a prodrug that is converted by hydrolysis to baloxavir, the active form that inhibits the endonuclease activity of the polymerase acidic (PA) protein found in influenza virus.[27]

Baloxavir activity is similar to oseltamivir with respect to timeline for decreasing patient symptoms. Peramivir is an intravenous neuraminidase inhibitor approved as a single dose for adults with uncomplicated influenza. It may be used in hospitalized patients in whom oral therapy is contraindicated or not tolerated.[28] For active infection beyond the first 48 hours, none of these agents are effective in treating infection, and supportive care is the best treatment for these patients. Neuraminidase resistance rates in influenza A strains prevalent prior to 2009 were high and rates in strains prevalent after 2009 are low.[25] Seasonal information on resistance patterns and treatment recommendations should be evaluated.

▶ *Coronavirus*

Coronavirus causes pneumonia in adults more than in children. The spectrum of the diseases causes by coronavirus range from mild to severe and treatment recommendations are based on the severity of illness as well as the time frame for severe disease. This chapter was written during the pandemic and clinical trials to clearly define treatment options were limited and remdesivir was the only FDA-approved antiviral for coronavirus. As clinical trials are performed, these treatment recommendations could change. For mild-to-moderate disease and the patient is not hospitalized, no antiviral or antibody treatment is recommended, and patients should not receive corticosteroids.[29] Treatment of body aches or fever with over-the-counter acetaminophen or nonsteroidal anti-inflammatory drugs can be used.

If a patient is hospitalized but oxygen therapy is not required, and risk of disease progression is high, then remdesivir 200 mg IV × 1, then 100 mg IV q24h for 4 days or until discharge from the hospital can be administered. It is not recommended to use corticosteroids in these patients.[29]

For patients hospitalized and requiring non-high-flow supplemental oxygen and not intubated, the recommendation is based on the amount of oxygen needed. For those who require minimal oxygen, remdesivir monotherapy is recommended.[29] If the patient requires increasing amounts of oxygen, then remdesivir plus dexamethasone 6 mg IV or PO q24h (or equivalent dose of other corticosteroids) for 10 days or until discharge is recommended.[29] Monotherapy with a corticosteroid should only be used if remdesivir is not available or cannot be used in a patient.

Patients hospitalized and receiving high-flow oxygenation, the recommendations are for a corticosteroid monotherapy or in combination with remdesivir.[29] If a patient is mechanically ventilated, the recommendation is to administer corticosteroids monotherapy.[29] These patients are often later in the disease process and it is believed the symptoms are driven by an overactive immune and inflammatory response to the virus.

Other antiviral therapies that have been used but are not recommended at this time due to the lack of clinical trials are chloroquine, hydroxychloroquine, lopinavir/ritonavir combination, or other protease inhibitors. Several immune-based therapies are under investigation but not recommended at this time include: COVID-19 convalescent plasma, immunoglobulins (specific and nonspecific for SARS-CoV-2), interferons, IL-6 inhibitors, IL-1 inhibitors, Bruton tyrosine kinase inhibitors, and Janus kinase inhibitors.[29]

▶ *Pediatric Outpatient*

Guidelines have been published for treating CAP in children. The most predominant pathogens in preschool children in the outpatient setting are viruses, and often supportive therapy (maintaining hydration, antipyretics) is all that is needed.[30] For appropriately immunized infants, children, and adolescents

Patient Encounter 2, Part 3: Creating a Care Plan

A 66-year-old man was admitted to the hospital for abdominal aortic aneurysm surgery. He developed complications postoperatively and was intubated 7 days ago. The nurses note an increase in the amount and purulence of his sputum. Attempts yesterday and today to wean him off the ventilator have failed. Your hospital antibiogram for Gram-negative organisms is below; values are percentage of isolates susceptible to the antibiotic. Boxes without values indicate you should not use that antibiotic for that organism.

	Total No. Tested	Amikacin	Ampicillin	Amp/Sulbactam	Cefazolin	Cefepime	Ceftriaxone	Ciprofloxacin	Gentamicin	Imipenem/ Meropenem	Levofloxacin	Piperacillin/ Tazobactam	TMX/SMX	Tobramycin	Nitrofurantoin
Acinetobacter baumannii	29	62	0	69	0	45	17	34	48	66	38	55	41	62	
Citrobacter freundii complex	23		0	74	0	85	97	78	82	100	78	91	78	82	82
Klebsiella (Enterobacter) aerogenes	24		0	13	0	100	92	100	100	100	100	92	96	100	63
Enterobacter cloacae	61		0	9	0	95	82	80	87	100	74	79	82	84	79
Escherichia coli	375		2	40	63	93	90	65	88	96	65	72	60	90	98
Klebsiella pneumoniae	142		0	79	88	92	88	80	80	90	80	80	80	80	73
Proteus mirabilis	87		2	40	50	98	98	40	80	88	40	65	60	84	0
Serratia marcescens	31		6	29	0	100	100	97	100	100	97	97	97	81	3
Pseudomonas aeruginosa	132	52				85		45	50	70	45	90		65	

Based on the information presented, create a care plan for this patient's pneumonia. Your plan should include: (a) a statement of drug-related needs and/or problems; (b) a patient-specific detailed therapeutic plan; and (c) monitoring parameters to assess efficacy and safety.

Table 74–3

CAP Antimicrobial Dosing in Pediatric Patients

	Body Weight < 2000 g		Body Weight > 2000 g		
Drug (Route)	**0–7 Days Old**	**7–28 Days Old**	**0–7 Days Old**	**7–28 Days Old**	**> 28 Days Old**
Amoxicillin (po)				15 mg/kg every 12 hours	17 mg/kg every 8 hours
Amoxicillin-clavulanate (po)			15 mg/kg every 12 hours	15 mg/kg every 12 hours	45 mg/kg every 12 hours
Cefotaxime (IV)	50 mg/kg every 12 hours	50 mg/kg every 8 hours	50 mg/kg every 12 hours	50 mg/kg every 8 hours	50 mg/kg every 8 hours
Ceftriaxone (IM/IV)				50 mg/kg every 24 hours	50 mg/kg every 24 hours
Cefuroxime (po)					15 mg/kg every 12 hours
Azithromycin (po/IV)	5 mg/kg every 24 hours	10 mg/kg every 24 hours	5 mg/kg every 24 hours	10 mg/kg every 24 hours	10 mg/kg every 24 hours
Clarithromycin (po)					7.5 mg/kg every 12 hours

with mild-to-moderate pneumonia in an area lacking high-level penicillin-resistant pneumococcus, high-dose amoxicillin is the recommended first-line therapy. If atypical organisms are considered likely, then a macrolide is recommended. If moderate-to-severe CAP is diagnosed, and it is during influenza season, then treatment with oseltamivir, zanamivir (Relenza), amantadine, or rimantadine is recommended; however, seasonal resistance rates need to be evaluated.[29] Fluoroquinolones and tetracyclines should not be used in children younger than 5 years. Dosing of antibiotics for pediatric patients is presented in Table 74–3.

▶ *Pediatric Inpatient*

If the infant or child is fully immunized, then the guidelines recommend the use of IV penicillin G or ampicillin. Alternative β-lactams include IV cefotaxime or ceftriaxone. If the infant or child is not fully immunized, then the third-generation cephalosporins (eg, cefotaxime or ceftriaxone) should be administered.[30] If atypical organisms are suspected, add azithromycin to the β-lactam. If community-acquired MRSA is suspected, then vancomycin or clindamycin should be added to the regimen.[30]

Pharmacologic Therapy for HAP/VAP

Nosocomial pneumonia has since been replaced by the terms *HAP*, and *VAP*. **KEY CONCEPT** Empirical selection of antimicrobial therapy for ventilator- and hospital-associated pneumonia is broad spectrum; however, once culture and susceptibility information is available, the therapy should be narrowed (de-escalation) to cover the identified pathogen(s). Three factors important to the empirical selection of antibiotics for these types of pneumonia are risk of mortality, MRSA risk factors predominantly being in a hospital unit with an incidence of MRSA ≥ 20%, and the intravenous use of antibiotics in the prior 90 days.[1] MDR organisms that need to be considered include *P. aeruginosa*, extended-spectrum β-lactamase–producing *K. pneumoniae*, *Acinetobacter* spp., and MRSA. Empirical therapy for HAP and VAP is listed in Table 74–4 and is stratified by these three factors. If there is low risk of mortality and no MRSA risk factors, then recommended antibiotics include cefepime, piperacillin/tazobactam, or levofloxacin. If risk of mortality is high, or intravenous antibiotics have been used in the prior 90 days, then double coverage for Gram-negative bacilli including *P. aeruginosa* is recommended. If MRSA is suspected, then either vancomycin or linezolid should be added to the regimen.[1]

Currently, there is debate over whether or not double coverage for *Pseudomonas* is required. In vitro studies have shown that aminoglycosides exhibit synergistic killing against Gram-negative bacilli when combined with β-lactams. Dosing of the aminoglycosides is dependent on the patient's renal function. A high-dose once-daily regimen (eg, 4–7 mg/kg gentamicin or tobramycin or 15–20 mg/kg amikacin) can be utilized in patients with good renal function. Most of the studies enrolled patients with estimated creatinine clearances of at least 70 mL/min (1.17 mL/s). Meta-analyses have shown high-dose once-daily regimens to be as efficacious as and less toxic than divided-daily dosing.[31-35] Divided-daily dosing (eg, 1–2 mg/kg gentamicin or tobramycin or 7.5 mg/kg amikacin) has been utilized since the 1970s, and the dosing interval is based on the patient's renal function to achieve a trough concentration of less than 2 mcg/mL (2 mg/L; 4 μmol/L) for gentamicin and tobramycin and less than 5 mcg/mL (5 mg/L; 9 μmol/L) for amikacin.

In addition to obtaining a synergistic effect, the primary reason for double coverage when treating VAP, or HAP, is to broaden the coverage empirically to increase the likelihood of covering the majority of resistant pathogens. VAP is the most studied of these types of pneumonias and is often the most severe. There is an increase in mortality when inadequate therapy is initiated for VAP. Crude mortality ranges are quite large (35%–92%) compared with estimates of attributable mortality (approximately 9%); however, attributable mortality studies are limited by the large sample size needed to accurately measure this outcome.[36-38]

KEY CONCEPT Once a pathogen or pathogens have been identified, therapy should be narrowed (de-escalated) to cover only those pathogens. Use of broad-spectrum antibiotics for prolonged durations increases the risk of colonization with MDR pathogens.

Duration of Antimicrobial Therapy

KEY CONCEPT The duration of therapy for pneumonia should be kept as short as possible and depends on several factors: type of pneumonia, inpatient or outpatient status, patient comorbidities, bacteremia/sepsis, and the antibiotic chosen. If the duration of therapy is too prolonged, then it can have a negative impact on the patient's normal flora in the respiratory and gastrointestinal tracts, vaginal tract of women, and on the skin. This can result in colonization with resistant pathogens, *C. difficile*, or overgrowth of yeast. In addition, the longer antibiotics are administered, the greater the chance for toxicity from the agent, as well as an increase in cost.

Table 74–4

Empirical Therapy HAP in Adults

Low Risk of Mortality and No Risk Factors for MRSA	Low Risk of Mortality With Risk Factors for MRSA	High Risk of Mortality or Received Intravenous Antibiotics in the Prior 90 Days
One of the following Piperacillin/tazobactam[c] 4.5 g IV q6h OR Cefepime[c] 2 g IV q8h OR Levofloxacin 750 mg PO/IV once daily	One of the following Piperacillin/tazobactam[c] 4.5 g IV q6h OR Cefepime[c] or Ceftazidime 2 g IV q8h OR Levofloxacin 750 mg PO/IV once daily Ciprofloxacin 400 mg IV q8h OR Imipenem[c] 500 mg IV q6h Meropenem[c] 1 g IV q8h OR Aztreonam[a] 2 g IV q8h PLUS Vancomycin[d] 15 mg/kg IV q8–12h OR Linezolid 600 mg IV/PO q12h	Two of the following Piperacillin/tazobactam[c] 4.5 g IV q6h OR Cefepime[c] or Ceftazidime 2 g IV q8h OR Levofloxacin 750 mg PO/IV once daily Ciprofloxacin 400 mg IV q8h OR Imipenem[c] 500 mg IV q6h Meropenem[c] 1 g IV q8h OR Aztreonam[a] 2 g IV q8h OR Amikacin[b] 15–20 mg/kg IV q24h Gentamicin[b] or Tobramycin[b] 5–7 mg/kg IV q24h PLUS Vancomycin[d] 15 mg/kg IV q8–12h OR Linezolid 600 mg IV/PO q12h

[a] Aztreonam should be reserved for a patient with a severe β-lactam allergy.

[b] Trough concentrations ideally should be nondetectable; < 1 mcg/mL for gentamicin and tobramycin (1 mg/L; 2 μmol/L) and < 4–5 mcg/mL (4–5 mg/L; 7–9 μmol/L) for amikacin.

[c] Extended infusions can be utilized.

[d] Target area under the curve (AUC) > 400 (400–650) or target trough concentration of 15–20 mcg/mL.

The IDSA recommends treatment for CAP for a minimum of 5 days, and if the patient has been afebrile for 48 to 72 hours and has no more than 1 CAP-associated sign of instability (heart rate ≤ 100 beats/min, respiratory rate ≤ 24 breaths/min, systolic blood pressure ≥ 90 mm Hg, oxygen saturation ≥ 90% on room air, tolerating oral intake or normal mental status) then treatment can be discontinued.[24] For treatment of CAP in adult patients admitted to the hospital, the duration is dependent on whether or not blood cultures were positive. In the absence of positive blood cultures, the criteria for the 5-day duration of therapy listed above was validated for hospitalized patients and demonstrated similar clinical success as compared to longer durations of therapy.[39] If blood cultures were positive, the duration of therapy should be 2 weeks from the day blood cultures first became negative. The duration of therapy in pediatric patients is 10 days for uncomplicated CAP, with the exception of azithromycin, which is approved for 5 days.[30]

The duration of therapy cited in the literature for HAP or VAP ranges from 10 to 21 days. The ATS and IDSA guidelines (Table 74–5) recommend a shortened duration of therapy from the traditional 14 to 21 days to 7 days.[1] The ratings for the recommendations is a strong recommendation with moderate quality of evidence for VAP and a strong recommendation with very low quality of evidence for HAP.[1] Shorter or longer durations of therapy could be appropriate and should be based on the rate of improvement of clinical, radiological, and laboratory parameters. Shortening the duration of therapy was found to be beneficial with regard to secondary infections, colonization, toxicity, and cost issues. Several studies evaluated mortality, clinical success, recurrence, or the development of resistance with shorter courses of therapy for VAP and found no differences when compared with longer courses of therapy.[37,40]

OUTCOME EVALUATION

For CAP, outcomes include preventing hospitalization, shortening the duration of hospitalization, and minimizing mortality. Improvement of symptoms should occur within 24 to 72 hours after initiation of therapy for most patients with CAP. Response to therapy could be slowed in patients with underlying pulmonary disease such as moderate-to-severe asthma, COPD, or emphysema. In patients not responding to therapy, consider patient comorbid conditions, other infectious and noninfectious reasons, and a drug-resistant pathogen as a causative agent. Noninfectious reasons to consider include pulmonary embolus, congestive heart failure, carcinoma, lymphoma, intrapulmonary hemorrhage, and certain inflammatory lung diseases.

Outcome parameters for VAP and HAP are similar to those with CAP. Clinical improvement should occur within 48 to 72 hours of the start of therapy. If a patient is not responding to therapy, then, again, consider infectious and noninfectious reasons. Infectious explanations are the same as for CAP stated above, but noninfectious are not. They include atelectasis, ARDS, pulmonary embolism or hemorrhage, cancer, empyema, or lung abscess.

PREVENTION

KEY CONCEPT Prevention of both pneumococcal and influenza pneumonia by the use of vaccination is a national goal (Table 74–6). Vaccination is used to prevent or minimize the severity of pneumonia caused by *S. pneumoniae* or the influenza virus. Further information on vaccination can be found in Chapter 86.

The influenza vaccine is available in two forms: trivalent and quadrivalent. The trivalent vaccines are injectable and inactivated,

Table 74–5

Empirical Therapy VAP in Adults[a,b]

MRSA Coverage	Gram-Negative β-Lactam Antibiotics with Antipseudomonal Activity	Gram-Negative Non-β-Lactam Antibiotics with Antipseudomonal Activity
Vancomycin[c] 15 mg/kg IV q8–12h	Piperacillin/tazobactam[d] 4.5 g IV q6h	Levofloxacin 750 mg PO/IV once daily Ciprofloxacin 400 mg IV q8h
OR	OR	OR
Linezolid 600 mg IV/PO q12h	Cefepime[e] or Ceftazidime 2 g IV q8h	Amikacin[e] 15–20 mg/kg IV q24h Gentamicin[e] or Tobramycin[b] 5–7 mg/kg IV q24h
	OR	OR
	Imipenem[d] 500 mg IV q6h or Meropenem[d] 1 g IV q8h	Colistin 5 mg/kg IV × 1 followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h Polymyxin B 2.5–3 mg/kg/day IV divided in two daily doses
	OR	
	Aztreonam[f] 2 g IV q8h	

[a] Choose one agent for MRSA coverage PLUS one β-lactam antibiotic PLUS one non-β-lactam antibiotic.

[b] The hospital antibiogram or intensive care unit specific antibiogram should influence the selection from each column.

[c] Target area under the curve (AUC) > 400 (400–650) or target trough concentration of 15–20 mcg/mL.

[d] Extended infusions can be utilized.

[e] Trough concentrations ideally should be nondetectable; < 1 mcg/mL for gentamicin and tobramycin (1 mg/L; 2 μmol/L) and < 4–5 mcg/mL (4–5 mg/L; 7–9 μmol/L) for amikacin.

[f] Aztreonam should be reserved for a patient with a severe β-lactam allergy.

consisting of 2 type A and 1 type B influenza viruses, and are being phased out.[41]

The quadrivalent vaccines contain 2 type A and 2 type B influenza viruses. Each manufacturer has different age approvals and should be evaluated prior to use in pediatric patients.[41] The ability of influenza vaccine to protect a person depends on two key factors: the age and health status of the person getting the vaccine, and the similarity or "match" between the virus strains in the vaccine and those in circulation. Protective antibodies are detected approximately 2 weeks after vaccination. The Centers for Disease Control and Prevention (CDC) adopted a universal influenza vaccination policy, thus recommending all persons 6 months of age and older to be vaccinated annually prior to the start of during influenza season.

Table 74–6

Immunizations

Type	Approved Ages and Conditions
Influenza	
Quadrivalent—Killed	>6 months of age
• High dose, killed	Adults 65 years and older
• Live-attenuated	Healthy individuals 2–49 years, not during pregnancy
Trivalent	Adults 65 years and older
Pneumococcal	
PSV 23 valent	Adults 65 years and older; individuals 19–64 years at increased risk due to health conditions[a,b]
Conjugated 13 valent	2–15 months, recommended schedule; adults 65 years and older based on shared decision-making; children or adults at increased risk due to health conditions[b]

[a] Chronic heart (excluding hypertension), lung, or liver disease, diabetes, alcoholism, or cigarette smoking.

[b] Chronic heart disease; chronic lung disease; diabetes mellitus; cerebrospinal fluid leak; cochlear implants, sickle cell disease; hemoglobinopathies; asplenic; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; leukemia; Hodgkin disease; malignancy; long-term immunosuppressive therapy; solid organ transplant; multiple myeloma.

There are currently three different types of coronavirus, specifically COVID-19 vaccines under development or approved for emergency use authorization (EUA) by the FDA. Two different mRNA vaccines are approved for EUA in December 2020. The mRNA vaccines are taken up into host cells to allow expression of the SARS-CoV-2 S antigen by host cells, eliciting an immune response to the S antigen. Vector vaccines use a weakened/attenuated virus (not coronavirus), which contains COVID-19 genes for making COVID-19 proteins/antigens, to elicit an immune response. The third type of vaccines are protein subunit vaccines, which are pieces of the COVID-19 virus to elicit an immune response.[42] (please refer to Upper Respiratory Tract Infections Chapter 75).

Pneumococcal conjugate vaccine (PCV) comprises 13 serotypes and is recommended for all babies and children younger than 2 years old, adults 65 years or older based on shared decision making, and people 2 through 64 years old with certain medical conditions. Pneumococcal polysaccharide vaccine (PSV) comprises 23 serotypes and is recommended for all adults 65 years or older, people 2 through 64 years old who are at increased risk for disease due to certain medical conditions, and adults 19 through 64 years old who smoke cigarettes. The serotypes in the PCV13 are the most common disease-causing strains of pneumococcus.[43,44] A reliable immunologic response to the PCV13 has been demonstrated, along with a favorable safety profile.[44,45] The 23 capsular types in the PPSV23 represent at least 85% to 90% of the serotypes that cause invasive pneumococcal infections among children and adults in the United States. Ten years after vaccination, a sample of elderly individuals demonstrated significant quantity of protective antibodies.[46] Individuals 65 years and older should receive the PSV23 vaccine every 5 years for a maximum of three doses.[47] Additional information on these vaccines is available on the CDC website, Advisory Committee on Immunization Practices (ACIP; https://www.cdc.gov/vaccines/acip/index.html).

Patient Care Process

KEY CONCEPT Monitoring response to therapy is essential for determining efficacy, identifying adverse reactions, and determining the duration of therapy.

Collect Information:

- Perform a medication history for the use of prescription and nonprescription medications and dietary supplements.
- Identify allergies to medications, including the reaction.
- Review the medical history and physical assessment findings.
- Speak with the patient (except for VAP patients) or family members to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Evaluate the symptoms, and status (ie, inpatient, outpatient, or intubated) to determine the type of pneumonia.
- Identify comorbid conditions of asthma, COPD, or emphysema, smoking history to determine if there are factors that could slow or alter the rate of response to therapy due to bronchial or lung damage or impact the pathogen list.
- Review chest X-ray, pulse oximetry, laboratory values, microbiology data, and vital signs available.
- Assess allergies and drug intolerances, noting the severity of the reaction.
- Identify any significant drug interactions or adverse drug effects.

Develop a Care Plan:

- Determine the top two to three organisms associated with the type of pneumonia for the patient (Table 74–1).
- Select an appropriate empirical antibiotic regimen for the patient and type of pneumonia, ensuring that the doses are correct for renal function and medication allergies or intolerances (see **Tables 74–2** and **74–3**).

Implement the Care Plan:

- Educate the patient on the importance of completing their antibiotic therapy, medication adverse effects, and drug interactions.
- Address any patient concerns regarding their pneumonia and its management.
- Determine whether the patient has insurance coverage or if the recommended agent(s) are included on the institution's formulary.

Follow-up: Monitor and Evaluate:

- Assess the effectiveness of the antibiotic therapy after 24 to 72 hours looking for improvement in signs and symptoms.
- If the patient responds to therapy within the first 72 hours, consider a 5- to 7-day course of therapy for CAP and HAP/VAP, respectively. If inpatient status, assess the patient for conversion from IV to oral therapy.
- If the patient is not improving, then reevaluate the diagnosis and pathogen list, and make appropriate changes to therapy.
- Assess the patient for the presence of adverse drug reactions, drug allergies, and drug interactions.
- Discuss with the patient the value of vaccination against *S. pneumoniae* and/or influenza. Recommend and administer vaccinations annually during the season for influenza and as appropriate for the patient for *S. pneumoniae*.

Abbreviations Introduced in This Chapter

ARDS	Acute respiratory distress syndrome
ATS	American Thoracic Society
BUN	Blood urea nitrogen
CA-MRSA	Community-acquired methicillin-resistant *Staphylococcus aureus*
CAP	Community-acquired pneumonia
CDC	Centers for Disease Control and Prevention
COPD	Chronic obstructive pulmonary disease
DFA	Direct fluorescence antigen
GER(D)	Gastroesophageal reflux (disease)
H	Hemagglutinin
HAP	Hospital-acquired pneumonia
IDSA	Infectious Diseases Society of America
MDR	Multidrug resistant
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
N	Neuraminidase
PBP	Penicillin-binding protein
PCR	Polymerase chain reaction
PCV13	Pneumococcal 13-valent conjugated vaccine
PPSV23	Purified-capsular polysaccharide 23-antigen vaccine
TNF-α	Tumor necrosis factor alpha
VAP	Ventilator-associated pneumonia

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75 Upper Respiratory Tract Infections

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. List common bacteria that cause acute otitis media (AOM), acute bacterial rhinosinusitis (ABRS), and acute pharyngitis.
2. Explain the pathophysiology of and risk factors for AOM, ABRS, and streptococcal pharyngitis.
3. Identify clinical signs and symptoms associated with AOM, ABRS, streptococcal pharyngitis, and the common cold.
4. List treatment goals for AOM, ABRS, streptococcal pharyngitis, and the common cold.
5. Develop a treatment plan for a patient with an upper respiratory tract infection (URI) based on patient-specific information.
6. Create a monitoring plan for a patient with a URI based on patient-specific information and the treatment regimen.
7. Formulate appropriate educational information for patients about URIs and proper antibiotic use.

INTRODUCTION

Upper respiratory tract infection (URI) is a comprehensive term for upper airway infections, including otitis media, sinusitis, pharyngitis, laryngitis, and the common cold. Over 1 billion URIs occur annually in the United States, triggering millions of antibiotic prescriptions each year, of which up to 50% are considered inappropriate for use for acute respiratory conditions.[1] **KEY CONCEPT** Most URIs are caused by viruses, have nonspecific symptoms, and resolve spontaneously.[2] Antibiotics are not effective for viral URIs, and their excessive use has contributed to resistance, which has prompted development of clinical guidelines and national campaigns to reduce inappropriate prescribing.[2-7] This chapter focuses on acute otitis media (AOM), sinusitis, and pharyngitis, which are frequently caused by viruses but may be caused by bacteria. Proper management of the common cold is also reviewed.

OTITIS MEDIA

Otitis media, or middle ear inflammation, is the most common childhood illness treated with antibiotics. It can be subclassified as otitis media with effusion (OME) or AOM. OME is characterized by the presence of a noninfectious effusion, or fluid, in the middle ear and is not an acute illness. AOM is a rapid, symptomatic infection with middle ear effusion that usually results from an initial nasopharyngeal viral infection. Antibiotics are only useful for the treatment of some AOM episodes. While the use of antibiotics for otitis media has declined since the mid-1990s, antibiotic prescription rates remain as high as 60% to 80%.[1,8]

Epidemiology and Etiology

AOM occurs in all ages but has a peak incidence in the first year of life. By 3 years of age, about 60% of children have had at least one episode of AOM and nearly 25% have had at least three episodes of AOM.[9] Many risk factors (Table 75–1) predispose children to otitis media.[9,10]

Although AOM occurs frequently with viral URIs, bacteria are isolated from middle ear fluid in 70% to 90% of children with AOM.[3,9] Historically, *Streptococcus pneumoniae* was the most common organism, responsible for up to half of bacterial cases.[3,9] *Haemophilus influenzae* and *Moraxella catarrhalis* caused up to 30% and 20% of cases, respectively. Routine childhood pneumococcal vaccination has altered the microbiology such that *H. influenzae* is now responsible for up to 60% of bacterial cases.[9,11] Viruses are isolated from middle ear fluid with or without concomitant bacteria in up to 70% of cases.[12] Lack of improvement with antibiotics is usually a result of viral infection and subsequent inflammation rather than antibiotic resistance.

Antibiotics should have adequate activity against *S. pneumoniae* because pneumococcal AOM is unlikely to resolve spontaneously and commonly results in more ear pain and fever.[3,11] Penicillin-resistant *S. pneumoniae* (PRSP) exhibit intermediate resistance (minimum inhibitory concentrations [MIC] between 0.12 and 1.0 mcg/mL [0.12 and 1.0 mg/L]) or high-level resistance (MIC of 2.0 mcg/mL [2.0 mg/L] and higher). Altered penicillin-binding proteins cause resistance in 30% to 35% of pneumococci with up to half of these strains exhibiting high-level resistance.[9,13,14] Recent data show that the prevalence of high-level penicillin resistance is less than 5% in pneumococci obtained from children.[15] Amoxicillin resistance is less common than penicillin resistance, occurring in 2% to 4% of pneumococci.[14,15] PRSP are frequently resistant to other drug classes, including sulfonamides, macrolides, and clindamycin but are usually susceptible to levofloxacin.[14] β-Lactamase production occurs in 20% to 45% of *H. influenzae* and 90% to 100% of *M. catarrhalis* strains.[9,11] Although infections caused by these organisms are more likely to

Table 75–1

Risk Factors for Otitis Media[9,10]

- Adenoid hypertrophy
- Atopy
- Craniofacial defects
- Daycare attendance
- Gastroesophageal reflux
- Immunodeficiency
- Lack of breast-feeding
- Low socioeconomic status
- Male sex
- Non-Hispanic White race
- Pacifier use
- Positive family history/genetic predisposition
- Siblings
- Tobacco smoke exposure
- Upper respiratory tract infection
- Winter season
- Young age

resolve without treatment, they should be considered when failure occurs or when there is recurrent disease.[3,11]

Pathophysiology

AOM is caused by an interplay of factors. Viral URIs impair eustachian tube function and cause mucosal inflammation, impairing mucociliary clearance and promoting bacterial proliferation and infection. Children are predisposed because they have shorter, more flaccid, and more horizontal eustachian tubes than adults, which are less functional for middle ear drainage and protection. Clinical manifestations of AOM result from host immune response and cellular damage from inflammatory mediators released by bacteria.

Viscous effusions caused by allergy or irritant exposure contribute to impaired mucociliary clearance and AOM in susceptible individuals. Effusions can persist for up to 6 months after an episode of AOM. Atopic children experience chronic OME that may require **tympanostomy tube** placement to reduce complications such as hearing and speech impairment and recurrent AOM.

Patient Encounter 1, Part 1

A 9-month-old Caucasian boy presents to the family medicine clinic with 18 hours of fever (maximum temperature of 38.7°C [101.7°F]) and 3 days of rhinorrhea and nasal congestion. His mother states that her son is irritable and was crying intermittently last night with interrupted sleep. He has not eaten well this morning. Both of the child's parents have had upper respiratory tract infection symptoms with rhinorrhea and nasal congestion over the past week. The child attends daycare 3 days a week.

What information is suggestive of acute otitis media (AOM)?

What risk factors does this child have for AOM?

Is there any additional information you need to know before recommending a treatment plan?

Treatment

The goals of treatment are to alleviate ear pain and fever; eradicate infection; prevent complications; and avoid unnecessary antibiotic use.

▶ *General Approach to Treatment*

Most uncomplicated cases of AOM do not require antibiotic treatment and will resolve spontaneously. Untreated AOM improves in over 80% of children between days 2 and 3 of illness without increasing complications.[16] Antibiotics improve **otalgia** in only 5% of children between days 2 and 3 of therapy while *increasing* the risk of adverse effects by 38%.[16] Antibiotics significantly improve recovery in children younger than 2 years with bilateral AOM and in those with AOM and otorrhea.[16] Children

Clinical Presentation and Diagnosis of AOM

Patients with AOM usually have URI symptoms, including rhinorrhea, cough, or nasal congestion, before or at diagnosis.

Symptoms

- Young children: ear tugging or rubbing, irritable, poor sleeping and eating
- Older patients: ear pain, ear fullness, hearing impairment

Signs[3]

- Fever: not common in older children; often in younger children
- Middle ear effusion
- Otorrhea with tympanic membrane perforation
- Bulging tympanic membrane
- Limited or absent mobility of tympanic membrane
- Distinct erythema of tympanic membrane
- Opaque tympanic membrane that obscures middle ear visibility

Laboratory Tests

- Gram stain, culture, and sensitivities of ear fluid if draining spontaneously or obtained via **tympanocentesis** (not performed routinely in practice)

Complications

- Infectious (rare; occur in < 1%): mastoiditis, meningitis, osteomyelitis, intracranial abscess
- Structural: perforated eardrum (occurs in up to 20%), **cholesteatoma** (rare; occurs in < 1%)
- Hearing and/or speech impairment (transient impairment occurs in most patients)

Diagnosis[3]

AOM should be diagnosed if any of the following are present:

- Moderate-to-severe bulging of tympanic membrane (usually with impaired mobility as assessed by **pneumatic otoscopy**)
- Mild bulging of tympanic membrane *and* recent onset (< 48 hours) of otalgia (or ear rubbing/tugging in nonverbal child) or intense erythema of tympanic membrane
- New onset otorrhea not caused by acute otitis externa
- Severe AOM: Moderate-to-severe otalgia or otalgia for at least 48 hours *or* temperature of 39.0°C (102.2°F) or greater

younger than 2 years have a higher incidence of PRSP infections, and children between 6 months and 3 years have higher clinical and bacteriologic failure rates and complications without initial antibiotic treatment as compared with older children.[3,17] Patients with severe AOM have lower spontaneous recovery rates than those with less severe disease, particularly in children less than 2 years.[3,18] **KEY CONCEPT** Therefore, antibiotics should be reserved for patients most likely to benefit, which is dependent on proper diagnosis, patient age, and illness severity. Current guidelines stratify patients using these criteria in order to identify those most likely to benefit from antibiotics.[3]

▶ *Nonpharmacologic Therapy*

Watchful waiting and delayed antibiotic prescriptions (prescription given to the patient but only filled if symptoms persist or worsen within 48–72 hours after diagnosis) are approaches used to attenuate microbial resistance and avoid unnecessary antibiotic adverse effects and costs. Initial observation and use of delayed prescriptions in older children and those with less severe disease can reduce antibiotic use by 60% without increasing complications.[16,19] These approaches should only be considered in otherwise healthy children (Figure 75–1) as a joint decision between the clinician and the parent/caregiver and only if close follow-up and good communication exist.[3]

Children with recurrent AOM or chronic OME with impaired hearing or speech may benefit from surgery (tympanostomy tube placement with or without adenoidectomy).

▶ *Pharmacologic Therapy*

Adjunctive Therapy Pain is a central feature of AOM but it is often overlooked. Analgesics provide relief within 24 hours and should be used regardless of antibiotic therapy.[3] Acetaminophen and ibuprofen are commonly used for mild-to-moderate pain. Ibuprofen provides longer relief than acetaminophen but should be avoided in children younger than 6 months because of increased toxicity concerns. Alternating ibuprofen with acetaminophen is not recommended because of the potential for dosing error in ambulatory settings and a lack of safety and efficacy data. Aspirin should be avoided in children because of the risk for Reye syndrome. Myringotomy provides immediate relief but is rarely performed. Decongestants, antihistamines, and corticosteroids have no role in AOM treatment and can prolong effusion duration.[3,20] Data are lacking on the safety and efficacy of complementary and alternative treatments.

Antibiotic Therapy When antibiotics are necessary, clinicians must consider drug factors (eg, antimicrobial spectrum, likelihood of response, middle ear fluid penetration, side effects, drug interactions, and cost) and patient factors (eg, risk factors for resistance, allergies, regimen complexity, medication palatability, and the presence of other medical conditions). Studies in uncomplicated AOM have not revealed significant differences between antibiotics in clinical response rates, but most were confounded by spontaneous resolution in children likely to have had viral URIs. Bacteriologic response varies among antibiotics and does not always correlate well with clinical response but is considered important when selecting therapy.[3]

The American Academy of Pediatrics (AAP) developed clinical guidelines for healthy children between 6 months and 12 years of age with uncomplicated AOM (Figure 75–2).[3] **KEY CONCEPT** Amoxicillin is the drug of choice in most patients because of its proven effectiveness, high middle ear concentrations, excellent safety profile, low cost, palatable suspension, and relatively narrow spectrum (Table 75–2). High-dose amoxicillin (80–90 mg/kg/day) is preferred over conventional doses (40–45 mg/kg/day) because higher middle ear fluid concentrations can overcome pneumococcal penicillin resistance without substantially increasing adverse effects.[3,21] High-dose amoxicillin–clavulanate is preferred for children who received amoxicillin in the previous 30 days, have concurrent purulent conjunctivitis,

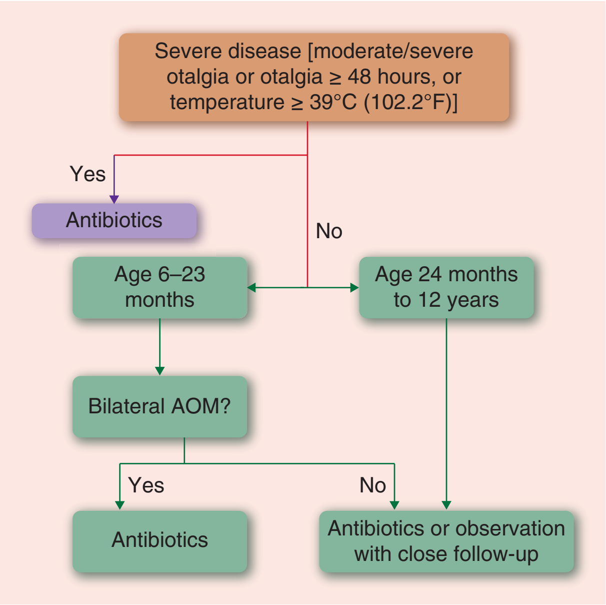
Severe disease [moderate/severe otalgia or otalgia ≥ 48 hours, or temperature ≥ 39°C (102.2°F)]
Yes
Antibiotics
No
Age 6–23 months
Age 24 months to 12 years
Bilateral AOM?
Yes
No
Antibiotics
Antibiotics or observation with close follow-up

FIGURE 75–1. Treatment algorithm for initial antibiotics or observation in children 6 months to 12 years of age with uncomplicated AOM. (Data from Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013;131(3):e964–e999.)

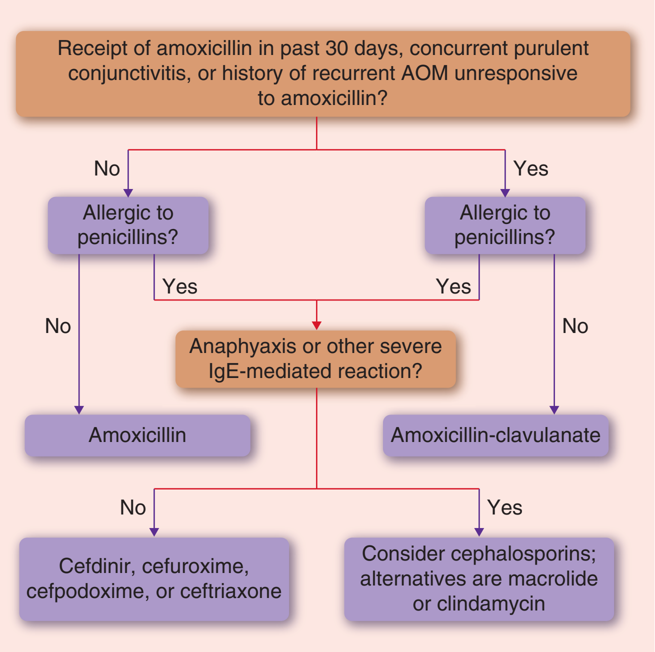
Receipt of amoxicillin in past 30 days, concurrent purulent conjunctivitis, or history of recurrent AOM unresponsive to amoxicillin?
No
Yes
Allergic to penicillins?
Allergic to penicillins?
Yes
Yes
No
No
Anaphyaxis or other severe IgE-mediated reaction?
Amoxicillin
Amoxicillin-clavulanate
No
Yes
Cefdinir, cefuroxime, cefpodoxime, or ceftriaxone
Consider cephalosporins; alternatives are macrolide or clindamycin

FIGURE 75–2. Treatment algorithm for uncomplicated AOM in children 6 months to 12 years of age. (Data from Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013;131(3):e964–e999.)

Table 75–2

Antibiotics[a] for the Treatment of Acute Otitis Media

Drug	Usual Dose and Schedule	Common Adverse Effects	Relative Cost[b]	Comments
Amoxicillin	80–90 mg/kg/day divided in two doses (adult: 875 mg twice daily)	Nausea, vomiting, diarrhea, rash	$	Drug of choice for AOM; experts recommend high dose to overcome penicillin resistance
Amoxicillin–clavulanate	90 mg/kg/day divided in two doses (adult: 875 mg twice daily)	Nausea, vomiting, diarrhea, rash, diaper rash	$$	More diarrhea than amoxicillin; amoxicillin:clavulanate ratio of 14:1 preferred because of lower daily clavulanate component
Cefdinir	14 mg/kg/day divided in one to two doses (adult: 300 mg twice daily or 600 mg once daily)	Diarrhea, rash, vomiting, diaper rash, yeast infections	$$	Preferred oral cephalosporin (pleasant taste); separate from Fe supplements by 3 hours
Cefpodoxime proxetil	10 mg/kg/day divided in two doses (adult: 200 mg twice daily)	Diarrhea, diaper rash, vomiting, rash, yeast infections	$$$–$$$$	Suspension is bitter tasting
Ceftriaxone	50 mg/kg IM or IV for 1 or 3 days (max 1 g/dose)	Injection site pain, swelling, or erythema; diarrhea, rash	$$$–$$$$	3-day regimen preferred for PRSP
Cefuroxime axetil	30 mg/kg/day divided in two doses (adult: 250 mg twice daily)	Nausea, vomiting, diarrhea, rash, diaper rash	$$–$$$	Suspension is no longer available in the United States

[a] Other FDA-approved antibiotics for AOM not recommended in AAP guidelines: azithromycin, cefaclor, cefixime, cefprozil, ceftibuten, cephalexin, clarithromycin, erythromycin-sulfisoxazole, and trimethoprim–sulfamethoxazole.

[b] Approximate cost per course: $ (under $25), $$ ($25–$50), $$$ ($50–$100), $$$$ (over $100).

AAP, American Academy of Pediatrics AOM, acute otitis media; Fe, iron; IM, intramuscular; IV, intravenous; PRSP, penicillin-resistant *S. pneumoniae.*

Data from Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013;131(3):e964–e999.

have a history of recurrent AOM unresponsive to amoxicillin, and when coverage for β-lactamase–producing organisms is desired.[3] Despite reported high rates of penicillin allergies, only those with immunologic penicillin or amoxicillin allergies, such as hives, require alternative therapy (see Figure 75–2). There is limited cross-reactivity between penicillins and newer cephalosporins, which supports AAP recommendations to use cephalosporins in penicillin-allergic patients because they are more effective than alternatives.[3,22] Trimethoprim–sulfamethoxazole and macrolides are less active against *S. pneumoniae* and *H. influenzae* than the preferred cephalosporins, making them less appropriate for most penicillin-allergic patients.[3,14,23] Single-dose intramuscular ceftriaxone is effective for children who cannot tolerate oral medications, but a 3-day course may be preferred to prevent recurrence caused by resistant pneumococci and because of reported treatment failures with single doses.[3] Ototopical antibiotic and glucocorticoid combinations are more effective than systemic antibiotics for patients with acute otorrhea and tympanostomy tubes.[24]

If there is no improvement or worsening with initial therapy during the first 48 to 72 hours, proper diagnosis and antibiotic selection must be reassessed.[3] Tympanocentesis can assist with guiding therapy in difficult cases.

Duration of antimicrobial therapy depends on antibiotic selection, patient characteristics, and acceptability of failure if a short treatment course is used. The risk of treatment failure within 1 month is modestly higher with short-course therapy (3–5 day regimens) than standard-course therapy (minimum 7 days), but failure rates with short-course therapy are significantly higher in children with perforated eardrums.[25] Failure with short-course amoxicillin–clavulanate is also significantly more common in children 6 to 23 months of age as compared to 10 days of therapy.[26] Short-course regimens have not been proven to reduce the rates of adverse events or emergence of microbial resistance.[25,26] Standard 10-day regimens are recommended for all severe infections and for children younger than 2 years.[3] 7-day regimens and 5- to 7-day regimens can be considered for mild-to-moderate AOM in children 2 to 5 years and children 6 years and older, respectively.[3]

Prevention

Influenza vaccines and pneumococcal conjugate vaccines may prevent AOM in certain patients, but their benefits are small, and they should not be administered solely for this purpose.[27,28] Antibiotic prophylaxis is not recommended because of selection pressure on microbial resistance. Exclusive breast-feeding for the first 6 months of life, avoiding supine feeding, and reducing or eliminating pacifier use in the second 6 months of life have been associated with a reduced incidence and recurrence of AOM.[3] Avoidance of tobacco smoke and treatment of gastroesophageal reflux (if present) are advised, but the effects of these interventions on AOM remain unproven.

Outcome Evaluation

Improvement of signs and symptoms (ie, pain, fever, and tympanic membrane inflammation) should be evident by 72 hours of proper therapy. Children can appear clinically worse during the first 24 hours but often stabilize during the second day. If symptoms persist or worsen, reevaluate the patient for the proper diagnosis and treatment. Counsel patients and caregivers regarding common antibiotic adverse effects such as rash, diarrhea, and vomiting that may prompt additional medical attention.

Patient Care Process for Upper Respiratory Tract Infections

Collect Information:

- Perform a medication history including prescription and nonprescription medications or therapies and dietary supplements. Identify allergies and adverse reactions to medications or other substances and document reaction(s) that occurred. Gather information on immunization history from the patient or patient's parent or caregiver and medical records including immunization registry, if applicable.
- Review the medical history and physical examination findings.
- Speak with the patient or patient's parent or caregiver to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Based on patient history and physical examination findings, determine if the patient has a bacterial infection and, if present, whether it is severe and/or recurrent.
- Determine if antibiotic therapy is indicated.
- Determine if the patient is current or behind on recommended immunizations.
- Determine if modifiable risk factors are present, such as exposure to tobacco smoke.
- Assess the effectiveness, safety, and patient adherence of current pharmacotherapy, where applicable.
- Identify comorbidities or conditions that may complicate the treatment plan or prompt referral to a specialist.

Develop a Care Plan:

- Select appropriate analgesic therapy that will provide optimal pain relief and appropriate adjunctive therapies to relieve symptoms.
- If appropriate, select antibiotic therapy that is likely to be effective and safe.
- Select an optimal antibiotic dose and an appropriate duration of treatment based on patient age and illness severity.

Implement the Care Plan:

- Discuss expectations for improvement of signs and symptoms with the patient, parent, or caregiver.
- Discuss importance of medication adherence to treat symptoms and infection.
- Discuss potential medication adverse effects and how to manage them.
- When appropriate, recommend and/or administer influenza and pneumococcal conjugate vaccinations to reduce risk for future infections.

Follow-up: Monitor and Evaluate:

- Reevaluate patient if symptoms persist or worsen.

The presence of middle ear effusion in the absence of symptoms is not an indicator of treatment failure. Evaluate hearing in children who are otherwise healthy and have persistent effusion lasting 3 months in duration. Preschool-aged and younger children or those at risk for developmental difficulties may need reexamination earlier because speech and hearing impairment is more difficult to assess in these populations.

SINUSITIS

Sinusitis, or paranasal sinus inflammation, occurs in nearly all viral URIs and is often described as rhinosinusitis because it involves contiguous nasal mucosa. Acute rhinosinusitis is characterized by symptoms that persist for up to 4 weeks, whereas chronic rhinosinusitis lasts for more than 12 weeks. Acute bacterial rhinosinusitis (ABRS) refers to an acute bacterial sinus infection that occurs independently of or is superimposed on chronic sinusitis. This section will focus on ABRS.

Epidemiology and Etiology

Rhinosinusitis affects 12% of adults annually in the United States.[4] It is caused mainly by respiratory viruses but can also be triggered by allergies or environmental irritants. Viral rhinosinusitis is complicated by secondary bacterial infection in 0.2% to 2% of adults and 5% to 7% of children.[5,6] Sinusitis is the most common diagnosis associated with antibiotic prescriptions; they are used in 70% to 85% of cases, of which up to half are considered inappropriate.[1] URIs of less than 7 to 10 days' duration are usually viral, whereas more prolonged or severe symptoms are often caused by bacteria. Common risk factors for ABRS include

Patient Encounter 1, Part 2

On further questioning, his mother states that he is allergic to cephalexin. He was treated for impetigo 2 months ago and experienced diarrhea while taking this antibiotic. He has not received antibiotics since that time, and this is his first ear infection.

Immunizations: Up to date but has not received any influenza vaccines

Meds: Acetaminophen 120 mg orally every 4 to 6 hours as needed for fever

ROS: (+) rhinorrhea, nasal congestion, and fever, (–) vomiting, diarrhea, or cough

PE:

Gen: Irritable child but consolable

VS: BP 86/58 mm Hg, P 140 beats/min, RR 28 breaths/min, T 38.6°C (101.5°F), Weight 10 kg

HEENT: Moderate bulging of the left tympanic membrane with air–fluid levels observed; marked erythema and moderate bulging of the right tympanic membrane

Identify your treatment goals for this child.

Given this information, what nonpharmacologic and pharmacologic therapy do you recommend?

Patient Care Process for Acute Otitis Media

See Patient Care Process for Upper Respiratory Tract Infections.

Assess the Information:

- Determine if antibiotic therapy is indicated or if observation can be employed (see Figure 75–1).

Develop a Care Plan:

- If appropriate, select an antibiotic (see Figure 75–2) and optimal dose and duration (see Table 75–2).

Implement the Care Plan:

- Educate parents or caregivers that pain, fever, and/or other symptoms should improve but may not resolve completely within 48 to 72 hours and can be present for up to 7 days or longer in some patients.
- After joint decision with parent or caregiver, refer children with recurrent AOM (three distinct episodes within 6 months or four episodes within 12 months with at least one episode in preceding 6 months) and/or chronic OME to an otolaryngologist for surgical evaluation and treatment.

Follow-up: Monitor and Evaluate:

- Reevaluate patient if symptoms persist after 48 to 72 hours of initial evaluation and treatment or worsen at any time.
- Monitor for middle ear effusion resolution at an appropriate interval based on age and the presence of conditions that interfere with recognition of hearing impairment.
- Evaluate hearing if middle ear effusion is present for 3 months in healthy children and earlier in children who are at risk for speech, language, or learning problems.

viral URI, allergic rhinitis, and dental infections or procedures (Table 75–3).[6,29,30]

Bacteria that cause sinusitis are similar to those in AOM. *S. pneumoniae* and *H. influenzae* cause more than half of ABRS cases, with an additional 8% to 16% of cases caused by *M. catarrhalis*.[4-6] Similar to AOM, an increased prevalence of *H. influenzae* has been reported in ABRS, and certain factors predict the presence of drug-resistant pathogens.[4-6]

Pathophysiology

Rhinosinusitis is typically caused by mucosal inflammation and mucociliary dysfunction from viral infection or allergy. Increased mucous production and reduced clearance lead to blockage of the sinus ostia. This environment is ideal for bacterial growth and promotes a cycle of local inflammation and mucosal injury characterized by increased concentrations of interleukins, interferons, and tumor necrosis factor.[31] Damage to the host defense system perpetuates bacterial overgrowth and persistence of infection.

Table 75–3

Risk Factors for Acute Bacterial Rhinosinusitis[6,29,30]

Allergic or nonallergic rhinitis
Anatomic defects (eg, septal deviation)
Aspirin allergy, nasal polyps, and asthma
Cystic fibrosis or ciliary dyskinesia
Dental infections or procedures
Immunodeficiency
Intranasal medications or illicit drugs
Mechanical ventilation
Nasogastric tubes
Swimming or diving
Tobacco smoke exposure
Trauma or barotrauma
Upper respiratory tract infection (predominant risk factor)
Winter season

Treatment

The goals of treatment are to relieve symptoms; promote sinus drainage; avoid unnecessary antibiotic use or, when appropriate, use safe and effective antibiotics to eradicate bacterial infection and minimize resistance development; and prevent development of chronic disease or complications.

▶ *General Approach to Treatment*

Initial management should focus on symptom relief and identification of patients with ABRS who are most likely to benefit from antibiotics. **KEY CONCEPT** Antibiotics should be prescribed only when ABRS is most likely and when the benefits of treatment outweigh the potential harms. ABRS is more likely than viral involvement alone in instances where symptoms persist without evidence of improvement for at least 10 days after the onset of illness; when

Clinical Presentation and Diagnosis of Acute Bacterial Rhinosinusitis

Signs and Symptoms[4-6]

- *Adults:* Purulent nasal and/or postnasal discharge *plus* nasal congestion/obstruction and/or facial pain, pressure, or fullness; diminished sense of smell; fever; cough; maxillary tooth pain; fatigue; ear fullness, pressure, or pain
- *Children:* Persistent nasal or postnasal drainage; nasal congestion and mouth breathing; persistent cough (particularly at night) or throat clearing; fever; pharyngitis; ear discomfort; halitosis; morning periorbital edema or facial swelling; fatigue; facial or tooth pain

Laboratory Tests

- *Laboratory studies/nasopharyngeal cultures:* not recommended
- *Radiographic studies:* Useful for assessing presence of complications
- *Paranasal sinus puncture:* "Gold standard"; not routine but can be useful in complicated or chronic cases

Complications

- Orbital cellulitis or abscess, periorbital cellulitis, meningitis, cavernous sinus thrombosis, ethmoid or frontal sinus erosion, chronic sinusitis, and exacerbation of asthma or bronchitis

Diagnosis[4-6]

- *Clinical diagnosis:* Most common method; signs and symptoms that persist *without evidence of improvement* for at least 10 days *or* that worsen after initial improvement *or* severe symptoms (fever ≥ 39.0°C [102.2°F] and purulent nasal discharge) for at least 3 to 4 days at illness onset. Respiratory secretion color is unreliable for diagnosis because neutrophil presence causes color and is found in viral sinusitis.[4]

symptoms suddenly worsen within 10 days after initial improvement; or when symptoms are severe (fever ≥ 39.0°C [102.2°F] and purulent nasal discharge) in the first 3 to 4 days of illness onset.[4-6]

▶ *Nonpharmacologic Therapy*

Humidifiers, nasal saline sprays or drops, and nasal saline irrigation devices moisturize the nasal canal, impair crusting of secretions, and promote mucociliary clearance. Although many patients report benefit from these therapies, few controlled studies exist to support their efficacy in acute sinusitis.[32] Nasal irrigation with isotonic or hypertonic saline may reduce medication use and improve symptoms, especially in patients with allergic rhinitis and recurrent or chronic sinusitis, and it has a low risk of adverse reactions.[32-34]

▶ *Pharmacologic Therapy*

Adjunctive Therapy Medications that target rhinosinusitis symptoms are commonly used despite a lack of published evidence supporting their efficacy.[4] Analgesics/antipyretics are used to treat facial pain and fever. Oral decongestants relieve congestion but should be avoided in children younger than 4 years and patients with ischemic heart disease or uncontrolled hypertension. Intranasal decongestants can be used for severe congestion in patients 6 years of age or older but use should be limited to 3 to 5 days to avoid rebound nasal congestion. Avoid antihistamines because they thicken mucus and impair clearance, but they may be useful in patients with allergic rhinitis or chronic sinusitis.[29] Similarly, intranasal corticosteroids usually are reserved for patients with allergies or chronic sinusitis, but they may be beneficial as monotherapy or with antibiotics in ABRS if the clinician and patient agree that their modest benefits after 15 to 21 days of use outweigh their cost and minor adverse effects (epistaxis, nasal itching, and headache).[4,5,35] Systemic corticosteroids modestly improve symptoms or resolution when given concurrently with antibiotics, but most studies enrolled adults with fewer than 10 days of symptoms.[36] There is no evidence to support the use of guaifenesin in ABRS.

Antibiotic Therapy Because diagnosis is usually based on clinical presentation, clinicians must differentiate ABRS from viral rhinosinusitis in order to minimize inappropriate antibiotic use. In addition, recent evidence suggests that ABRS resolves spontaneously in many cases. Studies in adults with clinically diagnosed nonsevere sinusitis report cure rates of nearly 50% at 7 days and 70% at 14 days with no statistical differences between antibiotics and placebo, but there are significantly more adverse effects with antibiotics (28%) as compared to placebo (15%).[4,37] Studies in children with persistent nasal discharge for at least 10 days report modest benefits with antibiotic therapy.[38] In some studies, antibiotics led to faster symptom resolution with lower failure rates compared with no treatment, particularly with more severe infection.[5,6]

Treatment guidelines outline management approaches that include observation with close follow up for uncomplicated infections (eg, those that do not extend beyond the sinuses or nasal cavity) or the use of antibiotics, depending on patient characteristics and illness presentation.[4-6] In adults, some experts recommend observation for up to 7 days after ABRS is diagnosed, but only through shared decision-making with patients and only if follow-up is available during this timeframe.[4] If symptoms worsen or fail to improve by 7 days after diagnosis, reevaluation should occur and antibiotics should be initiated (either with a repeat office visit or via use of a delayed antibiotic prescription). Alternatively, antibiotics may be prescribed at the time of diagnosis for adults who are willing to accept the risk of adverse effects and cost of therapy in exchange for the small benefit that antibiotics provide. Other experts recommend prompt antibiotic therapy in all patients when the diagnosis of ABRS is confirmed with the use of strict diagnostic criteria.[5] In children, 3 days of observation with close follow-up is an alternative approach for patients with persistent illness without symptom improvement for at least 10 days.[6] Severe or complicated infections should be treated in conjunction with specialists such as otolaryngologists or infectious diseases physicians.

Patient Encounter 2

A 50-year-old African American man presents to his primary care physician with purulent postnasal discharge, nasal congestion, headache, and ear fullness/pressure. He developed rhinorrhea and congestion 8 days ago while on his honeymoon in the Caribbean. After some initial improvement, his symptoms significantly worsened over the past 2 to 3 days. His wife had similar symptoms that started 1 day before his illness, but she recovered completely. He reports that he snorkeled and swam in the ocean frequently while in the Caribbean. He tried Dayquil LiquiCaps yesterday but received little to no relief. He has had two sinus infections in the past 5 years but has not taken antibiotics in the last 2 years.

Immunizations: Up to date with the exception of Tdap

Allergies: Tree and grass pollens; cat dander

Meds: Dayquil LiquiCaps (in each capsule: acetaminophen 325 mg, dextromethorphan 10 mg, phenylephrine 5 mg) two capsules every 6 hours as needed (he took two doses yesterday)

PE:

Gen: Tired-appearing, moderate distress, appears uncomfortable

VS: BP 120/70 mm Hg, P 82 beats/min, RR 14 breaths/min, T 38.2°C (100.7°F), Wt 81.8 kg (180 lb)

HEENT: Bilateral middle ear effusions; tympanic membranes dull with diminished light reflex; thick, purulent yellow–green postnasal discharge; nasal mucosal edema; frontal and maxillary facial tenderness upon palpation; no oral lesions; erythematous pharynx with no tonsillar hypertrophy

What information is suggestive of acute bacterial rhinosinusitis (ABRS)?

What risk factors are present?

What other diagnostic studies, if any, should be performed?

What are the treatment goals for this patient?

Create a care plan for this patient that includes nonpharmacologic and pharmacologic therapies and a monitoring plan.

When antibiotics are prescribed, empiric selection of an agent that is likely to result in favorable clinical and bacteriologic outcomes is recommended (Figure 75–3). Antibiotics (Table 75–4) should target *S. pneumoniae* and *H. influenzae*, but consideration must also be given to local resistance patterns and other bacteria. **KEY CONCEPT** Standard dose amoxicillin or amoxicillin–clavulanate is recommended for most patients.[4-6] Amoxicillin is effective for most infections and is less expensive and better

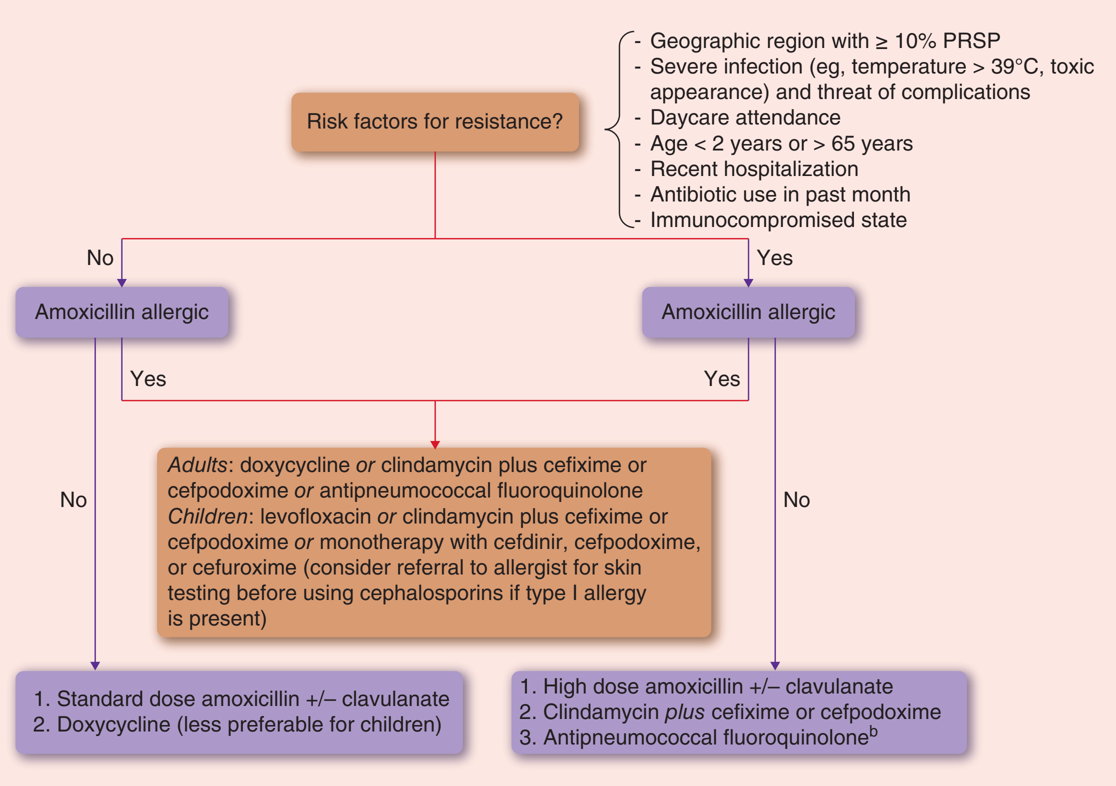
Risk factors for resistance?
- Geographic region with ≥ 10% PRSP
- Severe infection (eg, temperature > 39°C, toxic appearance) and threat of complications
- Daycare attendance
- Age < 2 years or > 65 years
- Recent hospitalization
- Antibiotic use in past month
- Immunocompromised state
No
Yes
Amoxicillin allergic
Amoxicillin allergic
Yes
Yes
No
No
Adults: doxycycline or clindamycin plus cefixime or cefpodoxime or antipneumococcal fluoroquinolone
Children: levofloxacin or clindamycin plus cefixime or cefpodoxime or monotherapy with cefdinir, cefpodoxime, or cefuroxime (consider referral to allergist for skin testing before using cephalosporins if type I allergy is present)
1. Standard dose amoxicillin +/– clavulanate
2. Doxycycline (less preferable for children)
1. High dose amoxicillin +/– clavulanate
2. Clindamycin plus cefixime or cefpodoxime
3. Antipneumococcal fluoroquinolone[b]

FIGURE 75–3. Treatment algorithm[a] for ABRS. [a]Antibiotics are listed in order of preference based on predicted clinical and bacteriologic efficacy rates, clinical studies, safety, and tolerability. Doses can be found in Table 75–4. [b]Antipneumococcal fluoroquinolone = levofloxacin, moxifloxacin.[4-6]

tolerated than amoxicillin–clavulanate, which provides expanded coverage against β-lactamase producers. Amoxicillin–clavulanate should be considered in patients who are at risk for infection with an amoxicillin-resistant organism, such as recent antibiotic use in the previous month, or if optimal coverage for β-lactamase–producing bacteria is desired. High-dose amoxicillin or amoxicillin–clavulanate is recommended for patients who are at high risk for infection from resistant bacteria, such as those who attend daycare, have moderate-to-severe illness, and when PRSP or other resistant bacteria are frequent in a community (Figure 75–3). Patients with penicillin allergies can be treated with an appropriate cephalosporin or doxycycline, depending on allergy severity. Cephalosporin monotherapy is less desirable because of increased pneumococcal resistance, so combination therapy with clindamycin may be required to optimize coverage for PRSP and β-lactamase producers, especially in moderate-to-severe illness.[4-6] Fluoroquinolones carry a risk of serious side effects that generally outweigh the benefits of treatment for ABRS. They should be reserved for patients who have no alternative treatment options and, when used, should have adequate antipneumococcal activity (eg, levofloxacin and moxifloxacin). Pregnant women who are allergic to beta-lactams can be treated with clindamycin, but this antibiotic only provides pneumococcal coverage. Doxycycline and fluoroquinolones should be avoided in pregnancy. Macrolides and trimethoprim–sulfamethoxazole are not recommended because of high pneumococcal and *H. influenzae* resistance. For uncomplicated infections, treatment duration ranges from 5 to 10 days in adults and 10 to

Patient Care Process for Acute Bacterial Rhinosinusitis

See Patient Care Process for Upper Respiratory Tract Infections.

Develop a Care Plan:

- If appropriate, select an antibiotic (see Figure 75–3) and optimal dose and duration (see Table 75–4).

Implement the Care Plan:

- Educate patient or patient's parent or caregiver that symptoms may resolve slowly and can be present for up to 7 days (or longer) after diagnosis, even when antibiotics are initiated.
- Manage patients with severe infection or complications in conjunction with otolaryngologists and/or infectious diseases physicians.

Follow-up: Monitor and Evaluate:

- Reevaluate patient if symptoms persist beyond 7 days or worsen at any time.
- If patient does not respond to first- or second-line therapy, refer to an otolaryngologist or infectious diseases physician.
- If recurrent infections or chronic sinusitis develop, refer to an otolaryngologist.

Table 75–4

Antibiotics[a] for the Treatment of Acute Bacterial Rhinosinusitis[4-6]

Drug	Adult Dose	Pediatric Dose[b]	Relative Cost[c]	Comments
Amoxicillin	1.5–4 g/day divided in two to three doses	45–90 mg/kg/day divided in two doses	$	Lacks coverage against β-lactamase producers
Amoxicillin–clavulanate	1.5–4 g/day divided in two to three doses	45–90 mg/kg/day divided in two doses	$$–$$$	Broad coverage particularly with high doses; Augmentin XR (2 g every 12 hours) targeted toward PRSP
Cefdinir	600 mg/day divided in one to two doses	14 mg/kg/day divided in one to two doses	$$	Preferred oral liquid cephalosporin owing to good palatability
Cefixime	200 mg twice daily	8 mg/kg/day divided in two doses	$$$–$$$$	IDSA recommends use only in combination with clindamycin
Cefpodoxime proxetil	200 mg twice daily	10 mg/kg/day divided in two doses	$$$–$$$$	IDSA recommends use only in combination with clindamycin
Cefuroxime axetil	250–500 mg twice daily	15–30 mg/kg/day divided in two doses	$$–$$$	Only included as an option in AAP guideline; suspension no longer available in the United States
Ceftriaxone	1 g IM/IV every 24 hours	50 mg/kg IM/IV every 24 hours	$$$–$$$$	Experts recommend a 5-day treatment course; useful for patients who are vomiting and cannot tolerate oral therapy
Doxycycline	100 mg twice daily	4 mg/kg/day divided in two doses	$–$$$	Can cause photosensitivity and GI effects (abdominal pain, esophagitis, or esophageal ulcers); tooth staining in children younger than 8 years is unlikely with durations of therapy that are 21 days or less; many drug–drug interactions (antacids, iron, calcium)
Levofloxacin	500–750 mg once daily (750 mg × 5 days)	10 mg/kg/dose every 12–24 hours	$–$$$$	Common fluoroquinolone side effects are nausea, vaginitis, diarrhea, dizziness, photosensitivity; many drug–drug interactions (antacids, iron, calcium); serious side effects (tendon rupture, muscle or joint pain, confusion, hallucinations, neuropathies, hypoglycemia, QT prolongation, aortic ruptures or tears) limit their broad utility for ABRS
Moxifloxacin	400 mg once daily	Not available	$$–$$$	
Clindamycin	300–450 mg three times daily	30–40 mg/kg/day divided in three doses	$–$$$	No Gram-negative coverage; use only in combination with cephalosporin

[a]Refer to Table 75–2 for more information on antibiotics. Other FDA-approved antibiotics for ABRS not included in the Infectious Diseases Society of America, American Academy of Pediatrics, or American Academy of Otolaryngology-Head and Neck Surgery Foundation guidelines: azithromycin, cefaclor, cefprozil, clarithromycin, ciprofloxacin, erythromycin, and trimethoprim–sulfamethoxazole.

[b]Maximum dose not to exceed adult dose.

[c]Approximate cost per course: $ (under $25), $$ ($25–$50), $$$ ($50–$100), $$$$ (over $100).

AAP, American Academy of Pediatrics; ABRS, acute bacterial rhinosinusitis; IDSA, Infectious Diseases Society of America; IM, intramuscular; PRSP, penicillin-resistant *S. pneumoniae*.

14 days in children.[4-6] While short-course therapy with some fluoroquinolones and β-lactams are as effective as longer courses in adults with uncomplicated ABRS, data are lacking to support shorter courses in more severe infections or in children.[39]

Failure to improve within 7 days of therapy or worsening at any time requires reevaluation to confirm the diagnosis, consider changing antibiotics, and examine for complications.[4]

Outcome Evaluation

Clinical improvement (eg, defervescence, reduced nasal congestion, and discharge, improvements in pain or facial pressure) should be evident within 7 days of therapy. Monitor for common adverse effects and refer to a specialist if clinical response is not obtained with first- or second-line therapy. Referral is also important for severe, recurrent, or chronic infection. Surgery may be indicated in complicated cases.

PHARYNGITIS

Pharyngitis is an inflammation of the throat often caused by infection. Most infections are viral and self-limited, but antibiotics are frequently prescribed because of difficulty in clinically distinguishing between viral and bacterial infection and the fear of untreated streptococcal illness.

Epidemiology and Etiology

Pharyngitis is a common manifestation of viral URIs. *Streptococcus pyogenes* (Group A streptococci) is the most common bacterial cause, responsible for 20% to 30% of cases in children and 5% to 15% of adult infections.[7,40] It is most common in late winter and early spring and spreads easily through direct contact with contaminated secretions. Children between 5 and 15 years have the highest incidence of streptococcal pharyngitis. Clusters of infection are common within families, classrooms, and other crowded settings. Although rarer than *S. pyogenes*, *Fusobacterium necrophorum* is becoming more common among adolescents and young adults.[41] This pathogen is associated with pharyngitis and lymphadenopathy, but it can progress to more serious findings including peritonsillar abscesses and jugular venous thrombophlebitis (Lemierre's syndrome).

Pathophysiology

Group A streptococcal pharyngeal colonization occurs in up to 20% of children and is a risk factor for developing pharyngitis if

Clinical Presentation and Diagnosis of Streptococcal Pharyngitis

Signs and Symptoms of Streptococcal Pharyngitis[7,40]

- Abrupt onset of sore throat and severe pain while swallowing
- Fever
- Headache, abdominal pain, nausea, or vomiting (especially in children)
- Tonsillopharyngeal erythema with or without exudates
- Tender, anterior cervical lymphadenitis
- Swollen erythematous uvula
- Halitosis
- Soft palate petechiae
- Scarlatiniform rash
- Absence of conjunctivitis, hoarseness, cough, rhinitis, discrete ulcerations, and diarrhea (suggestive of viral etiology)
- Centor criteria: tonsillar exudates; tender anterior cervical adenopathy; fever; absence of cough

Complications

- Nonsuppurative: acute rheumatic fever, scarlet fever, streptococcal toxic shock syndrome, poststreptococcal glomerulonephritis or reactive arthritis, pediatric autoimmune neuropsychiatric disorder associated with group A streptococci (PANDAS)
- Suppurative: peritonsillar or retropharyngeal abscesses, cervical lymphadenitis, otitis media, sinusitis, necrotizing fasciitis

Diagnosis[7,40]

- Tests should be performed *only* when there is clinical suspicion for streptococcal pharyngitis. The likelihood of having streptococcal infection increases with the number of Centor criteria that are present. Centor criteria are most useful for identifying patients for whom testing and antimicrobial therapy are unnecessary (ie, fewer than three criteria). Pharyngeal streptococcal carriage occurs in up to 20% of healthy children.
- Rapid antigen detection test (RADT): 70% to 90% sensitivity; results available within minutes.
- Throat culture: "gold standard"; results available within 24 to 48 hours. Should be performed after all negative RADTs in children and adolescents; consider in adults with significant pediatric contact. Also recommended in outbreaks and to monitor for resistance.
- Rapid polymerase chain reaction (PCR) test: point-of-care test with results in 15 minutes or less; if sensitivity is 97% or more, negative result does not require follow-up throat culture. These point-of-care tests can be used in community pharmacies along with treatment algorithms to expand access to patients without leading to antibiotic overuse.[42,43]

there is disruption in mucosal integrity.[7] Symptoms of streptococcal pharyngitis usually are self-limited and resolve within a few days of onset *without* antibiotic treatment.[7] Historically, untreated or inappropriately treated infection caused acute rheumatic fever, heart valve damage, and other infectious complications. Antibiotic therapy given up to 9 days after symptom onset can prevent these sequelae. Proper diagnosis of streptococcal pharyngitis is important to minimize inappropriate antibiotic use for viral infections and prevent complications of untreated streptococcal infection.[7,40]

Treatment

KEY CONCEPT The goals of therapy for streptococcal pharyngitis are to shorten the disease course, reduce spread, and prevent complications. Certain immune-mediated complications such as glomerulonephritis and reactive arthritis are not impacted by antibiotics.[7]

▶ *Nonpharmacologic Therapy*

Pain and throat irritation are key features of pharyngitis. Consumption of warm fluids, such as tea or soup, or cold items, such as ice chips or popsicles, can soothe dry throat tissue and provide hydration. Food items that coat the throat, such as honey or hard candies, can provide temporary relief of throat pain. Environmental approaches, such as adjusting room humidity to avoid a dry environment and avoiding smoke exposure, and warm saline gargles can also relieve throat irritation.

▶ *Pharmacologic Therapy*

Adjunctive Therapy Oral analgesics provide pain relief within 1 to 2 hours and can allow patients to maintain normal eating and drinking habits. Topical therapies, including medicated lozenges or sprays, provide quicker but temporary relief of throat pain and can be used in conjunction with oral analgesics. There is no evidence to support enhanced efficacy of one type of lozenge or spray over another; however, benzocaine should be avoided because of rare but serious reports of methemoglobinemia associated with benzocaine sprays.

Antibiotic Therapy **KEY CONCEPT** Antibiotics should be used only in cases of laboratory-confirmed streptococcal pharyngitis with associated clinical symptoms (Figure 75–4).[7,40] Effective therapy (Table 75–5) reduces the infectious period from approximately 10 days to 24 hours and results in clinical improvement in 1 to 2 days.[2,7,40] **KEY CONCEPT** Penicillin is the drug of choice because it is the only antibiotic studied for prevention of acute rheumatic fever, in addition to its narrow spectrum, documented safety and efficacy in nasopharyngeal streptococcal eradication, and low cost.[7,40] Amoxicillin is an alternative agent, particularly for children because of its improved taste and its enhanced adherence with once-daily dosing.[7,40] Cephalosporins may be more effective than penicillin for relapse prevention and nasopharyngeal eradication, particularly in asymptomatic carriers and adults.[44] Cephalosporins can be used in patients with non–type I penicillin allergies (eg, maculopapular rash) and preference should be given to first-generation agents that are more narrow in spectrum. Azithromycin or clindamycin can be used in patients with severe penicillin reactions (eg, anaphylaxis, angioedema, or serious delayed reactions).[7,40] Usual duration of therapy is 10 days, but shorter courses of cefpodoxime, cefdinir, and azithromycin are Food and Drug Administration (FDA)-approved.

Resistance plays a smaller role in pharyngitis treatment compared with other URIs. **KEY CONCEPT** Penicillin resistance is

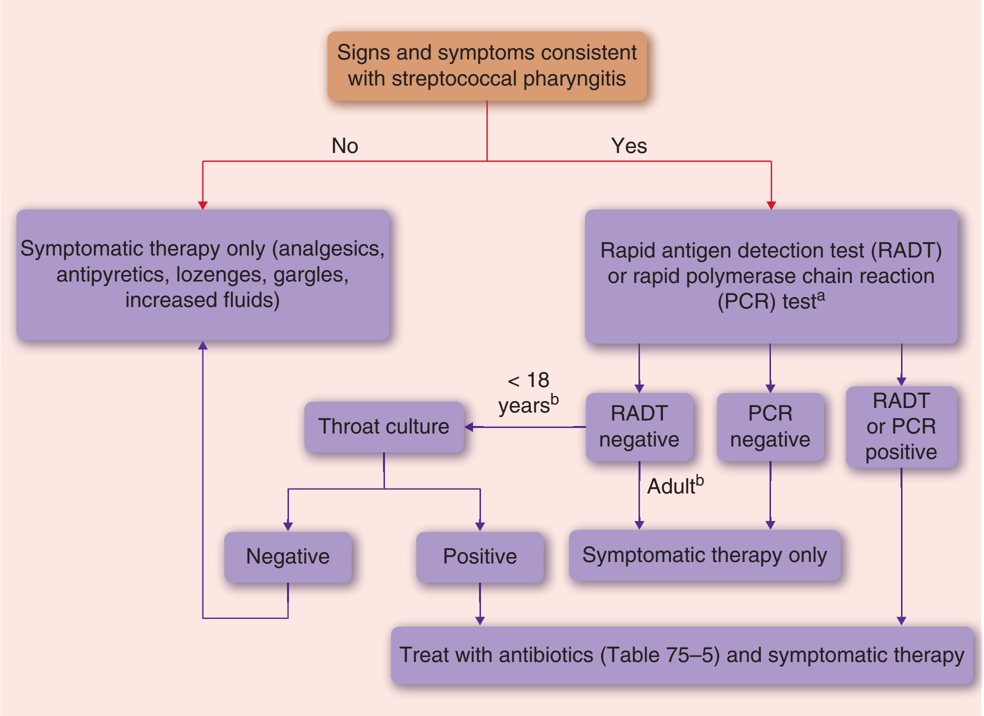
Signs and symptoms consistent with streptococcal pharyngitis
No
Yes
Symptomatic therapy only (analgesics, antipyretics, lozenges, gargles, increased fluids)
Rapid antigen detection test (RADT) or rapid polymerase chain reaction (PCR) test[a]
< 18 years[b]
Throat culture
RADT negative
PCR negative
RADT or PCR positive
Adult[b]
Negative
Positive
Symptomatic therapy only
Treat with antibiotics (Table 75–5) and symptomatic therapy

FIGURE 75–4. Treatment algorithm for management of pharyngitis in children and adults. [a]If using a rapid polymerase chain reaction (PCR) test, one with 97% sensitivity or higher is preferred. [b]It is the clinician's discretion to perform a throat culture in adults who have a negative RADT.[7,40]

Table 75–5

Antibiotics[a] for the Treatment of Streptococcal Pharyngitis[7,39]

Drug	Adult Dose	Pediatric Dose[b]	Duration	Relative Cost[c]	Comments
Penicillin V	500 mg two to three times daily	250 mg two to three times daily (if ≤ 27 kg); 500 mg two to three times daily (if > 27 kg)	10 days	$	Drug of choice but increasing reports of treatment failures
Penicillin G benzathine	1.2 million units	600,000 units (if ≤ 27 kg); 1.2 million units (if > 27 kg)	1 IM dose	$$$$	Useful for patients with poor adherence or emesis; painful injection but pain can be reduced if warmed to room temperature prior to administration
Amoxicillin	500 mg twice daily or 1 g once daily	50 mg/kg once daily; max 1 g	10 days	$	Preferred drug for young children because of improved palatability and once-daily dosing
Cephalexin	500 mg twice daily	25–50 mg/kg/day divided in two doses	10 days	$	Recommended in non–type I penicillin allergy
Cefadroxil	1 g once daily	30 mg/kg once daily	10 days	$–$$	Recommended in non–type I penicillin allergy
Cefdinir	300 mg twice daily or 600 mg once daily	14 mg/kg/day divided in one to two doses	5–10 days	$$	Broad spectrum; can be used in non–type I penicillin allergy
Azithromycin	500 mg once daily	12 mg/kg once daily; 12 mg/kg on day one, then 6 mg/kg once daily for 4 days	3 days (5 days for children)	$–$$	Recommended in severe penicillin hypersensitivity; increasing resistance
Clindamycin	300 mg three times daily	20 mg/kg/day divided in three doses	10 days	$–$$$	Recommended in severe penicillin hypersensitivity; useful for recurrent infections

[a]Other FDA-approved agents include amoxicillin–clavulanate, cefixime, cefaclor, cefprozil, cefpodoxime, cefuroxime, erythromycin, and clarithromycin.

[b]Maximum dose not to exceed adult dose.

[c]Approximate cost per course: $ (under $25), $$ ($25–$50), $$$ ($50–$100), $$$$ (over $100).

IM, intramuscular.

Patient Encounter 3

A 7-year-old Hispanic boy presents to an urgent care clinic with a sore throat and fever of 39.0°C (102.2°F) that have been present for 12 hours. He says his "throat stings," and he is refusing to eat or drink. He has no other symptoms and takes no medications on a regular basis. His father gave him acetaminophen 4 hours ago, but it did not provide much relief. He has no known drug allergies. His father reports that the child's 9-year-old sister has recurrent episodes of "strep throat," but she is currently healthy with no symptoms. The child has no known sick contacts. Physical examination reveals pharyngeal and tonsillar erythema, enlarged tonsils with white exudates, and tender cervical lymphadenopathy.

Does this child have streptococcal pharyngitis?

Is antibiotic therapy indicated? If so, what agent should be initiated and for how long?

What education should be provided to his father regarding treatment?

extremely rare in group A streptococci, but resistance and clinical failures occur more frequently with tetracyclines, trimethoprim–sulfamethoxazole, and to a lesser degree macrolides. Recurrent infections or treatment failures can be retreated with the same initial antibiotic or treated with amoxicillin–clavulanate, a cephalosporin, clindamycin, or penicillin G benzathine.[7,40]

Outcome Evaluation

Antibiotics relieve symptoms of streptococcal pharyngitis within 3 to 5 days, and patients can return to work or school if improved after the first 24 hours of therapy. A lack of improvement or worsening after 72 hours of therapy requires reevaluation. Follow-up throat cultures are not recommended unless symptoms persist or recur. Recurrent symptoms following an appropriate treatment course should prompt reevaluation for possible retreatment.

COMMON COLD

The common cold is a viral URI associated with a significant health care burden, including medical visits, work or school absenteeism, and widespread use of cough and cold medication for treatment or prevention.[45,46] Clinicians must be aware of evidence regarding the use of cough and cold products in order to make appropriate recommendations for this commonly encountered condition.

Epidemiology and Etiology

Many viruses cause the common cold, including rhinoviruses (most common), coronaviruses (including severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2), parainfluenza viruses, respiratory syncytial virus, and adenoviruses. Infection rates increase during the fall through spring seasons and are highest in the winter months. Adults experience 1 to 3 colds each year, whereas children have 6 to 11 colds per year.[45,46] Colds usually resolve over 10 to 14 days but can be complicated by bacterial superinfections, including AOM and ABRS. Factors associated with an increased incidence of colds are young age, daycare attendance, contact with school-age children, crowded conditions and poorly ventilated areas, cigarette smoke exposure, and inadequate physical or mental rest. Children are more likely than adults to transmit viruses because of poorer hand hygiene, closer casual contacts, and sharing of toys. Viral antigenic drifts and host immune system evasion contribute to the persistence of URIs in the community.

Pathophysiology

Viruses enter the respiratory tract mucosa via inhalation of aerosols or infected droplets or direct contact with contaminated secretions. After cell entry, viral replication and shedding occur for several days to weeks. Symptoms arise from epithelial cell damage, inflammation, vasodilation, local tissue edema, increased mucous production, and impaired mucociliary clearance. Tracheobronchial inflammation and irritation induce cough via afferent nerve impulse transmission to the medulla. Antibody production halts viral replication and inflammation as symptoms diminish.

Patient Care Process for Streptococcal Pharyngitis

See Patient Care Process for Upper Respiratory Tract Infections.

Assess the Information:

- If streptococcal pharyngitis is likely, perform an RADT or rapid PCR test (and follow-up throat culture, if necessary) to confirm the diagnosis.
- Determine if antibiotic therapy is indicated based on diagnostic testing (see Figure 75–4).

Develop a Care Plan:

- If streptococcal pharyngitis is confirmed with laboratory testing, select antibiotic therapy that is likely to be effective and safe (Table 75–5).

Implement the Care Plan:

- Educate patient or patient's parent or caregiver that symptoms should improve within 1 to 2 days and resolve completely within 3 to 5 days with appropriate antibiotic therapy (if streptococcal pharyngitis is confirmed).
- Discuss the need to avoid close contact with others for 24 hours to minimize spread.
- Discuss the importance of medication adherence to treat infection, minimize spread, and reduce chances of recurrence.

Follow-up: Monitor and Evaluate:

- Reevaluate patient if symptoms persist after 72 hours or worsen at any time.
- Reevaluate patient if symptoms recur after completion of therapy.

Clinical Presentation and Diagnosis of the Common Cold

Symptoms typically begin 24 to 72 hours after infectious contact. They peak at day 3 to 5 of illness, begin to wane by day 7, and usually resolve by day 10 to 14.

Signs and Symptoms[45,46]

- *Onset:* Malaise, fatigue, headache, pharyngitis, mildly elevated temperature (can be higher in infants and children)
- *Secondary:* Nasal and/or postnasal drainage (often clear at onset but can become thick and purulent); congestion; cough and/or throat clearing; sneezing; conjunctivitis; irritability; impaired smell or taste
- *Coronavirus disease (COVID-19):*[47] Causes a wide range of signs and symptoms, from asymptomatic infection to severe illness (see Lower Respiratory Tract Infections chapter); common presentation includes fever and/or chills, cough, shortness of breath, new loss of smell and/or taste, fatigue, myalgias, headache, sore throat, congestion and/or rhinorrhea, nausea or vomiting, diarrhea

Complications

- AOM, ABRS, chronic bronchitis, bronchiolitis (in infants and children < 2 years), laryngotracheobronchitis (croup), pneumonia, asthma exacerbation

Diagnosis

- *Clinical diagnosis:* Most common method; based on history, presence of symptoms, and physical examination
- *Radiographic studies:* Useful for assessing complications such as pneumonia
- *Laboratory studies:* Rapid viral antigen detection tests or real-time reverse transcription PCR tests of nasopharyngeal samples may be helpful for epidemiology and diagnosis in acute and severe illness; authorized SARS-CoV-2 tests include nasopharyngeal, oropharyngeal, nasal mid-turbinate, anterior nares, or saliva specimens[47]

Treatment

The treatment goal is to minimize discomfort from symptoms to allow patients to function as normally as possible. Preventative measures are also important to limit the spread of infection. Antibiotics are not effective, but they are often prescribed to patients with viral URIs and purulent secretions, which have contributed to increased resistance.[1,2] Treatment should focus on symptom relief.

▶ *Nonpharmacologic Therapy*

Supportive measures include air humidification, intranasal saline drops or sprays with or without bulb suctioning, nasal saline irrigation, increased fluid intake, throat lozenges or saline gargles, and rest. Nasal strips may relieve congestion by lifting the nares and opening the anterior nasal passages. Honey may provide relief of cough symptoms in childen, but it should not be used in infants because of the risk of botulism.[48] These nondrug measures are particularly useful for children younger than 6 years and pregnant women, for whom medication safety is a significant concern. Although studies proving their benefits are lacking, these nondrug treatments are safe.

▶ *Pharmacologic Therapy*

Nonprescription cough and cold preparations are used frequently despite a lack of evidence to support their safety and efficacy. Reports of serious adverse events and deaths led to efforts to eliminate the use of these medications in young children.[48,49]

Patient Encounter 4

A 48-year-old Caucasian woman presents to her primary care provider's office with a "sinus infection." 3 days ago, she developed a scratchy, mild sore throat and clear rhinorrhea. Her throat pain has improved, but today her nasal discharge is thicker and brownish in color and she is moderately congested. She used intranasal phenylephrine this morning, which provided relief but only for a few hours. She also feels more tired than usual and has a mild headache. She has seasonal allergic rhinitis and migraines, but she has not had a migraine for 2 years. She is divorced with two daughters (19 years of age and 15 years of age); the youngest daughter has similar symptoms.

Immunizations: Up to date; needs influenza vaccine this season

Allergies: Trimethoprim–sulfamethoxazole (rash); ragweed

Meds: Cetirizine 10 mg once daily during allergy season (fall); intranasal fluticasone propionate one spray each nostril daily during allergy season (fall); rizatriptan 10 mg orally as needed for migraine headaches; *Echinacea purpurea* 400 mg three times daily (started this morning); intranasal phenylephrine 1% two sprays in each nostril every 6 hours as needed (started this morning; has used one time only)

PE:

Gen: No apparent distress

VS: BP 102/62 mm Hg, P 62 beats/min, RR 12 breaths/min, T 37.1°C (98.8°F), Wt 57.3 kg (126 lb)

HEENT: Conjunctiva clear; no photophobia; brown nasal and postnasal discharge with swollen nasal mucosa; mildly erythematous pharynx; mild pain upon frontal palpation; tympanic membranes dull appearing bilaterally

Lungs: Clear to auscultation; no crackles

What signs and symptoms are suggestive of the common cold? Which are suggestive of ABRS?

What diagnostic studies should be performed?

Create a care plan that includes nonpharmacologic and pharmacologic therapies and a monitoring plan. Include preventative measures in your plan.

Manufacturers have removed product labeling for all children younger than 4 years. Hundreds of products are available to manage cold symptoms. **KEY CONCEPT** Choice of therapy is influenced by patient age, presence of comorbid conditions, and balance of effectiveness and safety. Single-ingredient agents are preferred to target only symptoms that are present and to minimize toxicity that can result from confusion and a lack of knowledge about active ingredients in multiple ingredient formulations. Cautious use of nonprescription products is warranted in certain patient populations: pregnant or lactating women, children, elderly, and patients with cardiovascular disease, diabetes, or glaucoma. Table 75–6 summarizes some of the available agents used for cold symptoms. Antipyretics and analgesics are used for fever, pain, and discomfort. Local anesthetics (eg, phenol, dyclonine) temporarily relieve throat pain and are available in lozenges and sprays. Decongestants cause vasoconstriction that can improve congestion, but the use of intranasal products should be limited to 3 to 5 days to avoid rebound congestion.

Table 75–6

Select Nonprescription Medications for the Common Cold for Patients 6 Years of Age and Older[42–44]

Class/Drug	Adults and Children > 12 Years of Age	Children 6–12 Years of Age[a]	Comments
Analgesics/Antipyretics			
Acetaminophen[b,c]	325–650 mg every 4–6 hours as needed or 1000 mg every 6 hours as needed (max 3.25 g/day or 4 g/day if directed by health care provider); extended-release 1300 mg every 8 hours as needed (max 3.9 g/day)	10–15 mg/kg/dose every 4–6 hours as needed (max 5 doses/day and not to exceed 4 g/day)	Use with caution in preexisting liver disease; monitor acetaminophen dose from all sources (prescription, nonprescription, and combination products); some experts recommend a maximum dose of 3 g/day in adults
Ibuprofen[d]	200–400 mg every 4–6 hours as needed (max 1200 mg/day)	4–10 mg/kg/dose every 6–8 hours as needed (max 4 doses/day and maximum single dose of 400 mg)	Use with caution in cardiovascular disease and those with history of peptic ulcer disease or GI bleeding; avoid use in elderly, renal impairment, and heart failure; avoid in third trimester of pregnancy
Decongestants			
Intranasal:			
Oxymetazoline 0.05%[c]	Two to three sprays every 12 hours as needed (max 2 doses/24 hours)	One to two sprays every 12 hours as needed (max 2 doses/24 hours)	Limit use of intranasal decongestants to 3–5 days to minimize risk of rebound congestion; use with caution in patients with cardiovascular disease, diabetes, hyperthyroidism, or prostatic hypertrophy
Phenylephrine 0.25%, 0.5%, 1%	Two to three sprays no more than every 4 hours as needed	One to three sprays no more than every 4 hours as needed (0.25% only)	
Systemic:			
Pseudoephedrine	60 mg every 4–6 hours as needed; extended release 120 mg every 12 hours or 240 mg every 24 hours as needed (max 240 mg/day)	30 mg every 4–6 hours as needed (max 120 mg/day)	Avoid use in patients with cardiovascular disease; children and elderly have increased risk of adverse effects (cardiovascular or CNS stimulation); use with caution in patients with diabetes, hyperthyroidism, prostatic hypertrophy; avoid in first trimester of pregnancy
Phenylephrine	10 mg every 4 hours as needed (max 60 mg/day)	5 mg every 4 hours as needed (max 30 mg/day)	
Cough Suppressants			
Dextromethorphan[c]	10–20 mg every 4 hours or 20–30 mg every 6–8 hours as needed; extended release 60 mg twice daily as needed (max 120 mg/day)	10 mg every 4 hours as needed; extended release 30 mg twice daily as needed (max 60 mg/day)	Increased adverse effects in children and poor metabolizers (5%–10% of Caucasians; 2% in African Americans and Asians); can cause dysphoria and serotonin syndrome; use caution in those taking psychotropic medications
Expectorants			
Guaifenesin	200–400 mg every 4 hours as needed; extended release 600–1200 mg every 12 hours as needed (max 2.4 g/day)	100–200 mg every 4 hours as needed (max 1.2 g/day)	May cause nausea and abdominal pain, particularly in high doses
Anticholinergics			
Intranasal ipratropium 0.06%[c]	Two sprays 3–4 times/day	Two sprays 3 times/day	Used for rhinorrhea only; does not improve congestion, postnasal drip, or sneezing; can cause epistaxis and nose/mouth dryness

[a] Maximum dose not to exceed adult dose.

[b] Preferred antipyretic/analgesic for children; can be used in newborns.

[c] Safe to use in pregnancy.

[d] Can be used in children older than 6 months of age.

Antihistamines should generally be avoided: first-generation agents can dry secretions through their anticholinergic effects, but they impair mucociliary clearance of thick mucus, which can worsen congestion, and there is not a clear benefit for cough or cold symptoms when these agents are used alone.[45,46,48] When used in combination with decongestants, certain antihistamines may provide some improvement in symptoms in adults and older children only but not in young children.[48] Cough suppressant use is not supported by strong evidence showing benefit.[42,44] They can cause significant neurologic adverse effects and have been linked to abuse by teens for their euphoric effects in high doses.[49] Guaifenesin, an expectorant, may reduce sputum thickness in adults, but it has been poorly studied in children.[48,50] Regular high-dose vitamin C (> 200 mg/day) supplementation may result in mild reductions in cold severity or duration, but it is most useful for prevention in patients exposed to intense physical exercise/training or cold stress.[51] Echinacea has limited benefit for treatment in adults, and its use is discouraged for prevention and in all children because of adverse effects including gastrointestinal distress and rash.[52] It should also be avoided in patients with allergies to ragweed, daisies, chrysanthemums, or marigolds because of the risk of cross sensitivity. Zinc lozenges are not consistently effective, but when used within 24 hours of symptom onset, they may slightly reduce the duration and severity of cold symptoms.[45,46,48]

Prevention

Prevention of the common cold is best achieved by minimizing contact with infected people and secretions. Frequent hand washing with soap and water or the use of an alcohol-based hand sanitizer (at least 60% alcohol) is vital. Coughing or sneezing into the elbow should be taught rather than using tissues or covering the mouth and nose with hands. Other methods that are advocated for preventing the spread of viruses include smoking cessation, maintenance of a healthy lifestyle through diet and exercise, and minimizing stress. Specific mitigation strategies for preventing the spread of COVID-19 include wearing a mask that covers the mouth and nose, staying at least 6 ft away from people who do not co-reside, avoiding crowds and poorly ventilated indoor spaces, and frequent hand washing.

While most colds cannot be prevented with vaccines, there are two viral vaccines available to prevent respiratory tract infections: influenza (please see Lower Respiratory Tract Infections, Chapter 74) and COVID-19. In response to the COVID-19 pandemic, the FDA provided Emergency Use Authorization (EUA) of two mRNA vaccines for use in the United States in December 2020 and a recombinant viral vector vaccine in February 2021.[53] The mRNA vaccines encode the prefusion spike glycoprotein of SARS-CoV-2 whereas the recombinant vaccine is a replication-incompetent adenovirus expressing the SARS-CoV-2 spike protein. These vaccines have been shown to be highly effective in preventing hospitalization and death from COVID-19.[53] Each vaccine has different authorized age-groups for use, administration schedules, and storage requirements and are not considered interchangeable. Expected postvaccination symptoms include local reactions (eg, pain, swelling, erythema, and axillary lymphadenopathy) and systemic reactions (eg, fever, chills, fatigue, headache, myalgia, and arthralgia) in most patients.[53] These reactions are usually mild to moderate, occur in the first few days, and resolve within 1 to 3 days of onset. They are more common after the second dose (for mRNA vaccines) and occur more frequently in younger patients (< 55 years of age). Hypersensitivity and anaphylaxis have been rarely reported, in addition to myocarditis and pericarditis in adolescents and young adults (mRNA vaccines) and blood clots with low platelets in women younger than 50 years of age (viral vector vaccine). These vaccines may be given to individuals with underlying medical conditions, including immunocompromised states, autoimmune conditions, or history of Guillain–Barre syndrome or Bell's palsy, as long as no contraindications are present. The Centers for Disease Control and Prevention (CDC) considers the following to be contraindications to the COVID-19 vaccines: severe allergic reaction (eg, anaphylaxis) or immediate allergic reaction of any severity after a previous dose of the vaccine or any of its components (including polyethylene glycol); or an immediate allergic reaction of any severity to polysorbate.[53] Although there are limited data, women who are pregnant or lactating can choose to be vaccinated after weighing the benefits and the risks. With the rapid changes in the COVID-19 pandemic, health care providers must stay abreast of current vaccine recommendations as additional information becomes available and new vaccines are authorized for use.

Outcome Evaluation

Most colds resolve within 7 to 10 days. Monitor patients for persistent symptoms lasting longer than 10 to 14 days, worsening symptoms, and complications such as wheezing, difficulty breathing, significant facial or ear pain, and high fevers. If complications are suspected, refer to a clinician for evaluation.

Patient Care Process for Common Cold

See Patient Care Process for Upper Respiratory Tract Infections

Assess the Information:

- Based on patient history, review of systems, and physical examination, determine if the presentation is consistent with the common cold.
- Determine if pharmacologic therapy is indicated or if nonpharmacologic measures alone can be employed.

Develop a Care Plan:

- Select nonpharmacologic and/or nonprescription therapies that will provide optimal relief of symptoms and that are safe for the patient.

Implement the Care Plan:

- Educate patient or patient's parent or caregiver that symptoms may resolve slowly and can be present for up to 10 to 14 days. If symptoms persist without improvement for longer than 10 days or worsen, refer the patient for medical evaluation.
- Discuss preventative measures for minimizing spread and future illnesses.

Follow-up: Monitor and Evaluate:

- Reevaluate patient if symptoms persist beyond 10 to 14 days or worsen at any time.
- If complications develop such as wheezing, difficulty breathing, significant facial or ear pain, or high fevers, refer to a clinician for evaluation.

Abbreviations Introduced in This Chapter

ABRS	Acute bacterial rhinosinusitis
AOM	Acute otitis media
OME	Otitis media with effusion
PRSP	Penicillin-resistant *S. pneumoniae*
RADT	Rapid antigen detection test
URI	Upper respiratory tract infection

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76 Skin and Skin Structure Infections

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Discuss skin structure and function responsible for preventing infection.
2. Describe the epidemiology, etiology, pathogenesis, diagnostic criteria, and clinical manifestations associated with acute bacterial skin and skin structure infections (ABSSSIs).
3. Identify goals of therapy associated with clinical response in patients with ABSSSI.
4. Recommend effective empiric and definitive antimicrobial regimens when given a diagnosis, patient history, physical examination, and laboratory findings.
5. Monitor chosen antimicrobial therapy for safety and efficacy.
6. Apply the Patient Care Process to the management of a patient with ABSSSI.

INTRODUCTION

Skin and skin structure infections, also known as acute bacterial skin and skin structure infections (ABSSSIs), are frequently encountered in both acute and ambulatory care settings and account for a significant number of outpatient visits and hospitalizations annually.[1] ABSSSIs range in severity from mild, superficial, and self-limiting to life-threatening deep tissue infections requiring intensive care, surgical intervention, and intravenous (IV) broad-spectrum antibiotics. Gram-positive pathogens, primarily *Staphylococcus aureus* and *Streptococcus* species, are the most common causative bacteria.[2-5] Polymicrobial infections are more likely in complicated or deeper infections and in persons with immune suppression, diabetes, vascular insufficiency, or recent surgery.[2,5]

The role of methicillin-resistant *S. aureus* (MRSA), particularly community-acquired MRSA (CA-MRSA), in ABSSSI is of increasing importance. In many US cities, MRSA is the most frequently isolated pathogen from patients presenting to emergency departments with ABSSSI, and antimicrobial prescribing has largely shifted toward empiric use of MRSA-active agents.[3] Historically, MRSA infections were associated with healthcare exposure or defined populations such as injection drug users or athletes[4,6]; however, despite some modest decline in the proportion of *S. aureus* isolates in recent years, a high MRSA prevalence in the community means that risk stratification may be more difficult to perform. In areas with high rates of CA-MRSA, and in patients with recurrent infections or infections that persist despite appropriate antimicrobial therapy, empiric therapy, including antibiotics active against MRSA, must be considered.[2,7] The general management of ABSSSIs is discussed throughout this chapter.

Intact skin generally is resistant to infection. In addition to providing a mechanical barrier, its relative dryness, slightly acidic pH, colonizing bacteria, frequent desquamation, and production of various antimicrobial defense chemicals, including sweat (which contains IgG and IgA), prevent invasion by various microorganisms.[8] Conditions predisposing patients to ABSSSIs include trauma to the skin, alterations in vascularization, and oxygenation leading to decreased skin perfusion, fluid stasis, and altered immune function impairing the body's ability to fight infection.[9]

IMPETIGO

EPIDEMIOLOGY AND ETIOLOGY

KEY CONCEPT Impetigo is a common skin infection that can occur in any age-group but most frequently affects children between 2 and 5 years. β-Hemolytic streptococci (*Streptococcus pyogenes* or Group A *Streptococcus* [GAS]) and *S. aureus* are the most common pathogens.[5] Impetigo is a superficial infection and spreads easily, especially in settings of poor hygiene and crowding, and particularly during summer months. The offending microorganisms colonize the skin surface and invade through abrasions, insect bites, or trauma. The crusty eruption of impetigo ensues. These lesions may occur anywhere on the body but are most common on the face and extremities.[7]

CLINICAL PRESENTATION AND DIAGNOSIS

Impetigo lesions are numerous, well localized, and **erythematous**. **KEY CONCEPT** They begin as small, thin-walled blisters that quickly evolve into ruptured lesions, with the dried discharge forming a honey-colored crust reminiscent of cornflakes.[5,7] Impetigo lesions are rarely painful but are **pruritic**. Scratching the lesions can spread the infection to other areas of the body. Scarring is rarely problematic, unless ulceration occurs, as in ecthyma.[5]

In order to avoid further spread and complications, antibiotic therapy is usually indicated. Sequelae of impetigo are uncommon. Rare manifestations of disease include transformation into cellulitis, progression to sepsis requiring hospitalization, or development of glomerulonephritis secondary to GAS.[5]

TREATMENT

The primary goals of impetigo therapy include preventing infection spread within the patient and to others, infection resolution, and preventing recurrence. Secondarily, symptom relief (eg, itching) and improving cosmetic appearance are important. Prevention of the rare but serious complications of impetigo is an alternative goal.[10]

Nonpharmacologic Treatment

Because impetigo is rarely painful, there is often a delay in seeking medical attention. Lesions may improve with time and increased hygiene along with soaking and cleansing lesions with mild soap and water. The use of skin emollients to dry skin areas may reduce spread and urge to scratch itchy lesions. The use of natural remedies is controversial; however, tea tree oil and Manuka honey may provide some anecdotal benefit.[10]

Pharmacologic Treatment

Antibiotic therapy is recommended to prevent spread of infection and complications. Although GAS historically has been the primary causative organism and penicillin is recommended when cultures yield streptococci alone, KEY CONCEPT the incidence of S. aureus impetigo is common, and oral penicillinase–stable penicillins (such as dicloxacillin) or first-generation cephalosporins (such as cephalexin) are preferred. In skin cultures of children with impetigo, MRSA rates have only ranged from 7% to 10% of cases (other cases were due to GAS or MSSA). Clindamycin, sulfamethoxazole–trimethoprim, or doxycycline is preferred for the treatment of MRSA impetigo. These are also alternative choices when penicillin allergy is a concern; however, tetracyclines should be avoided in children younger than 8 years. KEY CONCEPT Topical antimicrobials are also effective in some cases of impetigo. Topical mupirocin or retapamulin twice daily for 5 days may be used alone in mild cases with few lesions or in individual outbreaks.[5,10] Ozenoxacin is a topical nonfluorinated quinolone antibiotic that was recently approved for treatment of impetigo in patients greater than 2 months of age. It has activity against MRSA and *S. pyogenes*. Ozenoxacin applied twice daily for 5 days may be effective in impetigo resistant to other topical antimicrobials, though mupirocin remains first line in most cases.[11]

FOLLICULITIS, FURUNCLES, AND CARBUNCLES

See Table 76–1 for summary.

CELLULITIS AND ERYSIPELAS

EPIDEMIOLOGY AND ETIOLOGY

Cellulitis and erysipelas are common bacterial infections involving the skin, with over 14 million cases annually.[12] KEY CONCEPT Cellulitis is an infection of the dermis and subcutaneous tissue, whereas erysipelas is a more superficial infection of the upper dermis and superficial lymphatics. Although both can occur on any part of the body, many infections involve the leg.[12,13] These infections develop after a break in skin integrity, resulting from trauma, surgery, ulceration, burns, tinea infection, or other skin disorder. However, they may occur after an inapparent break in the skin. In rare cases, cellulitis develops from blood-borne or contiguous spread of pathogens.[5]

Etiologic microorganisms vary according to the area involved, host factors, and exposures. KEY CONCEPT The predominant pathogens associated with cellulitis are streptococci, mainly Group A, and less frequently S. aureus, including methicillin-resistant strains. Persons who are immunocompromised, have diabetes or vascular insufficiency, or use injection drugs are at risk of polymicrobial cellulitis.[5]

CLINICAL PRESENTATION AND DIAGNOSIS

The manifestations of nonpurulent infections are compared to purulent infections as shown in Table 76–2.

With early diagnosis and appropriate therapy, the prognoses of cellulitis and erysipelas are excellent. Severe or repeated episodes can cause lymphedema. Blood cultures are often obtained, but the actual rate of bacteremia is difficult to determine, and the yield may be low since cellulitis is often treated empirically.[12] Patients at higher risk of bacteremia from cellulitis include those with malignancy, signs of systemic infection (such as fever), animal bites, and immunocompromised. Rare complications include the spread of infection to deeper skin and soft tissue layers and sepsis.[5]

Annual recurrence rates, especially for cellulitis of the leg, can be as high as 20%[5], and over 50% within 3 years from the initial infection.[13] Cases often recur at the same site as previous infections. Vascular and lymphatic insufficiencies increase the risk of recurrences; obesity, tobacco use, history of cancer, and homelessness also increase risk.[5]

TREATMENT

The goals of therapy for cellulitis and erysipelas are rapid and successful eradication of the infection and prevention of related complications.

Nonpharmacologic Treatment

Nonpharmacologic treatment includes elevating the involved limb to decrease swelling. Sterile saline dressings may be placed on open lesions to cleanse them of purulent materials. Surgical debridement may be indicated for severe infection and to assess for necrotizing infection. Incision and drainage of abscesses is imperative to achieving clinical cure and may be the only treatment necessary if abscesses are small (< 5 cm) with limited cellulitis.[5] The choice to treat with antibiotics after incision and drainage of an uncomplicated abscess is controversial.

Pharmacologic Treatment

Many patients with erysipelas or cellulitis are effectively treated with outpatient therapy. Hospitalization and treatment with IV antibiotics is recommended in the presence of systemic inflammatory response syndrome (SIRS) (eg, temperature $> 38°\text{C}$ or $< 36°\text{C}$, tachypnea > 24 breaths/min, tachycardia > 90 beats/min, or white blood cell $> 12 \times 10^3/\text{mm}^3$ $[12 \times 10^9/\text{L}]$ or $< 400/\text{mm}^3$ $[0.4 \times 10^9/\text{L}]$), altered mental status, or hemodynamic instability. Patients presenting with sepsis based on the Sepsis-3 definition and Sequential (Sepsis-related) Organ Failure Assessment (SOFA) should also be candidates for hospitalization and broad-spectrum antimicrobials.[12,14] Further, inpatient therapy should be considered when suspecting deep or necrotizing infections, severely immunocompromised patients, failure of outpatient therapy, or poor adherence to therapy.[5]

Antibiotic choices for nonpurulent cellulitis should have activity against streptococci and include penicillin, amoxicillin, amoxicillin–clavulanate, dicloxacillin, cephalexin, or clindamycin. In the inpatient setting, empiric intravenous options include penicillin, ceftriaxone, cefazolin, or clindamycin.[5] Monotherapy with a β-lactam is appropriate in uncomplicated cases.[15,16]

Table 76–1

Folliculitis, Furuncles, and Carbuncles

	Folliculitis	Furuncles	Carbuncles
Epidemiology/ etiology	**KEY CONCEPT** Folliculitis is a superficial inflammatory reaction involving the hair follicle. The most familiar form of folliculitis is acne. It can be infectious, caused by microorganisms such as Staphylococcus aureus, *Pseudomonas, and Candida.*	Also known as boils, furuncles might be described as a deep form of folliculitis. A furuncle is a bacterial infection that has spread into the subcutaneous skin layers but still only involves individual follicles. Furuncles occur primarily in young men. Diabetes and obesity are other predisposing factors. *Staphylococci* are the most common cause.	Carbuncles share all the characteristics of furuncles. However, a carbuncle is larger and involves several adjacent follicles and may extend into the subcutaneous fat. Carbuncles are more likely to occur in patients with diabetes and tend to form on the back of the neck.
Presentation and diagnosis	Folliculitis presents as small, pruritic, erythematous papules. Location of the lesions and patient history are often all that are required in the diagnosis of folliculitis. Although Gram stain and culture of the papules may be considered, they are not generally required as folliculitis typically resolves spontaneously.	Furuncles most commonly develop on the face, neck, axilla, and buttock. A furuncle typically starts as a small, red, tender nodule. Within a few days, the nodule becomes painful and pustular. Typically, a furuncle will spontaneously discharge pus, heal and leave a small scar.	Carbuncles are similar to furuncles; only they are larger and exquisitely painful.
Desired outcomes	The goals of therapy for folliculitis, furuncles, and carbuncles are resolution of infection with no or minimal scarring. A secondary goal of therapy for larger furuncles and all carbuncles is to minimize the risk of endocarditis or osteomyelitis by reducing bloodstream invasion.		
Nonpharmacologic treatment	**KEY CONCEPT** Warm compresses are generally sufficient.	*Moist heat is indicated to facilitate drainage. Large furuncles require incision and drainage.*	*Incision and drainage are indicated.*
Pharmacologic treatment	**KEY CONCEPT** Often resolves spontaneously. A topical antibiotic or antifungal may be used to control the spread of infection but generally is unnecessary. For staphylococcal or streptococcal folliculitis, antibiotic ointments such as mupirocin might be administered. Antifungal shampoo can be used for **dermatophytes**.	*Carbuncles and furuncles that are purulent with signs of infection (ie, fever) should be treated systemically with an antibiotic that will cover S. aureus, such as dicloxacillin or cephalexin. Trimethoprim–sulfamethoxazole or doxycycline is preferred if CA-MRSA is suspected or if the patient has a severe allergy to penicillin.* Treatment should continue until acute inflammation has resolved, usually a 5- to 10-day course. Immunocompromised patients and severe infections or abscesses in patients who fail incision and drainage plus oral antibiotics should be treated empirically with vancomycin, daptomycin, linezolid, or ceftaroline. Prevention for recurrent episodes may be warranted, including adequate skin hygiene with the use of soap and water and handwashing after contact with lesions. Proper care of clothing and dressings is also recommended to prevent autoinoculation.	

Data from Refs. [5,7].

However, when purulent drainage, abscess, or ulcer is present, or in cases of penetrating trauma, particularly IV drug use, antibiotics with activity against MRSA should be initiated.[5]

Vancomycin continues to be the drug of choice for severe cellulitis due to MRSA because of its efficacy, safety, and low cost. Daptomycin, linezolid, or ceftaroline are also acceptable and should be considered over vancomycin when the isolated organism has a minimum inhibitory concentration (MIC) of greater than 2 mcg/mL (eg, vancomycin-intermediate *S. aureus* [VISA] or vancomycin-resistant *S. aureus* [VRSA]).[17] Newer agents for

Patient Encounter 1, Part 1: Cellulitis

A 76-year-old man presents to the emergency department with a 6-day history of progressively worsening pain and swelling of his left lower extremity. Upon examination, you notice that in addition to the patient's complaints, the area is visibly erythematous. The left lower extremity also seems to have significant hyperpigmentation and evidence of chronic venous insufficiency/venous stasis when compared to the right lower extremity. When questioned, he says that his legs have ranged from pink to purple to red in color. He reports running a low-grade fever and some feelings of fatigue but otherwise feels fine. His vital signs in the emergency department reveal a temperature of 38.9°C, pulse 96 beats/min, blood pressure 142/89 mm Hg, and respiratory rate 18 breaths/min. The physician diagnoses the patient with cellulitis, and he is admitted to the inpatient care team.

What subjective and objective clinical manifestations are suggestive of cellulitis?

What additional information do you need before developing a therapeutic plan for this patient?

Table 76–2

Characteristics of Nonpurulent and Purulent ABSSSI

	Nonpurulent	Purulent
Clinical manifestation	Cellulitis, erysipelas	Abscess, carbuncle, furuncle
Initial presentation	Diffuse redness, edema, warmth, and tenderness	Painful and tender localized lesion
Microbiology	Often unable to obtain culture from infected area Blood cultures considered in complicated or severe cases	Often able to obtain culture data from localized lesion Blood cultures considered in complicated or severe cases
Nonpharmacologic management	Incision and drainage not recommended	Incision and drainage recommended
Common causative pathogens	Streptococcus *pyogenes*	*Staphylococcus aureus*, including MRSA

[a] Modified from Ref. [5] (Figure 1) and Ref. [12].

ABSSSI, including tedizolid, dalbavancin, and oritavancin, may have advantages over traditional therapy in terms of duration of activity and administration.[12,18,19] Delafloxacin is a broad-spectrum fluoroquinolone with activity against MRSA approved for ABSSSI.[20] Omadacycline is an aminomethylcycline (tetracycline-derivative) antibiotic that has activity against Gram-positive, Gram-negative, atypical, and anaerobic organisms.[21] Both delafloxacin and omadacycline are available orally and intravenously. Cost and availability may limit the use of these newer agents.

For less severe, uncomplicated infections, many CA-MRSA strains can be treated with clindamycin (isolates resistant to erythromycin should be evaluated with a D test), doxycycline, or trimethoprim–sulfamethoxazole.[5,17] Trimethoprim–sulfamethoxazole and doxycycline should be empirically combined with a β-lactam if GAS is also a suspected causative organism, since the activity of these agents against β-hemolytic streptococci is unknown.[5] Linezolid is an additional oral option approved for ABSSSI with activity against MRSA and streptococci. It is available in both intravenous and oral formulations. It should be avoided in combination with medications that have serotonin or monoamine oxidase activity as it can precipitate serotonin syndrome.[22]

KEY CONCEPT In addition to coverage for staphylococcal and streptococcal ABSSSI, patients with severe infections should receive treatment for gram-negative bacilli such as Escherichia coli and Pseudomonas aeruginosa, with or without anaerobic coverage. Empiric broad-spectrum antimicrobial coverage, including coverage for resistant organisms such as healthcare-associated MRSA (HA-MRSA) and *P. aeruginosa*, is appropriate for severe ABSSSI and/or severe systemic illness. Broad-spectrum antimicrobials, including activity against gram-negative bacteria, can also be considered in individuals who are neutropenic, receiving chemotherapy, or have immunodeficiency.[5] Vancomycin with an antipseudomonal β-lactam (ie, piperacillin–tazobactam, cefepime, meropenem) is recommended in these cases. Empiric therapy continuation is recommended in polymicrobial infections, whereas more defined therapy is recommended when a causative pathogen is isolated.[5]

Patient Encounter 1, Part 2: Cellulitis: Medical History, Physical Examination, and Diagnostic Tests

PMH: Hypertension, type 2 diabetes mellitus (last A1c of 9.6%), and transient ischemic attack.

FH: Father's family history unknown. Mother passed away at 72 years of age due to complications of coronary artery disease.

SH: Denies alcohol or tobacco use. Daily use of marijuana. Lives alone, retired.

Meds: Lisinopril 10 mg PO daily, aspirin 81 mg PO daily, metformin 1000 mg PO BID, glipizide 5 mg PO BID, atorvastatin 40 mg PO daily.

Allergies: No known drug allergies.

ROS: (+) chills, fatigue, erythema, and swelling of lower extremity; (–) headache, chest pain, shortness of breath, cough, nausea, vomiting, diarrhea, and weight loss.

PE:

Gen: Patient is an obese male who is alert, awake, and oriented. Wt 118 kg (260 lb); Ht 5′7″ (170 cm). BMI=40.7.

Chest: Lungs bilaterally clear to auscultation.

CV: Regular rate, rhythm. No murmurs/rubs/gallops.

Ext: Left lower extremity with significant erythema and hyperpigmentation. Left lower extremity warm to touch and tender to palpation. He has sensation to light touch in bilateral lower extremity and is able to move toes bilaterally. One small ulcer on left lower ankle that appears to be chronic, no purulence. Right lower extremity within normal limits.

Imaging:

Foot X-ray of left lower extremity: Diffuse soft tissue swelling of the foot and ankle. No subcutaneous gas or foreign body. No fracture or arthritic change.

Tibia–fibula X-ray of left lower extremity: No definitive fracture or other bone abnormalities identified.

Labs: WBC 17.8 × 10^3/mm^3 (17.8 × 10^9/L), serum creatinine 1.2 mg/dL.

What are the most likely causative organisms in this case of cellulitis?

What subjective or objective clinical criteria would be concerning for necrotizing fasciitis in this patient's presentation rather than the diagnosis of cellulitis?

What are the goals of therapy for this patient?

What antimicrobial therapy would you recommend? Include drug, dosage, route, interval, and duration of therapy.

How would you monitor your selected regimen for safety and efficacy?

Table 76–3

Empiric Antimicrobial Therapy for Cellulitis

Host Factors	Probable Etiologic Bacteria	Mild Infection or Step-Down Therapy[a] (Oral Antibiotic Therapy)	Moderate–Severe Infection[a] (IV Antibiotic Therapy)
Previously healthy	MSSA GAS MRSA	Dicloxacillin 500 mg every 6 hours Cephalexin 500 mg every 6 hours Clindamycin 300–600 mg every 6–8 hours CA-MRSA suspected or allergy to PCNs: Clindamycin[b] 300–600 mg every 6–8 hours Trimethoprim–sulfamethoxazole DS[c] one to two tablets every 12 hours Doxycycline[c] 100 mg every 12 hours Linezolid 600 mg every 12 hours	Nafcillin 1–2 g every 4 hours Cefazolin 1–2 g every 8 hours Clindamycin 600–900 mg every 8 hours CA-MRSA suspected or allergy to PCNs: Vancomycin 15–20 mg/kg every 8–12 hours (individualize dose to achieve a trough of 15–20 mcg/mL or AUC:MIC 400-600 mg·h/L) Linezolid 600 mg every 12 hours Daptomycin 4 mg/kg every 24 hours Ceftaroline[f] 600 mg every 12 hours
Immunocompromise, diabetes mellitus, vascular insufficiency, pressure ulcer infection, or other polymicrobial infection suspected	MSSA MRSA Enterobacteriaceae *Pseudomonas aeruginosa* Anaerobes	Amoxicillin–clavulanate[d] 875 mg every 12 hours Levofloxacin[e] 750 mg every 24 hours + clindamycin 300–600 mg every 6 hours Moxifloxacin[d] 400 mg every 24 hours	Vancomycin, daptomycin, or linezolid, in combination with one of the following choices: Piperacillin–tazobactam[e] 4.5 g every 6 hours Ampicillin–sulbactam 3 g every 6 hours Imipenem–cilastatin[e] 500 mg every 6 hours Ertapenem 1 g every 24 hours Meropenem 1 g every 8 hours Cefepime[e] 2 g every 8 hours ± metronidazole 500 mg every 8 hours Ceftazidime[e] 2 g every 8 hours + clindamycin 600–900 mg every 8 hours OR Ceftaroline 600 mg every 12 hours + clindamycin 600–900 mg every 8 hours or metronidazole 500 mg every 8 hours

[a] Doses given are for adults with normal renal function. IV therapy can be switched to oral therapy (as for mild infection) when the patient is afebrile and signs of infection are resolving. Extended infusion of β-lactams can be considered per protocol of individual institution.

[b] CA-MRSA isolates resistant to erythromycin should be evaluated for inducible clindamycin resistance via a D test.

[c] Limited clinical data exist for the treatment of MRSA infections. Poor activity against GAS; consider using in combination with clindamycin or cephalexin if empiric coverage for GAS is desired.

[d] If CA-MRSA suspected, clindamycin, trimethoprim–sulfamethoxazole, or doxycycline must be added to this regimen.

[e] *P. aeruginosa* generally is susceptible to this agent.

[f] Use caution in patients with known hypersensitivity to β-lactam antibiotics.

[g] MRSA coverage is indicated for patients with severe cellulitis or systemic illness, who have risk factors for HA-MRSA or CA-MRSA infection or reside in areas with high CA-MRSA prevalence. Otherwise, the broad-spectrum regimens listed below, without MRSA coverage, are appropriate.

Data from Refs. [5,7,12].

Table 76–3 lists some recommended antibiotic regimens for the treatment of ABSSSI. Because antimicrobial susceptibilities vary considerably between geographic locations, clinicians should select empiric treatment based on the antibiograms at their respective institutions. To decrease spread of resistance, antibiotic therapy should be narrowed based on culture and sensitivity results whenever possible. The duration of therapy for uncomplicated cellulitis typically ranges from 5 to 10 days. For complicated cellulitis, therapy with IV antibiotics is generally initiated, and a switch to oral therapy can be made once the patient is afebrile and skin findings begin to resolve. Typically, this is done after 3 to 5 days.[5,23] The complete duration of therapy may extend beyond 10 days if the patient's infection has a slower clinical response within the first 5 days.[5]

Recurrent cellulitis can be problematic, and reducing risk factors, such as obesity, edema, or toe abnormalities, may help with prevention, especially in the lower extremities. For patients with recurrent abscesses due to *S. aureus*, decolonization regimens can be considered. These include intranasal mupirocin, chlorhexidine rinses, and decontamination of towels or sheets. Efficacy of

Patient Encounter 1, Part 3: Cellulitis: Clinical Course

During the patient's hospitalization, he becomes afebrile. No microbiology data is available as the presentation is primarily diffuse redness without purulence. On day 4 of the patient's hospital stay, his cellulitis has significantly improved. The interdisciplinary team of clinicians is preparing the patient for discharge.

What would you suggest for modification of his antimicrobial regimen to an oral regimen?

What is the appropriate duration of his antibiotic course of therapy for his cellulitis?

How would you monitor his new regimen for safety and efficacy?

What are the patient's risk factors for recurrence of his cellulitis?

What strategies would you recommend to prevent recurrence of cellulitis?

decolonization has not been consistently proven to reduce rates of ABSSSIs.[5] Low-dose antibiotic prophylaxis with penicillin or erythromycin for up to 1 year may reduce recurrences, but the benefit subsides when therapy is discontinued and is not routinely recommended.[5,13] When edema is present, the use of compression stockings may decrease recurrent cellulitis.[24]

NECROTIZING FASCIITIS

EPIDEMIOLOGY AND ETIOLOGY

Necrotizing fasciitis (NF) is a rapidly progressive, life-threatening infection causing necrosis of subcutaneous tissue and fascia. When due to GAS infection, its associated mortality rate approaches 25%.[25] NF can affect any age-group. Although the risk of NF is higher in injection drug users and patients with diabetes or vascular insufficiency, healthy hosts can become infected as well.[5]

NF typically erupts after an initial trauma, which can range from a small abrasion to a deep penetrating wound. The infection begins in the fascia, where bacteria replicate and release toxins facilitating spread. Patients' pain is often out of proportion with the visible injury.[5]

NF may be monomicrobial, most often involving *S. pyogenes, S. aureus, Vibrio vulnificus,* or *Aeromonas hydrophila*. Polymicrobial NF may develop in the following clinical settings: after surgery or deep penetrating wounds involving the bowel; from decubitus ulcer, perianal, or vulvovaginal infection; or from the injection site in an IV drug user.[5]

CLINICAL PRESENTATION AND DIAGNOSIS

Patient outcomes rely on the clinician's ability to recognize NF early in the course of disease. This is often difficult because early disease tends to be indistinguishable from cellulitis. The clinical presentation of NF is presented in Table 76–4.

Table 76–4

Presentation of Necrotizing Fasciitis

Symptoms
- Early: Severe pain that is disproportionate to clinical signs and extends beyond the margins of the infected area.
- Late: Area may become numb secondary to muscle and nerve involvement.

Signs
- Early: Skin is erythematous, edematous, and warm; the clinical presentation is similar to that of cellulitis.
- Intermediate (within 24–48 hours): Blisters and bullae indicate severe skin and tissue ischemia.
- Late: The skin becomes violaceous and progressively gangrenous, and subcutaneous tissues have wooden-hard induration; hemorrhagic bullae may be present. Systemic signs may include fever, tachycardia, hypotension, and shock.

Laboratory Tests
- White blood count, serum creatinine, and C-reactive protein may be elevated.
- Deep tissue specimens obtained during surgical irrigation and debridement should be sent for Gram stain, culture, and sensitivity.

Imaging Studies
- MRI and CT scans may reveal fluid and gas along fascial planes.
- Typically, imaging studies are avoided when making a diagnosis because they may delay surgical intervention and increase mortality.

NF, necrotizing fasciitis.

Data from Refs. [5,26].

NF is perhaps the most devastating ABSSSI. Left untreated, it can invade the muscles and circulation, resulting in myonecrosis and septic shock, respectively. Many cases caused by GAS are accompanied by GAS toxic shock–like syndrome. The syndrome is bacterial exotoxin mediated and can be very evasive and highly lethal.[26] Amputation is common in patients with extremity infections. Once the patient recovers from acute NF, he or she often requires skin and/or muscle grafting and consequent physical rehabilitation depending on the amount and types of tissues removed during surgical intervention and the duration of hospital stay.[27]

TREATMENT

The goals of therapy for NF include eradication of infection and reduction of related morbidity and mortality.

Nonpharmacologic Treatment

KEY CONCEPT After resuscitation and hemodynamic stabilization, prompt surgical intervention is the key in the treatment of NF. Delayed operative debridement increases mortality, and most patients should return to the operating room frequently until debridement is no longer indicated.[5,27]

Pharmacologic Treatment

As an adjunct to surgery, high-dose, broad-spectrum IV antibiotic therapy should be initiated immediately in patients with NF until the patient has improved clinically and is afebrile for 48 to 72 hours, and no further need for debridement exists. Piperacillin–tazobactam, a carbapenem, ceftriaxone plus metronidazole, or a fluoroquinolone plus metronidazole is appropriate for empiric therapy. These agents should be used in combination with vancomycin, daptomycin, or linezolid until MRSA infection is ruled out.[5] Protein synthesis inhibitors, clindamycin or linezolid, are often utilized to decrease bacterial toxin production, thereby limiting tissue damage. This is particularly beneficial in streptococcal or clostridial infections.[28]

IV immunoglobulin (IVIG) dosed at 2 g/kg (ideal body weight) may also be a useful adjunctive treatment in patients with GAS NF who present with shock. Anecdotal evidence and data from small studies strongly support its use in improving 30-day survival and reducing mortality, although additional evidence is needed for a definitive recommendation.[5]

DIABETIC FOOT INFECTIONS

EPIDEMIOLOGY AND ETIOLOGY

Foot ulcers and related infections are among the most common, severe, and costly complications of diabetes mellitus. The lifetime risk of developing at least one foot ulcer in persons with diabetes is estimated at 30%.[29,30] Diabetic foot infections (DFIs) are the main risk factor for limb amputation, and in addition to significant morbidity and impact on quality of life, the healthcare costs associated with treating infected foot ulcers are enormous.[30]

KEY CONCEPT Staphylococci and streptococci are the predominant pathogens in acutely infected diabetic foot ulcers. *However, severe or more extensive chronically infected wounds are subject to polymicrobial infection*. Clinicians should suspect Gram-negative (such as *P. aeruginosa*) and possibly low-virulence pathogens (including enterococci and *Staphylococcus epidermidis*) in polymicrobial

Patient Encounter 2, Part 1: Diabetic Foot Infection

A 47-year-old woman presents to the emergency department with complaints of pain, redness, and swelling of her right foot. When she had her last visit with her primary care provider 11 months ago, she was told that she had a small ulcer on her big toe, which she thought had healed. As she moves to the exam table, she has difficulty walking because the foot is so painful. Upon examination, you see what appears to be a chronic, deep lesion on the plantar aspect of her right great toe approximately 3 cm (1.2 in.) in diameter, and a smaller, more superficial ulcer near the heel. Her foot is erythematous, warm, and she has lymphangitic streaking extending beyond her ankle up into the calf. The patient has poorly controlled type 1 diabetes mellitus and indicates difficulty affording her insulin because she lost her job 6 months ago. She also has neuropathy that has affected the sensation in her lower extremities. The patient is afebrile, and other vital signs are within normal limits.

What signs and symptoms present in this patient are indicative of a diabetic foot infection?

Based on presentation, classify this patient's diabetic foot infection using the PEDIS grading scale.

What additional information do you need before developing a therapeutic plan for this patient?

infections. Foul-smelling, necrotic, or gangrenous wounds are also commonly infected with anaerobic bacteria. MRSA may be isolated in up to 30% of DFIs and may be more common in patients recently hospitalized or treated with broad-spectrum antibiotics, or those with a previous history of MRSA infection.[31-33]

PATHOPHYSIOLOGY

KEY CONCEPT The pathogenesis of diabetic foot infection stems from multiple key factors, including repetitive shear stress, peripheral neuropathy, altered immune function, and, when present, ischemia from peripheral vascular disease.[30] **Neuropathy**, the most prominent risk factor for diabetic foot ulcers, develops when continuously high blood glucose levels damage motor, autonomic, and sensory nerves. Damage to motor neurons that supply the small intrinsic muscles of the foot causes deformation, resulting in altered muscular balance, abnormal areas of pressure on tissues and bone, and repetitive injuries. Damage to autonomic neurons results in the shunting of blood through direct arteriole-venous communications, thereby decreasing capillary flow. The secretion of sweat and oil is also diminished, producing dry, cracked skin that is more prone to infection. Finally, damage to sensory neurons produces a loss of protective sensation so that the patient becomes unaware of injury or ulceration.[30,34]

Persons with diabetes have altered immune function that predisposes them to infection. Leukocyte function and cell-mediated and humoral immunity are compromised in poorly controlled disease.[31] Achieving and maintaining controlled blood glucose levels should be a component of the prevention and management of diabetic foot infections.

Finally, peripheral arterial disease can nearly double the risk of DFI and contributes to poorer outcomes.[34] The presence of other

Patient Encounter 2, Part 2: Diabetic Foot Infection: Medical History, Physical Examination, and Diagnostic Tests

PMH: Type 1 diabetes mellitus × 39 years, hypertension, microalbuminuria, dyslipidemia, migraine headaches, and Celiac disease.

FH: Father alive with type 2 diabetes, hypertension, dyslipidemia, and gout at age 70. Mother died at age 61 from hemorrhagic stroke. One brother alive with hypertension. One sister died at age 44 from breast cancer.

SH: Divorced, one daughter age 26. Formerly a teller at a bank, currently unemployed. Smokes six cigarettes/day. Denies alcohol use. Tries to eat a gluten-free diet.

Meds: NPH 70/30 14 units BID, enalapril 20 mg BID, rosuvastatin 20 mg daily, sumatriptan 100 mg at onset of headache and repeated at 2 hours prn.

Allergies: penicillin (hives).

ROS: (+) right foot findings per HPI; (–) headache, chest pain, shortness of breath, cough, nausea, vomiting, diarrhea, and weight loss.

PE:

Gen: Patient is in no acute distress. Wt 79 kg (143.8 lb); Ht 5 ft 5 in (165.1 cm).

Chest: CTAB.

CV: RRR. No murmurs/rubs/gallops.

Ext: 3-cm purulent, erythematous lesion present on the plantar aspect of the right great toe. 2+ edema in the left foot; diminished sensation bilaterally. Lymphangitic streaking present; wound probe 1.5 cm deep.

Labs: Most recent labs were drawn at last outpatient visit 11 months ago: BUN 15 mg/dL, SCr 1.1 mg/dL, Glu 212 mg/dL, A1C 10.6%.

The patient is diagnosed with a diabetic foot infection and is admitted to the hospital.

Explain the role of neuropathy, ischemia, and immunopathy in the development of this patient's diabetic foot infection.

What are the best preventative strategies for diabetic foot infections and complications such as lower extremity amputation?

Antimicrobial therapy for this patient's infection should provide coverage for which microorganisms?

What antimicrobial therapy would you recommend? Include drug, dosage, route, interval, and duration of therapy.

How would you monitor your selected regimen for safety and efficacy?

risk factors, including hypertension, dyslipidemia, and smoking, can cause vasoconstriction, and together, ischemia and skin breakdown can occur as a cumulative result. In addition to managing blood glucose levels, encouraging smoking cessation and managing other risk factors of cardiovascular disease is imperative.

CLINICAL PRESENTATION AND DIAGNOSIS

Not all diabetic foot ulcers are infected. However, infection is often difficult to detect when perfusion and the inflammatory response are limited in the patient with diabetes. The common signs and symptoms (ie, pain, erythema, and edema) of infection may be absent.[34] Still, the diagnosis of diabetic foot infection depends mostly on clinical evaluation.

Purulent drainage from the ulcer is indicative of infection. When pus and inflammatory symptoms are not present, the clinician must be astute to more subtle findings. These include delayed healing, increase in lesion size, prolonged exudate production, malodor, and tissue friability. Abnormal granulation tissue also may be present, as evidenced by color change (from bright red to dark red, brown, or gray) and increased bleeding. The ability to probe the ulcer to the underlying bone is highly indicative of osteomyelitis.[34]

Diabetic foot infections are classified into four categories based on clinical presentation using the PEDIS scale (perfusion, extent/size, depth/tissue loss, infection, sensation). Grade 1 signifies no infection; grade 2, involvement of skin and subcutaneous tissue only; grade 3, extensive cellulitis or deeper infection; and grade 4, the presence of systemic inflammatory response syndrome.[31,35] Table 76–5 provides detailed information regarding these grades.

Table 76–5

Clinical Classification of a Diabetic Foot Infection

Infection Severity	PEDIS Grade	Clinical Manifestations of Infection
Uninfected	1	Wound lacking purulence or any manifestations of inflammation
Mild	2	The presence of at least two manifestations of inflammation (purulence or erythema, pain, tenderness, warmth, or induration), but any cellulitis/erythema extends no more than 2 cm around the ulcer, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness
Moderate	3	Infection (as above) in a patient who is systemically well and metabolically stable but who has at least one of the following characteristics: cellulitis extending > 2 cm, lymphangitic streaking, spread beneath the superficial fascia, deep tissue abscess, gangrene, and involvement of muscle, tendon, joint, or bone
Severe	4	Infection in a patient with systemic toxicity or metabolic instability (eg, fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia)

From Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54(12)132–173.

Patient Encounter 2, Part 3: Diabetic Foot Infection: Clinical Course

The patient received the empiric therapy you recommended for her diabetic foot infection. Two days later, deep wound cultures were reported positive for *MRSA*. Blood cultures revealed no growth. The patient remained hospitalized for an additional week, during which time her cellulitis improved on directed antimicrobial therapy. She was discharged to complete her antibiotic therapy and follow up as an outpatient in 1 week.

What modifications would you make to this patient's antimicrobial regimen knowing that the causative agent is MRSA?

What individualized foot care strategies can you suggest to this patient to prevent further infections?

Another DFI grading system, SINBAD, is based on clinical examination only and may simplify communication when triage is necessary. SINBAD evaluates site of infection, degree of ischemia based on palpation of pulse, the presence of neuropathy and bacterial infection, and area and depth of involvement. Other scoring systems may further predict amputation risk and benefit from revascularization.[35]

Imaging studies, such as X-ray and magnetic resonance imaging (MRI), can identify osteomyelitis. Blood cultures should be obtained from all patients with signs and symptoms of systemic illness. Deep tissue cultures may help to direct therapy. Bone also may be sent for culture in cases of osteomyelitis. Superficial cultures of ulcers are unreliable and should be avoided.[31]

Spreading soft tissue infection and osteomyelitis are often the first complications that develop from diabetic foot infection. Some patients develop bacteremia and sepsis. The most feared complication of infected diabetic foot ulcers is lower extremity amputation.[34]

TREATMENT

The goals of therapy for diabetic foot infection are eradication of the infection and avoidance of soft tissue loss and amputation.

Prevention

Comprehensive foot care programs and the utilization of multidisciplinary care teams can improve outcomes and decrease amputation rates.[31] Periodic foot examinations with monofilament testing and patient education regarding proper foot care, optimal glycemic control, and smoking cessation are key preventative strategies.

Nonpharmacologic Treatment

The nonpharmacologic treatment of diabetic foot ulcers may include debridement of necrotic or nonviable tissue, wound dressings, vascular or orthopedic surgery, and off-loading pressure from the wound.[31]

Pharmacologic Treatment

The severity of a patient's infection, based on the PEDIS scale, can help guide the selection of empiric antimicrobial therapy. Although most patients with grade 2 diabetic foot infections can be treated as outpatients with oral antimicrobial agents, all

Table 76–6

Empiric Pharmacologic Treatment of Diabetic Foot Infection

Infection Severity	PEDIS Grade	General Approach to Empiric Pharmacologic Treatment	Examples of Appropriate Empiric Antibiotics[a]
Uninfected	1	None. Avoid treating uninfected diabetic foot ulcers.	Not applicable
Mild	2	Oral, narrow-spectrum antibiotic therapy with activity against *Staphylococcus aureus* and streptococcal species. Include coverage for MRSA according to patient history and resistance patterns in the area. Duration of antibiotics: 1–2 weeks, may extend to 4 weeks if slow resolution	MRSA not suspected: cephalexin, dicloxacillin, clindamycin, amoxicillin–clavulanate, levofloxacin MRSA suspected: clindamycin[b], trimethoprim–sulfamethoxazole[c], doxycycline[c], or linezolid
Moderate	3	Difficult to define a general approach. In many patients, highly bioavailable oral therapy is appropriate. IV therapy should be initiated in patients with more extensive or chronic infections, or those with abscess, deep tissue, bone involvement, or gangrene. Duration of antibiotics: 1–3 weeks	Options for grade 3 infections: amoxicillin–clavulanate or ampicillin–sulbactam, cefoxitin, ceftriaxone, ertapenem, levofloxacin[d] + clindamycin, or moxifloxacin MRSA suspected: clindamycin[b], doxycycline[c], linezolid, daptomycin, trimethoprim–sulfamethoxazole[c], or vancomycin
Severe	4	Parenteral, broad-spectrum antibiotic therapy should be initiated. Ideally, drugs with activity against Gram-positive, Gram-negative, and anaerobic bacteria (especially if wound is malodorous) should be selected. Include coverage for MRSA. Duration of antibiotics: 2–4 weeks	IV options for grade 3–4 infection: gram-negative/anaerobic activity: ampicillin–sulbactam, aztreonam, cefepime, ceftazidime, ceftriaxone, ertapenem, imipenem–cilastatin[d], piperacillin–tazobactam, meropenem, moxifloxacin, levofloxacin[d] + clindamycin MRSA activity: vancomycin, daptomycin, or linezolid

[a] Please refer to Table 76–3 for dosing in adults with normal renal function.

[b] CA-MRSA isolates resistant to erythromycin should be evaluated for inducible clindamycin resistance via a D test.

[c] Poor activity against GAS; consider using in combination with clindamycin or cephalexin if empiric coverage for GAS is desired.

[d] *Pseudomonas aeruginosa* generally is susceptible to this agent.

Data from Refs. [29,31,34].

grade 4 and many grade 3 infections require hospitalization, stabilization of the patient, and broad-spectrum IV antibiotic therapy.[31,34]

Multiple antibiotic options exist for the treatment of diabetic wound infections. Table 76–6 provides both general treatment strategies and specific, although not all-inclusive, antibiotic recommendations. The duration of therapy correlates with infection severity. Antibiotics should be continued until the infection has resolved, but not necessarily until the ulcer has healed. Milder infections generally require 7 to 14 days of therapy; more severe infections may necessitate treatment durations of 2 to 3 weeks, or longer with bone involvement. Patients with osteomyelitis may require weeks to months of antibiotic therapy depending on whether the infected and necrotic bone is surgically debrided or amputated.[31,34]

INFECTED BITE WOUNDS

EPIDEMIOLOGY AND ETIOLOGY

Approximately one in two Americans will be bitten by an animal at least once during their lifetimes.[36] Although most bite wound injuries are minor, some will require medical treatment and account for 1% of all emergency department visits.[37]

Dogs cause most animal bites, typically open lacerations and crush injuries.[36,38] Cat bites are the second most common animal bite, most often puncture wounds involving the hand. Because cat bites are deep and penetrating, the development of infection is more common.[36]

Human bites result in up to 3% of hand bites. There are two types of human bite injuries. Occlusal injuries are inflicted by actual biting, whereas clenched-fist injuries are sustained when a person's closed fist hits another's teeth. Of the two, clenched-fist injuries typically are more prone to infectious complications.[36,39]

KEY CONCEPT Bite wound infections generally are polymicrobial.[5] Both the normal flora of the biter's mouth and that of the bite recipient's skin can be implicated. The bacteriology of the cat and dog mouth is quite similar. *Pasteurella multocida*, a gram-negative aerobe, is one of the predominant pathogens. Viridans streptococci are the most frequently cultured bacteria from human bite wounds, although empiric treatment should also provide coverage for *Eikenella corrodens*.[5,36] Table 76–7 provides a comprehensive list of cat-, dog-, and human bite–wound pathogens.

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of infected bite wounds is presented in Table 76–7.

Complications of infected bite wounds include abscess, septic arthritis, tenosynovitis, and osteomyelitis. Bites to the hand are particularly complication prone.[36] Unfavorable scarring may also be a complication.[38]

TREATMENT

The goals of therapy for an infected bite wound are rapid and successful eradication of infection and prevention of related complications.

Table 76–7

Etiology and Presentation of Infected Bite Wounds

Bacterial Pathogens

- *Dog and cat: Pasteurella multocida, Staphylococci*, streptococci *Moraxella* spp., *Eikenella corrodens, Capnocytophaga canimorsus, Actinomyces, Fusobacterium, Prevotella,* and *Porphyromonas* spp.
- *Human:* Viridans streptococci, *Staphylococcus aureus, E. corrodens, Haemophilus influenzae,* and β-lactamase–producing anaerobic bacteria.

Signs and Symptoms

- The onset of infectious symptomatology is typically 12–24 hours after the bite.
- Pain at the wound site is common.
- Erythema, edema, and purulent or malodorous drainage at the wound site are manifestations of infected wounds. The patient may be febrile.
- Limited range of motion may be present, especially if the hand is bitten.

Laboratory Tests

- Leukocytosis may be present.
- The clinician should obtain anaerobic and aerobic wound cultures only if the wound appears clinically infected.

Imaging Studies

- Radiographs should be obtained if the bite is on the hand, could have damaged bone or joints, or if an embedded object or tooth fragment is suspected.

Data from Refs. [5,36].

Nonpharmacologic Treatment

Thorough irrigation with normal saline is the first step in the care of an infected bite wound. The wound should be elevated and immobilized. Surgical closure may be advocated, especially for facial wounds. Wounds that are infected or at higher risk of infection, such as those on the hand, should be left open to close by secondary intention to decrease the risk of complications.[36,37]

Pharmacologic Treatment

Most bite wounds require antibiotic therapy only when clinical infection is present. *However, prophylactic therapy is recommended for wounds at higher risk of infection and bites requiring surgical repair*.[37] Antibiotic prophylaxis should be considered in patients at high risk of infection because of immunocompromise, or those with specific wound types, such as puncture wounds or crush injuries with tissue damage.[36]

The most effective agent for the treatment (and prophylaxis) of human and animal bite–wound infections is amoxicillin–clavulanate. Alternatives include second-generation cephalosporins, such as cefuroxime, plus coverage for anaerobes, such as clindamycin or metronidazole. Moxifloxacin, doxycycline, or a carbapenem may also be used. The duration of prophylaxis and treatment are generally 3 to 5 days.[5] Consider rabies prophylaxis as appropriate, based on recommendations from the Centers for Disease Control and local health department. Depending on the immunization status of the bite-wound victim, prophylaxis for tetanus may also be warranted.[36,39]

If the wound is associated with significant cellulitis and edema, systemic signs of infection, or possible joint or bone involvement, hospitalization and IV antibiotics (typically ampicillin–sulbactam 3 g IV every 6 hours) should be initiated. Bone and joint infections will require longer durations of therapy of up to 6 weeks.[5,39]

OUTCOME EVALUATION

Education of the patient, caregivers, and household members is important to limit further spread of infection and is a key component in ABSSSI case management. Table 76–8 lists several key prevention messages for patients with ABSSSIs.

Patients receiving antibiotic therapy for ABSSSIs require monitoring for efficacy and safety. Efficacy typically is manifested by reductions in temperature, white blood cell count, erythema, edema, and pain. Initially, signs and symptoms of infection may worsen owing to toxin release from certain organisms (ie, GAS); however, they should begin to resolve within 48 to 72 hours of treatment initiation. If no response or worsening infection is noted after the first 3 days of antibiotics, reevaluate the patient.[5] Lack of response may be due to a noninfectious or nonbacterial diagnosis, a pathogen not covered by or resistant to current antibiotic therapy, poor patient adherence, drug or disease interactions causing decreased antibiotic absorption or increased clearance, immunodeficiency, or the need for surgical intervention. To ensure the safety of the regimen, dose antibiotics according to renal and hepatic function as appropriate, and monitor for or minimize adverse drug reactions, allergic reactions, and drug interactions.

Table 76–8

Prevention Education for Patients with ABSSSIs

1. Draining wounds should be covered with clean, dry bandages.
2. Hands should be cleaned regularly with soap and water (or with alcohol-based hand gel if not visibly soiled) and immediately after touching infected skin or any item directly contacting a draining wound.
3. General hygiene should be maintained with regular bathing.
4. Items that may become contaminated with wound drainage or that directly touch the skin should not be shared.
5. Wash and dry thoroughly any clothing that has come in contact with wound drainage after each use.
6. If the wound is unable to be covered with a clean, dry bandage at all times, avoid activities with skin-to-skin contact until the wound is healed.
7. Equipment and environmental surfaces with bare skin contact should be cleaned with *Staphylococcus aureus*–active detergents or disinfectants.

From Gorwitz RF, Jernigan DB, Powers JH, et al. Strategies for clinical management of MRSA in the community: Summary of an experts' meeting convened by the Centers for Disease Control and Prevention [online]. 2006. [cited 2020 Aug 28]. https://www.cdc.gov/mrsa/pdf/MRSA-Strategies-ExpMtgSummary-2006.pdf.

Patient Care Process

Collect Information:

- Review the medical history and physical assessment findings.
- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. Identify allergies to medications and other substances.
- Speak with the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Based on physical examination and review of systems, determine whether the patient is experiencing signs or symptoms of an ABSSSI, and if so, its severity.
- Based on the history and presentation, determine the most likely causative microorganism of the patient's infection to select treatment.
- Document current temperature, blood pressure, and heart rate.
- Review relevant laboratory tests (eg, complete blood count, renal function, basic metabolic profile, and culture and sensitivity report)
- Identify any significant adverse drug effects or interactions with current drug therapy.

Develop a Care Plan:

- Determine the most appropriate nonpharmacologic or pharmacologic treatment option(s) for the patient's infection based on presentation and history.
- Select the most appropriate antibiotic therapy that is likely to be effective and safe.
- Choose medications, doses, routes, and treatment durations that are optimal for the patient and will result in the resolution of infection. In pediatric patients especially, consider method and ease of administration, and palatability and tolerability of oral formulations.

Implement the Care Plan:

- Educate the patient about their drug therapy, medication administration, potential adverse effects, and how to manage and report adverse effects that occur.
- Address any patient concerns about skin and skin structure infection and its management.
- Discuss importance of medication adherence to improve resolution of infection and reduce antimicrobial resistance.
- Determine whether the patient has insurance coverage or recommended agents are included on the institution's formulary.
- Abide by antimicrobial stewardship practices at the institution.

Follow-up: Monitor and Evaluate:

- Follow up at an appropriate interval to ensure resolution of infection.
- Review physical exam, vital signs, and lab tests to assess changes in clinical status and resolution of infection.
- Narrow antibiotic coverage when possible with the use of culture and sensitivity data.
- Reinforce proper infection prevention strategies.

Abbreviations Introduced in This Chapter

ABSSSI	Acute bacterial skin and skin structure infection
CA-MRSA	Community-acquired methicillin-resistant *S. aureus*
GAS	Group A *Streptococcus* (also known as *Streptococcus pyogenes*, one of the β-hemolytic streptococci)
GERD	Gastroesophageal reflux disease
HA-MRSA	Healthcare-associated methicillin-resistant *S. aureus*
IVIG	Intravenous immunoglobulin
MIC	Minimum inhibitory concentration
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *S. aureus*
MSSA	Methicillin-sensitive *S. aureus*
NF	Necrotizing fasciitis
SIRS	Systemic inflammatory response syndrome
SSSI	Skin and skin structure infection
VISA	Vancomycin-intermediate *S. aureus*
VRE	Vancomycin-resistant enterococci
VRSA	Vancomycin-resistant *S. aureus*

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Osteomyelitis

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. List common risk factors for osteomyelitis.
2. Discuss the pathophysiology of osteomyelitis.
3. Compare and contrast the classic signs and symptoms of acute and chronic osteomyelitis.
4. Evaluate microbiology culture data and other laboratory tests and imaging studies utilized for diagnosis of osteomyelitis.
5. List the most common pathogens isolated in acute and chronic osteomyelitis.
6. Develop a treatment plan for osteomyelitis.
7. Recommend parameters to monitor antimicrobial therapy for effectiveness and toxicity.
8. Describe how principles of antimicrobial stewardship can be applied to the management of osteomyelitis.
9. Educate patients regarding lifestyle modifications that may impact disease outcomes.

INTRODUCTION

KEY CONCEPT Osteomyelitis is an infection of the bone that may be either an acute or chronic process. The inflammatory response associated with acute osteomyelitis can lead to bone necrosis and subsequent chronic infection.[1] Bacterial pathogens, such as *Staphylococcus aureus*, are most commonly responsible for both acute and chronic infections.[1-8] Diagnosis and treatment present significant challenges to clinicians due to the complex nature of osteomyelitis.[1,2] Medical management is considered the cornerstone of treatment for acute infections; however, surgical intervention in addition to antimicrobial therapy is necessary to achieve cure for chronic infections.[1,2]

KEY CONCEPT Osteomyelitis is most often classified by duration of disease and route of infection.[1,2,9]

Two major osteomyelitis classification schemes exist. The Cierny–Mader classification focuses on the affected portion of bone, physiologic status of the patient, and factors impacting local vascularity.[1] In contrast, the Waldvogel classification scheme categorizes disease based on route of infection (**hematogenous** or **contiguous**) and duration of disease (acute versus chronic).[9] Using this classification scheme, osteomyelitis secondary to a contiguous focus can be further subdivided into infections with or without vascular insufficiency. Typical bone involvement in osteomyelitis depends on the route of infection.

- Hematogenous: long bones (femur, tibia) in children and vertebra in the elderly[2–5,10]
- Contiguous with vascular insufficiency: lower extremities[2,11,12]
- Contiguous without vascular insufficiency: bones affected by trauma, surgery, or adjacent soft-tissue infection[1,5]

A single pathogen is most often isolated in hematogenous osteomyelitis, whereas multiple organisms are often isolated in contiguous infections.[7,10,11,13]

While there are no validated definitions delineating acute versus chronic infection,[1,9,10] acute infection is often defined as the first episode or onset of symptoms within 2 weeks.[2,9-11] In comparison, chronic osteomyelitis is generally defined as disease relapse or symptoms persisting beyond 2 months.[2,9] Because there is no abrupt temporal demarcation, but rather a gradual shift from acute to chronic infection, many describe chronic osteomyelitis as the presence of necrotic bone.[1,2,10,11]

EPIDEMIOLOGY AND ETIOLOGY

The most common origin of osteomyelitis is dependent on the age of the patient. Children are more likely to suffer from hematogenous disease while adults are more likely to develop osteomyelitis due to contiguous spread.[1-4,6] However, hematogenous osteomyelitis can also be seen in older adults and in patients with a history of intravenous (IV) drug abuse, with the spine (vertebral osteomyelitis) being the most common site of infection.[1,2,5]

KEY CONCEPT *S. aureus* is the predominant pathogen seen in all types of osteomyelitis, with methicillin-resistant *S. aureus* (MRSA) being increasingly reported.[1-4,6,10] Patient-specific risk factors have the greatest impact on the potential pathogens including the following:

- Uncontrolled diabetes and/or peripheral vascular disease (polymicrobial including MRSA, Enterobacterales, and *Pseudomonas aeruginosa*).[11,14]
- Sickle cell disease (*Salmonella* spp.).[1,2,7]
- Individuals with prosthetic implants (coagulase-negative staphylococci).[7]
- Neonates (*Escherichia coli* or group B streptococci).[2]
- Patients with pressure sores (polymicrobial).[2,7]

Regardless of patient-specific risk factors all patients with deep or extensive wounds, particularly those that are nonhealing should be evaluated for underlying osteomyelitis.[11,14]

PATHOPHYSIOLOGY

Both microbial and patient-specific factors are important determinants in the development of osteomyelitis.[1] Healthy bone tissue is normally resistant to infection but may become susceptible under certain conditions.[1,2] Bone can become infected: (a) via the presence of bacteria in the bloodstream (hematogenous), (b) by direct inoculation from trauma or surgery, and (c) by spread from an adjacent site (eg, soft-tissue infection) (contiguous).[1] The latter is particularly problematic in patients with implantable devices (eg, hip replacement), vascular insufficiency, and chronic skin ulcers.[1,11]

Staphylococcus species possess bacterial adhesins, which promote their attachment to tissues and prosthetic material.[1] Microbial adherence to bone elicits an inflammatory response.[1] The subsequent release of leukocytes and cytokines leads to local edema and **ischemia** facilitating bone necrosis.[1] Pieces of dead bone may become separated, forming **sequestra**.[1] The presence of sequestra is often indicative of chronic disease. These areas typically cannot be penetrated by antimicrobials or phagocytic cells due to poor blood supply and, thus, require surgical intervention to eradicate the bacterial **nidus**.[1,11]

CLINICAL PRESENTATION AND DIAGNOSIS

General

The clinical presentations of osteomyelitis may vary depending on route and duration of infection, as well as patient-specific factors such as infection site, age, and comorbidities.[1-4,7,11,14]

KEY CONCEPT Bone biopsy is the gold standard for confirmatory diagnosis of osteomyelitis. A bone biopsy allows for isolation of microorganism(s) from culture in addition to verifying the presence of inflammatory cells and osteonecrosis on histologic exam.[1,2,11-14] Due to the invasive nature of the bone biopsy, the diagnosis of osteomyelitis is often based on clinical findings, laboratory tests, and imaging studies.[1,12,13]

KEY CONCEPT Typical signs and symptoms of osteomyelitis include local pain and tenderness over the affected bone, as well as inflammation, erythema, edema, and decreased range of motion.[1,3,4,6,9] Patients with acute hematogenous osteomyelitis may also present with systemic symptoms such as fever, chills, and/or malaise.[1,3,4,9] A cardinal sign of chronic osteomyelitis is the formation of a sinus tract (a channel from the infected site to the skin) with purulent drainage.[1]

Laboratory Tests

Though no single noninvasive laboratory test is currently available for the diagnosis of osteomyelitis, several nonspecific tests are commonly used to aid in the diagnosis and to monitor response to therapy.

Nonspecific inflammatory markers for infection include:[1,2,4-6]

- White blood cell (WBC) count
- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)
- Procalcitonin

WBC, ESR, and CRP are often elevated but may also be within normal limits. An elevated WBC is mostly seen in patients with acute osteomyelitis.[1,3,6,9] CRP rises faster than ESR during early stages of infection and also returns to normal levels more quickly than ESR. This makes CRP a more useful tool for both diagnosis and monitoring of therapeutic response.[4-6] Similar to CRP, procalcitonin may be useful for both diagnosis and monitoring of therapeutic response; however, it is often more expensive and may not be as readily available.[4]

Microbiologic Evaluation

Isolation of a causative pathogen from bone biopsy samples is essential for definitive antimicrobial therapy.[1-3,5,7,11,12] It is imperative cultures are obtained prior to initiation of antimicrobial therapy. If bone biopsy cannot be performed, quality specimens (eg, two consecutive samples with bone contact [deep samples] in patients with contiguous osteomyelitis[12,15] or blood cultures in patients with acute hematogenous osteomyelitis)[1,3,5] may assist in pathogen identification. Superficial swabs often represent colonization rather than infecting organism(s) and, thus, have little value in selecting therapy.[1,7,12,14]

Imaging Studies

Various imaging studies are used to assist in the diagnosis of osteomyelitis.[1,3,12,14,16,17]

- Magnetic resonance imaging (MRI) is considered the gold standard imaging modality for diagnosing of osteomyelitis.[1,3,4,11,13,14,16,17] Advantages include early detection (3–5 days after onset of symptoms), no radiation exposure, and high resolution.[1,6,16,17] Disadvantages include expense, inconvenience to patients (long examination time), movement artifacts, and the limitations to scanning patients with pacemakers and other implantable metal devices.[3,17]
- Computed tomography (CT) scans have high resolution and reproducibility.[17] CT scans have reduced sensitivity compared to MRI and should not be routinely used to diagnose osteomyelitis.[1,5,16] Advantages are that it is useful for the identification of sequestra and is less expensive than MRI.[3,16,17] Disadvantages include patient exposure to radiation and inability to use contrast medium to enhance images in patients with impaired renal function or previous allergic reactions.[3,4,17]
- Plain film radiographs (X-rays) are the initial imaging study of choice for skeletal infections.[1,5,6,12,16] Although changes in soft tissue may appear within 3 days of infection, bone lesions may not be visible for 10 to 21 days.[1,4,6,11,12,16] Advantages of radiographs are accessibility, cost, low radiation exposure, and they are easily repeatable.[5,16] A disadvantage is the inability to detect early bone infections.[1,3,4,6,11,16]
- Radionuclide imaging is also used for the early diagnosis of bone infections.[16] The most widely used nuclear medicine test is the three-phase bone scan.[16,17] An advantage is early detection within 24 to 48 hours after onset of symptoms.[5,6,16] Disadvantages include low specificity (increased risk of false positives) in patients with recent trauma, surgery, orthopedic prosthesis, diabetes, and ischemia, and high radiation dose required.[1,16] Using a labeled WBC scan in combination with the three-phase bone scan can increase sensitivity and specificity.[14,16]

TREATMENT

KEY CONCEPT The treatment goals for osteomyelitis are to eradicate the infection and prevent recurrence.[6-8,14,18]

General Approach to Treatment

KEY CONCEPT Antimicrobial therapy alone is the mainstay of treatment for acute osteomyelitis.[3-5,7] In comparison, treatment for chronic osteomyelitis typically requires a combination of antimicrobial therapy and surgical intervention.[7,11,14] If the patient is

Patient Encounter Part 1

A 55-year-old man presents to the emergency department complaining of pain and erythema in his left lower leg. On physical examination, the area is noticeably red and swollen (erythematous and inflamed). After reviewing his chart, you discover that he was recently discharged from the hospital approximately 3 weeks ago following a diagnosis of postsurgical osteomyelitis. During admission he underwent debridement and irrigation followed by IV daptomycin and wound VAC placement. He was discharged home with daptomycin to complete 8 weeks of therapy; however, he lost insurance coverage and only completed approximately 2 weeks of therapy in total.

What information is suggestive of osteomyelitis?

What risk factors, if any, does he have for osteomyelitis?

not a candidate for surgical intervention, prolonged antimicrobial therapy is generally necessary.[11-14]

▶ *Nonpharmacologic Therapy*

In addition to medical and surgical management, nonpharmacologic interventions for health promotion such as smoking cessation, weight-control, and good nutrition should be emphasized to the patient. Additionally, patients with diabetes should be counseled regarding the importance of frequent blood glucose monitoring and control, routine care and self-examination of lower extremities, and aggressive wound care.[14] Patients with chronic immobility should be counseled on skin care and techniques to prevent the development of pressure ulcers.[7]

▶ *Pharmacologic Therapy*

KEY CONCEPT Empiric antimicrobial therapy should target common pathogen(s) based on patient-specific risk factors and route of infection.[6] Empiric antimicrobial coverage against *S. aureus*, including MRSA, should be considered for all classifications of osteomyelitis.[1,2,6,7,19,20] In addition to MRSA coverage, patients with contiguous osteomyelitis with vascular insufficiency (eg, diabetic) should also receive empiric coverage for Enterobacterales, *P. aeruginosa*, and anaerobes.[11,14] Specific recommendations may vary based on factors such as patient allergies, potential for harboring resistant organisms, institution formulary, and cost considerations.[2,3,11]

Antimicrobial therapy should be guided by culture and susceptibility data of appropriately collected specimens when available (Table 77–1).[4,6,11,14] If MRSA is isolated, vancomycin is considered first-line therapy with an AUC/MIC target between 400 and 600 mg h/L.[22] However, if the minimum inhibitory concentration is greater than 2 mcg/mL (2 mg/L), alternative agents should be considered.[10,21,22] Alternative agents include daptomycin, linezolid, trimethoprim-sulfamethoxazole in combination with oral rifampin, or clindamycin.[21] Other MRSA active agents (tigecycline, telavancin, ceftaroline, dalbavancin, tedizolid, oritavancin) lack robust clinical data to support their routine use in osteomyelitis.[10,23] Clindamycin is commonly used in pediatric patients.[3,4,8,21] However, microbiology laboratories must screen with a disk diffusion test (D-test) for inducible resistance via the macrolide–lincosamide–streptogramin gene, as clindamycin failures have been associated with infections caused by isolates that are D-test positive.[3,24] For most institutions today, the D-test has been streamlined via automated susceptibility testing platforms. If methicillin-susceptible *S. aureus* (MSSA) is isolated and the patient has no β-lactam allergy, therapy should be changed to nafcillin/oxacillin or cefazolin.[1,2,5-7] Please refer to the Patient Assessment, Antimicrobial Selection and Stewardship chapter 72 for further discussion on general approach to antibiotic decision-making.

Patient Encounter Part 2

The medical team suspects incomplete resolution of osteomyelitis and ordered laboratory tests and imaging studies in addition to an orthopedic surgery service consult.

How would you classify the infection in this patient?

What laboratory test(s) should be ordered for this patient?

What imaging study(s) should be ordered for this patient?

In comparison to acute hematogenous osteomyelitis, chronic osteomyelitis is associated with higher failure rates, largely due to the presence of necrotic bone.[1,8,14,26] These patients typically require surgical intervention to remove the necrotic bone and tissue, and if applicable, to replace infected hardware.[7] Comorbidities such as vascular insufficiency can further contribute to poor treatment outcomes seen with chronic osteomyelitis.[1,7] Due to the high failure rates, treatment in this patient population may require prolonged courses of therapy, with the primary goal of preventing amputation of infected area(s).[1,11,14]

KEY CONCEPT Treatment is routinely initiated with IV antimicrobials in the inpatient or outpatient setting to optimize drug concentrations in bone.[7,14,16] Following initial IV therapy, a switch to oral antibiotics may be considered in patients with good clinical response, strict adherence, and reliable outpatient follow-up.[3,4,6,8,11,14,21] Moreover, findings from the Oral versus Intravenous Antibiotics for Bone and Joint Infection (OVIVA) study revealed patients may also be managed with oral therapy upfront after surgical intervention without adversely impacting outcomes.[25] Commonly used oral antimicrobials display high bioavailabilty including fluoroquinolones, doxycycline, clindamycin, linezolid, and trimethoprim-sulfamethoxazole.[1,6,7,19,21] Additionally, oral rifampin may be used in combination with another antibiotic in patients with osteomyelitis associated with prosthetic material or as part of step-down therapy for MRSA osteomyelitis in combination with trimethoprim-sulfamethoxazole.[1,7,11,21,26] For chronic osteomyelitis, some clinicians recommend placement of antibiotic impregnated beads or cement.[3,7,11,14] This enables antibiotics such as aminoglycosides and vancomycin to be delivered in high concentrations at the site of infection.[3,7]

KEY CONCEPT The duration of treatment is typically 4 to 8 weeks for acute and chronic osteomyelitis.[1-5,8,14,21] Shorter regimens may be considered for uncomplicated acute hematogenous infections due to *S. aureus* in children greater than 3 months of age.[4,6,8] Infectious Diseases Society of America (IDSA) MRSA guidelines recommend a minimum of 8 weeks for treatment of MRSA osteomyelitis in adults.[21] Suppressive therapy (> 3 months) may be necessary for certain populations such as patients with vascular insufficiency or patients with recalcitrant infections that do not respond to 4 to 8 weeks of therapy.[1,5,11,14,21]

Antimicrobial Stewardship Implications in the Management of Osteomyelitis

Stewardship programs have become increasingly common in an attempt to ensure appropriate antimicrobial use as well as to combat emerging resistance. Patients with osteomyelitis are typically subject to prolonged durations of therapy, and thus, much of the stewardship

Table 77–1

Pathogen-targeted Antimicrobial Therapy and Dosing Recommendations in Adults and Pediatrics

Microorganism	Antimicrobial Agent	Adult Dose	Pediatric Dose[a]
Staphylococcus aureus			
MRSA	Vancomycin[b]	15–20 mg/kg IV every 8–12 hours	15 mg/kg IV every 6 hours
	Daptomycin[b]	6–10 mg/kg IV every 24 hours	6–10 mg/kg IV every 24 hours
	Linezolid	600 mg IV/oral every 12 hours	10 mg/kg IV/oral every 8 hours(< 12 years old)
	Clindamycin[c]	600 mg IV every 8 hours 450 mg orally every 8 hours	10–13 mg/kg/dose IV/oral every 6–8 hours
	Trimethoprim-sulfamethoxazole[b] (+ rifampin[c] 600 mg oral daily)	3.5–4.0 mg/kg of trimethoprim component IV/oral every 8–12 hours (trimethoprim-sulfamethoxazole single strength tablet is 80 mg/400 mg; double strength tablet is 160 mg/800 mg)	–
	Doxycycline	100 mg IV/oral every 12 hours	–
MSSA	Nafcillin[d]/oxacillin[b]	1–2 g IV every 4–6 hours	100–200 mg/kg/day IV in divided doses every 4–6 hours
	Cefazolin[b]	1–2 g IV every 6–8 hours	50–100 mg/kg/day IV in divided doses every 6–8 hours
***Enterococcus* spp.**			
Ampicillin-susceptible	Ampicillin[b]	2 g IV every 4–6 hours	100–400 mg/kg/day IV in divided doses every 6 hours
Ampicillin-resistant	Vancomycin[b]	15–20 mg/kg IV every 8–12 hours	15 mg/kg IV every 6 hours
Vancomycin-resistant	Daptomycin[b]	6 mg/kg IV every 24 hours	–
	Linezolid	600 mg IV/oral every 12 hours	10 mg/kg IV/oral every 8 hours (< 12 years old)
***Streptococcus* spp.**	Penicillin G[b]	2–4 million units IV every 4–6 hours	250,000–400,000 units/kg/day IV in divided doses every 4–6 hours
	Ceftriaxone[d]	1–2 g IV every 24 hours	50–100 mg/kg/day IV in divided dose every 12–24 hours
Pseudomonas aeruginosa			
	Doripenem[b]	500 mg IV every 8 hours	–
	Imipenem/cilastatin[b]	500 mg IV every 6 hours	25 mg/kg IV every 6 hours
	Meropenem[b]	1 g IV every 8 hours	10–20 mg/kg IV every 8 hours
	Ceftazidime[b]	2 g IV every 8 hours	50 mg/kg IV every 8 hours
	Cefepime[b]	2 g IV every 12 hours	50 mg/kg IV every 8–12 hours
	Piperacillin/tazobactam[b]	4.5 g IV every 6 hours	100 mg/kg IV piperacillin component every 8 hours
	Ciprofloxacin[b,e]	400 mg IV every 8–12 hours; 750 mg oral every 12 hours	–
	Levofloxacin[b,e]	750 mg IV/oral every 24 hours	–
Enterobacterales (in addition to antipseudomonal agents listed above)	Ceftriaxone[d]	1–2 g IV every 24 hours	50–100 mg/kg/day IV in divided doses every 12–24 hours
	Cefotaxime[b,d]	1–2 g IV every 8 hours	50–200 mg/kg/day IV in divided doses every 6–8 hours
	Ertapenem[b]	1 g IV every 24 hours	–
	Moxifloxacin[c,e]	400 mg IV/oral every 24 hours	–
Anaerobes[f]	Clindamycin[c]	600–900 mg IV every 8 hours; 300–450 mg oral every 6–8 hours	25–40 mg/kg/day IV in divided doses every 6–8 hours
	Metronidazole[b,c]	500 mg IV/oral every 6–8 hours	30 mg/kg/day IV/oral in divided doses every 6–8 hours

[a] Refer to specialized pediatric reference for maximum neonatal and pediatric dosing recommendations.

[b] Dosage adjustment necessary in renal dysfunction.

[c] Dosage adjustment necessary in severe hepatic dysfunction.

[d] Dosage adjustment necessary in patients with concomitant renal and hepatic dysfunction.

[e] Fluoroquinolones: Not approved by the US FDA for use in children except for anthrax (ciprofloxacin, levofloxacin) and complicated UTI and pyelonephritis (ciprofloxacin).

[f] May consider β-lactam/β-lactamase inhibitor or carbapenem for broad-spectrum activity including anaerobes.

Data from Refs. [1,3,4,7,8,10,11,19,21-28].

focus should be on appropriate deescalation of empiric therapy and duration without sacrificing successful outcomes. Moreover, patients undergoing surgical amputation of the infected bone could receive abbreviated treatment courses of postsurgical antibiotics assuming clean margins are visualized by the surgical team.[14] As mentioned above, compliant patients with an identified organism may be switched to oral therapy, and those who require IV therapy should receive an agent with the narrowest spectrum. Stewardship opportunities may arise throughout the treatment course, and thus, opportunities to optimize patient care should be continually evaluated.

OUTCOME EVALUATION

Therapeutic success is measured by the extent to which the care plan (a) resolves signs and symptoms, (b) eradicates the microorganism(s), (c) prevents relapses, and (d) prevents complications such as amputation.[8,11,14] Patients should be evaluated for resolution of clinical signs and symptoms and normalization of laboratory tests (WBC, CRP, ESR, procalcitonin, and cultures).[3-6,8,10,14] Improvement in clinical manifestations may be seen within 2 to 4 days of initiation of IV antimicrobial therapy in patients with acute osteomyelitis.[4,8] A reduction in CRP should be seen within 1 week of therapy and should be monitored weekly throughout therapy for a continued downward trend.[3,4,6] ESR can also be monitored weekly, although normalization will be slower than for CRP.[3,6] Patients should also be closely observed with regard to therapeutic drug monitoring, antimicrobial tolerability, and toxicity[2] (Table 77–2). If poor response is noted, the

Patient Encounter Part 3: The Medical History, Physical Examination, and Diagnostic Tests

PMH: Morbid obesity, uncontrolled type 2 diabetes mellitus, obstructive sleep apnea, dyslipidemia, hypertension, history of DVT/PE, depression

SH: Tobacco smoker (one pack per day for 20 years), two to three cans of beer daily. Unemployed.

Allergies: Cefepime (leukopenia)

Meds: Warfarin 5 mg orally once daily; atorvastatin 40 mg orally at bedtime (held while receiving daptomycin); glargine 20 units subcutaneously at bedtime; metformin 1000 mg orally twice daily; hydrochlorthiazide 12.5 mg orally daily, metoprolol tartrate 100 mg orally twice daily; citalopram 20 mg orally daily

PE:

Gen: Moderate distress with exaggerated pain and tenderness in lower left leg

Skin: Erythema and inflammation

VS: BP 150/90 mm Hg, P 105 beats/min, RR 20 breaths/min, T 38.4°C (101.2°F), Ht 6′0″ (185.42 cm), Wt 142 kg (312.4 lb)

Labs: WBC 16.4×10^3/mm^3 (16.4×10^9/L), hemoglobin 13.0 g/dL (130 g/L; 8.07 mmol/L), hematocrit 37.0% (0.37), platelets 220×10^3/μL (220×10^9/L), BUN 23 mg/dL (8.2 mmol/L), serum creatinine (Scr) 1.3 mg/dL (115 μmol/L), total bilirubin 1.1 mg/dL (18.8 μmol/L), alkaline phosphatase 82 U/L (1.37 μkat/L), AST 28 U/L (0.47 μkat/L), ALT 13 U/L (0.22 μkat/L), albumin 3.7 g/dL (37 g/L), fasting blood glucose 210 mg/dL (11.6 mmol/L), ESR 110 mm/h, CRP 24 mg/dL (240 mg/L)

Microbiology: Previous intraoperative culture reveal methicillin-resistant *Staphylococcus aureus*, susceptible to daptomycin, vancomycin (MIC = 2 mcg/mL), linezolid, and trimethoprim/sulfamethoxazole.

Based on the information presented, create a care plan for this patient's osteomyelitis. Your plan should include (a) goals of therapy, (b) patient-specific detailed therapeutic plan, (c) nonpharmacologic interventions, and (d) follow-up plan to determine whether outcomes have been achieved.

Table 77–2

Monitoring Considerations for Select Antistaphylococcal Agents

Antimicrobial	Monitoring Considerations
Cefazolin	Monitor BMP and CBC once weekly.
Daptomycin	Muscle pain or weakness particularly of the distal extremities; monitor CPK weekly with more frequent monitoring in patients with renal insufficiency or receiving (or recent discontinuation) of HMG-CoA reductase inhibitors; consider temporarily discontinuing HMG-CoA reductase inhibitors while patient receiving daptomycin. Peripheral neuropathy: Monitor for neuropathy. Decreased efficacy was observed in patients with moderate baseline renal impairment.
Linezolid	Myelosuppression: Monitor CBC once weekly. MAO inhibitors; evaluate for potential drug–drug interactions. Linezolid should not be used concomitantly or within 2 weeks of medications that inhibit monoamine oxidases A or B. Serotonin syndrome; evaluate for potential drug–drug and drug–food interactions. Patients taking serotonergic antidepressants should receive linezolid only if no other therapies are available. Discontinue serotonergic antidepressants and monitor patients for signs and symptoms of both serotonin syndrome and antidepressant discontinuation. Peripheral and/or optic neuropathy has been reported with long-term therapy; perform routine neurologic and ophthalmic evaluations in these patients. Elevation of blood pressure in certain patients (eg, uncontrolled hypertension): monitor blood pressure. Hypoglycemia in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents: monitor glucose.
Nafcillin/oxacillin	Monitor BMP, CBC, LFTs once weekly.
Vancomycin	An AUC/MIC target between 400 and 600 mg h/L is recommended for serious infections such as osteomyelitis. Renal dysfunction: monitor weekly renal function (BUN/SCr) and troughs in stable patients; more often in nonstable patients. Potential for additive renal toxicity if being coadministered with a nephrotoxic agent (eg, aminoglycoside, piperacillin-tazobactam).

BMP, basic metabolic panel; BUN, blood urea nitrogen; CBC, complete blood count; CPK, creatine phosphokinase; LFT, liver function tests; MAO, monoamine oxidase; SCr, serum creatinine.

Data from Refs. [1,7,11,19,21-27,29].

following should be evaluated: (a) patient adherence, (b) significant drug–drug or drug–food interactions, (c) appropriate dosage to achieve therapeutic concentrations, (d) development of antimicrobial resistance necessitating a change in the treatment regimen, (e) need for additional imaging studies, and (f) diagnostic reevaluation.[8,14] Treatment is considered successful if all clinical signs and symptoms are resolved and all laboratory tests have returned to normal following 4 to 8 weeks of appropriate treatment. Due to high rates of relapse, patients should have medical follow-up for at least 1 year following resolution of symptoms.[4] Patients should be evaluated at predefined follow-up intervals (3–6 to 12 months) for any clinical manifestations of recurring infection and continued normalization of laboratory tests.[8,11] Follow-up imaging studies at 1 to 2 years may be useful in some patients to confirm therapeutic success.

Patient Encounter Part 4

The patient received 2 weeks of IV daptomycin therapy following debridement but has not improved due to the interrupted treatment course. After being readmitted, he resumed IV daptomycin. Due to barriers with drug costs for this patient, the multidisciplinary medical team elects to complete therapy with oral antibiotic(s) at discharge.

What oral antimicrobial therapy would you recommend for this patient?

Evaluate the patient's medication profile for drug–drug interactions.

Counsel the patient regarding this drug therapy.

Patient Care Process

Collect Information:

- Review the medical history for osteomyelitis risk factors.
- Based on physical examination and review of systems, determine whether the patient is experiencing signs or symptoms of osteomyelitis.
- Review available imaging studies and laboratory tests, especially WBC, ESR, and CRP.
- Obtain a thorough history of prescription, nonprescription, and natural drug product use.

Assess the Information:

- Review culture data for antimicrobial drug selection and stewardship.
- Evaluate drug allergies or intolerance, as well as drug–drug interactions that would impact antimicrobial selection.
- Assess available imaging studies and laboratory data to differentiate acute versus chronic disease.

Develop a Care Plan:

- Select an appropriate antimicrobial regimen, including drug, dose, and duration, given patient-specific information.
- Identify criteria for possible deescalation to oral therapy during treatment course.
- Establish monitoring parameters based on the antimicrobial regimen selected.

Implement the Care Plan:

- Provide patient education with regard to disease state and drug therapy. Stress the importance of adherence to the therapeutic regimen.

Follow-up: Monitor and Evaluate:

- Determine whether the antibiotic dosage regimen is optimal based on patient-specific factors and site of infection.
- Patients should be monitored for clinical and laboratory response, development of adverse drug reactions, potential drug–drug interactions, and therapeutic drug monitoring. Patients should also be closely monitored for adherence in the outpatient setting.

Abbreviations Introduced in This Chapter

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CBC	Complete blood count
CRP	C-reactive protein
CPK	Creatine phosphokinase
CT	Computed tomography
ESR	Erythrocyte sedimentation rate
IDSA	Infectious Diseases Society of America
IV	Intravenous
MAO	Monoamine oxidase
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
Scr	Serum creatinine
WBC	White blood cell

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78 Infective Endocarditis

Ronda L. Akins

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Differentiate the causes and development of infective endocarditis (IE).
2. Classify patient risk factors for potential causative organisms for IE.
3. Identify the clinical presentation and laboratory evaluation for IE.
4. Assess diagnostic criteria used to evaluate a patient suspected of having IE.
5. Discuss the most likely causative pathogens of IE, particularly in specific patient populations.
6. Develop appropriate pharmacologic treatment recommendations for patients with IE.
7. Describe oral step-down therapy options appropriate for specific types of IE and organisms.
8. Define appropriate patient populations requiring prophylactic treatment and differentiate appropriate drug regimens.
9. Devise a monitoring plan for patients with IE to determine treatment efficacy and discern any adverse effects.

INTRODUCTION

Infective endocarditis (IE) is a serious infection affecting the lining and valves of the heart. Although this disease is mostly associated with infection of the heart valves, whether native or prosthetic valves, septal defects or intravascular devices may also become involved in some cases. Bacteria are the primary cause of IE; however, fungi and atypical organisms may also be responsible pathogens.

Typically, IE is classified into two categories: acute or subacute. Differences between the two categories are based on the progression and severity of the disease. Acute disease is more aggressive, characterized by high fevers, leukocytosis, and systemic toxicity, with death occurring within a few days to weeks. This type of IE is often caused by more virulent organisms, particularly *Staphylococcus aureus*. Subacute disease is often caused by less virulent organisms, such as viridans group streptococci, producing a slower and more subtle presentation. It is characterized by nonspecific symptoms including fatigue, low-grade fever, and weight loss, with death occurring in several months.

Successful management of patients with IE is based on proper diagnosis, treatment with appropriate therapy based on organism identification and susceptibilities, and monitoring for complications, adverse events, or development of resistance. IE has varied clinical presentations; therefore, patients with this infection may be found in any medical subspecialty (ie, medicine, surgery, and critical care).

EPIDEMIOLOGY

In the United States, there are roughly 40,000 new cases annually, accounting for an incidence of approximately 3 to 15 cases per 100,000 persons-years.[1-4] Although the exact number of cases is often difficult to determine, owing to the diagnostic criteria and reporting methods for this disease, its incidence remains unchanged overall but is increasing in older patients, those with prosthetic valves, and infections due to *S. aureus*. IE is now considered the fourth leading cause of serious infectious diseases syndromes following sepsis, pneumonia, and intra-abdominal abscess.[5] Although IE occurs at any age, more than 50% of cases occur in patients older than 50 years.[1,3,4] IE in children continues to be uncommon and is mainly associated with underlying structural defects, surgical repair of the defects, or nosocomial catheter-related bacteremia.[1] With the increased use of mechanical valves, prosthetic-valve endocarditis (PVE) now accounts for approximately 16% to 35%.[6,7] Injection drug users are typically younger patients and also at an increased risk for IE, with 18 to 29 cases per 10,000 persons per year accounting for 5% to 15% of infection-related hospital admissions.[1,8,9] Additionally, others at high risk for IE include patients with any congenital or structural cardiac defects, including valvular disease, long-term hemodialysis, diabetes mellitus, poor oral hygiene, major dental treatment, previous endocarditis, hypertrophic cardiomyopathy, and mitral valve prolapse with regurgitation.[5,10]

Although almost any type of microorganism is capable of causing IE, the majority of cases are caused by Gram-positive bacteria. These consist primarily of streptococci, staphylococci, and enterococci. Consideration of Gram-negative, fungal, and other atypical organisms must be taken into account in select patient populations. In Table 78–1, approximate percentages are given for each organism based on the type of IE, including native valve (community-acquired vs healthcare-associated), prosthetic valve (grouped by months post surgery), and injection drug users. Additionally, other patient characteristics should be reviewed to assess risks of possible causative organisms and aid in empiric therapy choices (**see** Table 78–2).

Table 78–1

Etiologic Organisms of Infective Endocarditis

	Percentage of Cases							
	Native-Valve IE		PVE at Indicated Onset (Months) after Valve Surgery			IE in Injection Drug Users		
	Community-Acquired	HealthCare-Associated	< 2	2–12	> 12	Right-Sided	Left-Sided	Total
Streptococci[a]	40	13	1	9	31	5	15	12
Pneumococci	2	—	—	—	—	—	—	—
Enterococci[b]	9	16	8	12	11	2	24	9
Staphylococcus aureus	28	52[c]	22	12	18	77	23	57
CoNS	5	11	33	32	11	—	—	—
HACEK group	3	—	—	—	6	—	—	—
Gram-negative bacilli	1	1	13	3	6	5	13	7
Fungi (*Candida* spp.)	< 1	1	8	12	1	—	12	4
Polymicrobial/ miscellaneous	3	3	3	6	5	8	10	7
Diphtheroids	—	< 1	6	—	3	—	—	0.1
Culture-negative	9	3	5	6	8	3	3	3

[a] Includes viridans group streptococci; *S. gallolyticus* (formerly *S. bovis*); other nongroup A, groupable streptococci; and *Abiotrophia* and *Granulicatella* spp. (nutritionally variant streptococci).

[b] Primarily *E. faecalis* or nonspeciated isolates, occasionally *E. faecium*.

[c] Methicillin resistance is common among these *S. aureus* strains.

CoNS, coagulase-negative staphylococci; HACEK, *Haemophilus* spp. (primarily *H. paraphrophilus, H. parainfluenzae*, and *H. aphrophilus*), *Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens*, and *Kingella kingae*.

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PATHOPHYSIOLOGY

KEY CONCEPT For IE to develop, the occurrence of several factors is required. Typically, there must be an alteration of the endothelial surfaces of the heart valves to allow for organism attachment and colonization. These alterations may be produced by an inflammatory process such as rheumatic heart disease or by injury from turbulent blood flow. Platelets and fibrin are then capable of depositing on the damaged valves, forming a nonbacterial thrombotic endocarditis (NBTE). At this point, bacteria, through

Patient Encounter Part 1

A 42-year-old man with a history of uncontrolled type II diabetes, injection drug use, recurrent cellulitis, osteomyelitis of the right foot, hypertension, and chronic kidney disease (CKD) stage 3 was brought to the emergency department (ED) after becoming very confused, dizzy, and complaining of numbness/weakness to the left arm. Upon arrival to the ED, the patient reported having recent "really bad" headaches, fever, shortness of breath, and abdominal pain. The patient denies any recent use of alcohol or tobacco but admits to illicit drug injection in the past couple of weeks. The ED physician started vancomycin (pharmacy to dose) and ceftriaxone 2 g IV every 12 hours.

Does the patient have any specific presenting signs or symptoms that would make you suspect IE?

What, if any, risk factors does the patient have for developing IE?

Based on presentation, which causative organism(s) should be considered to empirically treat?

Is there any other information you would like to know before deciding on an empirical treatment for this patient?

Table 78–2

Patient Characteristics for IE due to Select Organisms

Organism	Risk Factors for Specific IE Organisms
Staphylococcus aureus	Soft tissue infections (recurrent/chronic), injection drug use, prosthetic valves (early, late), indwelling devices, diabetes, burns, immunocompromised
Coagulase-negative staphylococci	Indwelling devices, injection drug use, prosthetic valves (early, late)
Viridans group streptococci	Dental health issues/procedures, prosthetic valves (late); GI/GU (*S. gallolyticus*)
Enterococci	GI/GU, prosthetic valves (late), immunocompromised
HACEK	Dental health issues/procedures
Gram-negatives	Injection drug use, prosthetic valves (early), burns, indwelling devices, GI/GU
Fungal	Indwelling devices, injection drug use, TPN (particularly long-term use), burns, prosthetic valves (early, late), immunocompromised (particularly transplant)

Data from Cresti A, Chiavarelli M, Scalese M, Nencioni C, Valentini S, Guerrini F, D'Aiello I, Picchi A, De Sensi F, Habib G. Epidemiological and mortality trends in infective endocarditis, a 17-year population-based prospective study. Cardiovasc Diagn Ther. 2017 Feb;7(1):27–35. doi: 10.21037/cdt.2016.08.09. PMID: 28164010; PMCID: PMC5253443.

hematogenous spread (ie, bacteremia), adhere to and colonize the nidus, forming a vegetation. Further deposits of platelets and fibrin cover the bacteria, providing a protective coating that allows for development of a suitable environment for continued organism and vegetation progression, often producing an organism density of 10^9 to 10^{10} colony-forming units (CFU) per gram.

Acquisition of PVE differs in early stages, where direct inoculation may occur during surgery rather than through hematogenous seeding. In addition, causative organisms in early PVE are typically nosocomial, with increased likelihood of being drug-resistant.[6] The prosthetic valve also has a greater propensity for organism colonization than native valves. However, in late PVE, the process of colonization and vegetation formation is similar to that of native-valve IE (NVE), as described earlier.[6,11] Differentiation of NVE versus PVE is important in determining empiric therapy as well as impacting the risk of disease complications (discussed later).

Typically, vegetations are located on the line along valve closure on the atrial surface of the atrioventricular valves (tricuspid and mitral) or on the ventricular surface of the semilunar valves (pulmonary and aortic) (see Figure 78–1A and C). The vegetations can vary significantly in size, ranging from millimeters to several centimeters and may be single or multiple masses. Often, destruction of underlying tissue occurs and may cause perforation of the valve leaflet or rupture of the chordae tendineae, interventricular septum, or papillary muscle. Valve ring abscesses may occur, resulting in fistulas penetrating into the myocardium or pericardial sac, particularly with staphylococcal endocarditis (see Figure 78–1B).

Embolic events are also common. Embolization occurs as portions of the friable vegetation break loose and enter the bloodstream. These infected pieces are called septic emboli. Pulmonary abscesses are commonly formed as a result of septic emboli from right-sided IE (tricuspid and pulmonary valves). However, left-sided IE (mitral and aortic valves) is more likely to have an embolus travel to any organ, especially kidneys, spleen, and brain. Along with emboli, immune complex deposition may occur in organ systems, causing extracardiac manifestations of the disease. This commonly occurs in the kidneys, producing abscesses, infarction, or glomerulonephritis. Immune complexes or emboli may also produce skin manifestations of the disease, as seen with petechiae, Osler nodes, and Janeway lesions, or within the eye (ie, Roth spots).

CLINICAL PRESENTATION AND DIAGNOSIS

To aid in the diagnosis, it is crucial to obtain a thorough account of the patient's medical history, present illness and signs/symptoms, given the clinical presentation for IE is quite variable and often nonspecific. **KEY CONCEPT** A fever is the most frequent and persistent symptom in patients but may be blunted with previous antibiotic use, congestive heart failure, chronic liver or renal

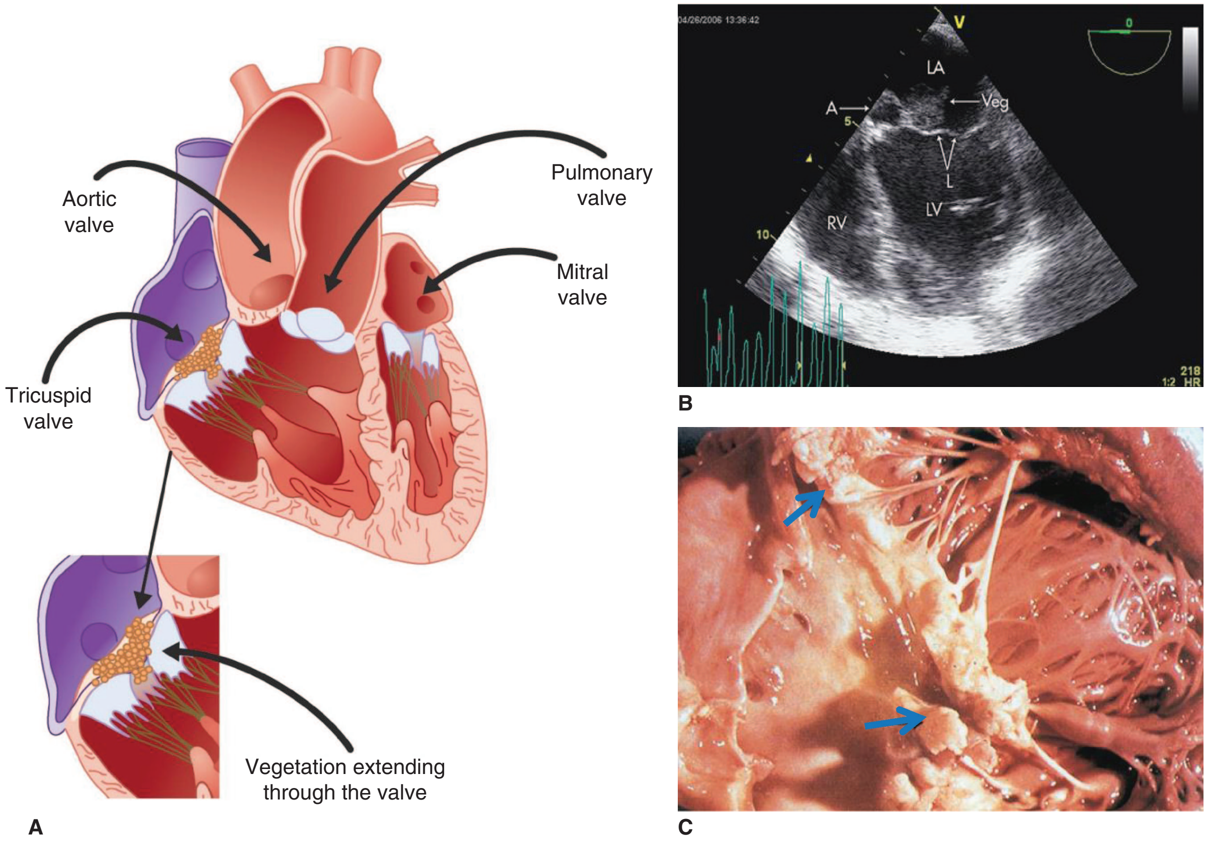

FIGURE 78–1. **A:** Diagram of heart and valves showing bacterial deposits and vegetation extending through the tricuspid valve. **B:** TEE of mitral heart valve infected with *Staphylococcus aureus* showing a large vegetation (Veg) with an adjacent echolucent abscess cavity (A), right ventricle (RV), left ventricle (LV), valve leaflets (L), and left atrium (LA). (with permission of Andrew Burger, MD.) (From Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. In: Harrison's Principles of Internal Medicine, 20th ed. New York, NY: McGraw Hill; Copyright 2018.) **C:** Vegetations (arrows) due to viridans group streptococcal IE on the mitral valve. (From Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. In: Harrison's Principles of Internal Medicine, 20th ed. New York, NY: McGraw Hill; Copyright 2018.)

Table 78–3

Clinical Presentation and Diagnosis of IE

General

Typically nonspecific and variable sign or symptoms of infection

Symptoms

Complaints from patients may include

- Fever (≥ 100.4°F)
- Chills
- Night sweats
- Weakness
- Dyspnea
- Weight loss
- Myalgia or arthralgias

Signs

- Fever (most common sign of IE)
- New or changing/worsening heart murmur (occurs in 48% or 20%, respectively)
- Embolic phenomena (emboli affect the heart, lungs, abdomen, or extremities)
- Skin manifestations (ie, petechiae, splinter hemorrhages, Osler nodes, Janeway lesions)
- Splenomegaly
- Mycotic aneurysms
- Clubbing of extremities

Laboratory Tests

- Blood cultures (most important laboratory test)
- Hematologic tests for anemia (normochromic, normocytic)
- WBC count may be elevated in acute disease but could be normal in subacute IE
- Nonspecific findings such as thrombocytopenia, elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), and abnormal urinalysis (ie, proteinuria or microscopic hematuria)

Imaging Studies

- Transthoracic echocardiogram (TTE) and/or transesophageal echocardiogram (TEE); key imaging to identify presence of vegetations
- Computer tomography (CT) or magnetic resonance imaging (MRI); may be used to assess involvement of other organ systems (ie, lungs, kidneys, and brain)

failure, or infection caused by a less virulent organism (ie, subacute disease).[1,4] Other common signs and symptoms are listed in Table 78–3 with some discussed further in detail below.

Peripheral manifestations are classical signs that historically could be found in up to one-half of adult patients with IE. However, recently the prevalence of these findings has been decreasing, only occurring in a minority of adult patients and is rarely seen in children.[1,5]

- **Skin:** *Petechiae* are very small (usually < 3 mm), pinpoint, flat, red spots beneath the skin surface caused by microhemorrhaging. They occur in 20% to 40% of patients with chronic IE and are often found on the buccal mucosa, conjunctivae (Figure 78–2A), and extremities.[1,7] *Splinter hemorrhages* appear as small dark streaks beneath the fingernails or toenails and occur most commonly proximally with IE, typically as a result of local vasculitis or microemboli in about 5% to 15% of patients (Figure 78–2B).[7] *Osler nodes* are small (usually 2–15 mm), painful, tender, subcutaneous nodules located on the pads of the fingers and toes (Figure 78–2C) caused primarily by either septic emboli or vasculitis. These nodes are rare in acute disease (~3%–10%) but are also nonspecific for IE despite occurring in 10% to 25% in subacute patients.[1,7] *Janeway lesions* are small, painless, hemorrhagic macular plaques on the palms of the hands or soles of the feet due to septic emboli (in ~5%–10% of patients) and more commonly associated with acute *S. aureus* IE (Figure 78–2D).[1,7]
- **Extremities:** *Clubbing* of the finger tips typically occurs in long-standing subacute illness and is present in approximately 10% to 20% of patients (Figure 78–2E).[1]
- **Eye:** *Roth spots* occur rarely (< 5% of IE cases) and are oval-shaped retinal hemorrhages with a pale center near the optic disc (Figure 78–2F).[1]

Diagnostic Criteria

A definitive pathological diagnosis of IE consists of invasive testing such as a biopsy or culture directly from specimens of the endocardium. Instead, the clinical diagnosis of IE relies on patient's presentation as well as laboratory and echocardiographic results. To guide the clinical diagnosis of IE, major and minor criteria, known as the Duke criteria, have been established (Table 78–4A).[12] The number of major or minor criteria demonstrated by a specific patient leads to a classification of definite, possible, or rejected diagnosis of IE (Table 78–4B).

Laboratory and Imaging Studies

KEY CONCEPT Blood cultures are the essential laboratory test for the diagnosis and treatment of IE. Blood culture results are critical for determining the causative organism, thus aids in selection of the most appropriate therapy. Typically, patients with IE have a low-grade consistent bacteremia.[1] This low concentration of bacteria can impact detection in blood cultures. Therefore, three blood culture sets from different venipuncture sites should be drawn within 24 hours of initial evaluation to increase the likelihood of isolating any organism present. Approximately 90% of the first two cultures may yield a positive result.

KEY CONCEPT Another important tool aiding in the diagnosis of IE is the echocardiogram. This imaging tool is used to visualize the heart valves to assess the presence of vegetations. Two methods of the echocardiogram are used: the **transthoracic echocardiogram** (TTE) and the **transesophageal echocardiogram** (TEE). The TTE has been used since the 1970s; however, it is less sensitive (historically 40%–60%, newer imaging for native valves 82%–89%) than the TEE (90%–100%).[7] Despite the TEE being more sensitive, use of the TTE for patients with suspected NVE is usually sufficient for diagnosis.[13] However, some patient conditions may impact the resolution window from the body surface to the heart structures, lowering the sensitivity of a TTE, such as morbid obesity, previous thoracic surgery or chronic obstructive pulmonary disease. The TEE may be used as a secondary test for patients whose TTE was negative in the setting of high clinical suspicion of IE and is often preferred in patients with complicated disease, including left-sided IE, prosthetic valves, or perivalvular extension of the vegetation (**see** Figure 78–1B).[14,15]

In addition to echocardiograms, other imaging (computed tomography [CT] and magnet resonance imaging [MRI]), as well as newer modalities such as three-dimentional TEE, cardiac computed tomography angiography (CTA), multislice CT (MSCT), ^{18}F-fluorodeoxyglucose positron emission tomography (PET) CT (^{18}F-FDG-PET/CT), may also be employed for providing a more detailed assessment of the vegetation and surrounding structure, detecting complications secondary to septic emboli, and determining need for surgical intervention.[16,17]

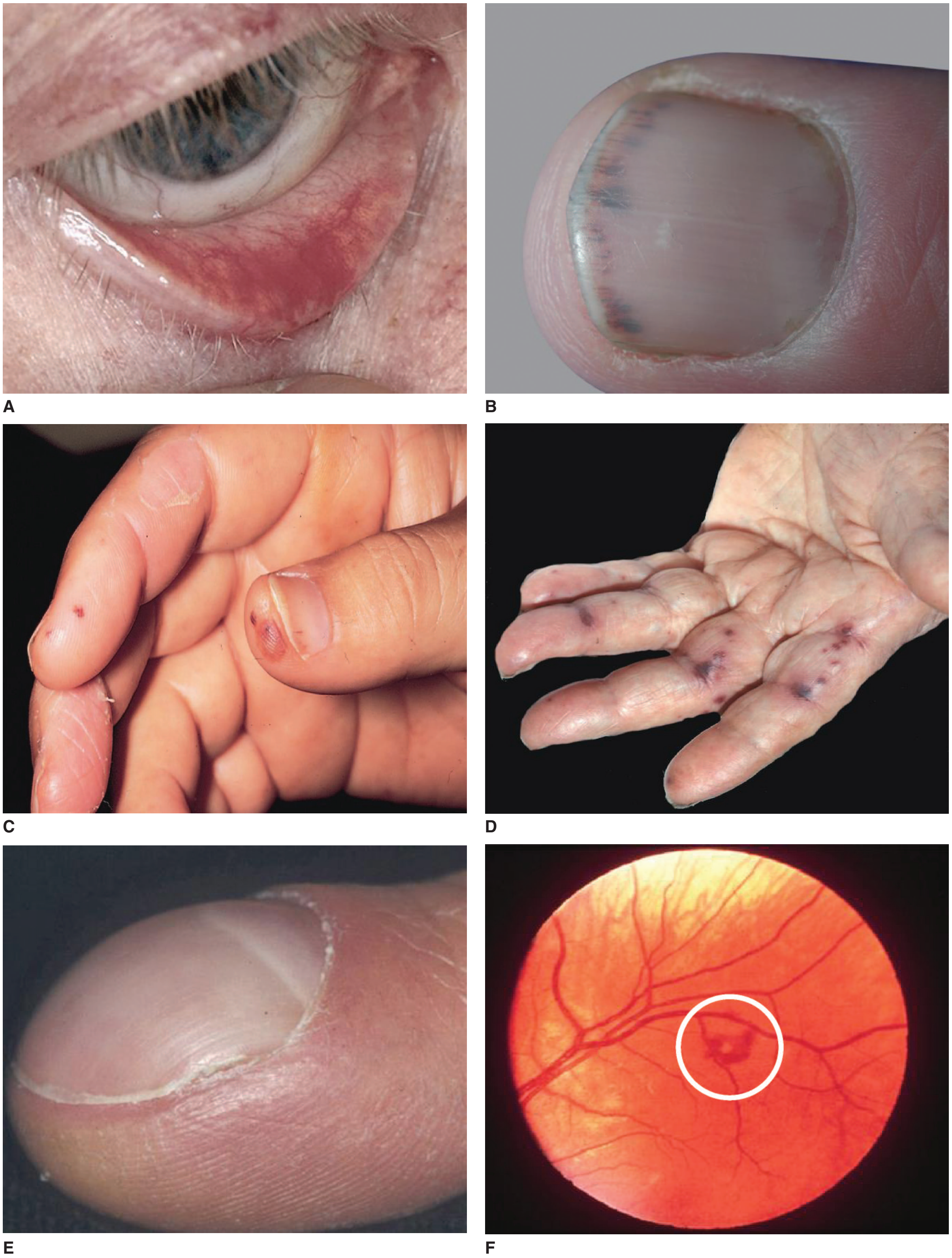

FIGURE 78–2. A: Conjunctival petechiae. (From Wolff K, Johnson R, Saavedra AP, Roh EK. In: Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 8th ed. New York, NY: McGraw Hill; Copyright 2017.) **B:** Splinter hemorrhage. (From Knoop KJ, Stack LB, Storrow AB, Thurman AB. In: Atlas of Emergency Medicine. 4th ed. New York, NY: McGraw Hill; Copyright 2016.) **C:** Osler nodes. (From Knoop KJ, Stack LB, Storrow AB, Thurman AB. In: Atlas of Emergency Medicine, 4th ed. New York, NY: McGraw Hill; Copyright 2016.) **D:** Janeway lesions. (From Wolff K, Johnson R, Saavedra AP, Roh EK. In: Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 8th ed. New York, NY: McGraw Hill; Copyright 2017.) **E:** Clubbing of finger. (From Tosti A, Piraccini BM. In: Fitzpatrick's Dermatology in General Medicine, 7th ed. New York, NY: McGraw Hill; Copyright 2007.) **F:** Roth spots (From Effron D, Forcier BC, Wyszynski RE. In: Atlas of Emergency Medicine, 4th ed. New York, NY: McGraw Hill; Copyright 2016.)

Table 78–4

Modified Duke Criteria for Diagnosis of IE

4A. Definitions of Modified Duke Criteria

Major Criteria

- *Blood culture positive for IE:*
  - Typical microorganisms consistent with IE from two separate blood cultures:
    - Viridans streptococci, *S. bovis*, HACEK group, *S. aureus,* or community-acquired enterococci in the absence of a primary focus, or
  - Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
    - At least two positive cultures of blood samples drawn > 12 hours apart, or
    - All of three or a majority of four separate cultures of blood (with first and last sample drawn at least 1 hour apart)
  - Single positive blood culture for *C. burnetii* or antiphase I IgG antibody titer > 1:800
- *Evidence of endocardial involvement:*
  - Echocardiogram positive for IE (TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:
    - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or
    - Abscess, or
    - New partial dehiscence of prosthetic valve
    - New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor Criteria

- Predisposition: predisposing heart condition or injection drug use
- Fever: temperature > 38°C (100.4°F)
- Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
- Microbiologic evidence: positive blood culture but does not meet a major criterion as noted above[a] or serologic evidence of active infection with organism consistent with IE

4B. Modified Duke Criteria to Diagnose IE

Definite IE

- *Pathologic criteria:*
  - (1) Microorganisms demonstrated by culture or histologic examination of a vegetation that has embolized, or an intracardiac abscess specimen, or
  - (2) Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis
- *Clinical criteria*[b]:
  - (1) Two major criteria, or
  - (2) One major criterion and three minor criteria, or
  - (3) Five minor criteria

Possible IE

- (1) One major criterion and one minor criterion, or
- (2) Three minor criteria

Rejected

- (1) Firm alternate diagnosis explaining evidence of IE, or
- (2) Resolution of IE syndrome with antibiotic therapy for less than or equal to 4 days, or
- (3) No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for ≤ 4 days, or
- (4) Does not meet criteria for possible IE, as above

[a] Excludes single positive cultures for CNS and organisms that do not cause endocarditis.

[b] See above for definitions of major and minor criteria.

TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Data from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000; 30:633–638; by permission of Oxford University Press, 2000 by the Infectious Diseases Society of America.

ETIOLOGY

Gram-positive bacteria are the most common causative organisms in IE. Streptococci and staphylococci species account for the majority of cases at more than 80% to 90%.[1,18,19] Staphylococci are now considered the dominant causative organisms, with *S. aureus* being the most common (see Table 78–1).[1,5,17,19] Other Gram-positive, Gram-negative, atypical, and fungal organisms are less common, but still must be considered in certain patient populations (see Table 78–2).

▸ *Streptococci*

Streptococci causing IE are typically a group of species called viridans group streptococci. The most common of species in this group: *Streptococcus salivarius*, *Streptococcus mutans*, *Streptococcus mitis/oralis*, *Streptococcus anginosus*, and *Streptococcus sanguinis*. This group of bacteria is α-hemolytic and considered normal flora in the human mouth; thus, a common cause of oral infections but can result in bacteremia and subsequent development of IE after dental procedures. IE caused by these streptococci typically has a subacute clinical course. The current cure rate is often greater than 90% unless complications arise, which do occur in more than 30% of patients.[1,20]

Based on similarities of these organisms, most clinical microbiology laboratories do not differentiate all isolates to exact species. Viridans group streptococci are also a predominant pathogen of IE associated with mitral valve prolapse, NVE, and in children (particularly in those with congenital heart disease).[1,20,21] Another streptococcal species commonly associated with IE is *Streptococcus gallolyticus* (formerly *bovis*), classified as group D streptococci, which is frequently found in the gastrointestinal (GI) tract. Other streptococcal species (eg, *S. pneumoniae*, beta-hemolytic streptococci) are a rare cause of IE.

▶ *Staphylococci*

Staphylococcal endocarditis continues to increase in prevalence, causing 30% or more of all cases of IE, with the majority (80%–90%) being due to *S. aureus* (coagulase-positive staphylococci).[1-3,5,7] This increase in staphylococci has been primarily attributed to expanded use of venous catheters, more frequent valve replacement, and increased injection drug use.[1,5,7] Coagulase-negative staphylococci (CoNS) is also a cause of IE. However, these organisms frequently infect prosthetic valves over native valves or foreign material such as indwelling catheters; thus, staphylococci is the predominate causative pathogen in PVE.[1,6,22,23]

Patients with *S. aureus* bacteremia are at an increased risk of developing IE. *S. aureus* may infect "normal" heart valves (no prior detected valvular disease) in one-third of cases.[1,5] Therefore, it is imperative to assess these patients adequately for the presence of vegetations. Any heart valve may be affected; however, the mitral or aortic valve is most commonly involved, often resulting in extensive infection with a mortality rate of approximately 40% to 45%.[1,24] When managing *S. aureus* IE, one must consider whether the isolate displays methicillin resistance, the location of infection (right or left side), presence of prosthetic valves, and history of injection drug use. Despite significantly decreased activity of penicillinase-resistant penicillins (PRP; eg, oxacillin and nafcillin), most isolates remain susceptible to vancomycin. However, there is an increasing incidence of *S. aureus* with an elevated vancomycin MIC of 2 mcg/mL (2 mg/L) that may impact clinical outcome.[5,25,26] Additionally, strains with intermediate or fully resistant MICs to vancomycin have been rarely reported.[27-29]

The predominant coagulase-negative organism causing IE has been *S. epidermidis*. However, there has been an increase in isolation of another coagulase-negative species, *S. lugdunensis*.[30,31] Typically, coagulase-negative staphylococcal IE has a subacute course with numerous complications. Management (with or without surgical intervention) is usually successful. On the other hand, *S. lugdunensis* produces a more virulent infection, which is more comparable to that of *S. aureus* and, despite similar antibiotic susceptibilities to other CoNS, has a much higher mortality rate.[30]

▶ *Enterococci*

Enterococci are normal flora of the human GI tract and sometimes found in the anterior urethra. Affected patients are typically older men who have undergone genitourinary manipulations or younger women who have had obstetric procedures. Although enterococci are a less common cause of IE, there are two predominant species: *Enterococcus faecium* and *Enterococcus faecalis*. *E. faecalis* is the most common and more susceptible of the strains. However, enterococcal IE represents one of the most problematic Gram-positive bacterial infections to treat and cure. Enterococci, especially *E. faecium*, frequently display intrinsic and acquired resistance to multiple antibiotics, including penicillins, vancomycin, aminoglycosides, linezolid, and daptomycin.[32]

▶ *Gram-Negative Bacteria*

Gram-negative bacterial IE is much less common (~2%) but is typically much more difficult to treat than Gram-positive bacterial infections.[1,33] Fastidious organisms, such as the HACEK group, tend to predominate, causing approximately 3% of all NVE.[1,34,35] HACEK organisms consist of *Haemophilus* spp. (primarily *H. paraphrophilus, H. parainfluenzae*, and *H. aphrophilus*), *Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens*, and *Kingella kingae*. The clinical presentation of IE by these organisms is subacute, with approximately 50% of patients developing complications. These complications are primarily due to the presence of large, friable vegetations, and numerous emboli along with development of acute congestive heart failure often requiring valve replacement.[33,34,36] Traditionally, it was important to allow cultures sufficient incubation time (often 2–3 weeks) to isolate these organisms. Newer media and current automated incubation systems are now favored for recovery with timeframe similar to standard blood cultures (ie, 2–3 days). Despite improvements in culturing, these organisms may still present as culture-negative IE.

Other Gram-negative organisms, such as *Pseudomonas* spp., can cause IE, especially in injection drug users, healthcare exposure, and in patients with prosthetic valves. Additionally, IE may be caused by *Salmonella* spp., *Escherichia coli, Citrobacter* spp., *Klebsiella* spp., *Enterobacter* spp., *Serratia marcescens, Proteus* spp., and *Providencia* spp.[1,33]

Historically, Gram-negative IE typically had a poor prognosis with high mortality rates. Management, in addition to antimicrobial therapy, now often includes valve replacement in many patients. Therefore, as nondrug therapy advances to include cardiac surgery in more than half of patients, in-hospital mortality has improved to ~14% to 24%.[1,33]

▶ *Culture-Negative IE*

Negative blood cultures are reported in approximately 2% to 40% of IE cases, often resulting in delayed diagnosis and treatment.[1,7,19] Cultures that do not grow bacteria may be the result of previous antibiotic use, subacute right-sided disease, slow growth of fastidious organisms, nonbacterial endocarditis (eg, fungal or intracellular parasitic infections), non-IE, or improper collection of blood cultures. If nonbacterial or fastidious organisms are suspected, additional testing is essential.

▶ *Other Organisms*

Numerous other bacteria, including Gram-positive bacilli, unusual Gram-negative bacteria, atypical bacteria, and anaerobes, as well as spirochetes, are rare causes of IE.[1,5,37] Some of the more common organisms include *Legionella, Coxiella burnetii* (Q fever), and *Brucella*. These rare organisms occur primarily in at-risk patients such as those with prosthetic valves or injection drug users. A comprehensive discussion of these organisms is not feasible for this chapter; for further information, other references (particularly references 1, 5–7, 10, 20, 33, and 37 at the end of this chapter) should be examined. Identification of these organisms is difficult, and cure rates are low; thus, patients with these organisms should be managed by an infectious diseases specialist or endocarditis team.

▶ *Fungi*

Fungal endocarditis is quite uncommon but has significant mortality and typically affects patients with a history of cardiovascular surgery, pacemaker or prosthetic valves, total parenteral nutrition (TPN), prolonged courses of broad-spectrum antibiotics, long-term catheter placement, immunocompromised, or injection drug users.[7,38,39] Survival rates were historically poor with a current range of ~30% to 80%. Improvements in outcome have been reported owing to advances in diagnosis and treatment.[38,39] Poor prognosis has been attributed to large vegetations, propensity for organism invasion into the myocardium, extensive septic emboli, poor antifungal penetration into vegetations, and low toxic-to-therapeutic ratio and lack of cidal activity of certain antifungals.[38] The two most commonly associated organisms are *Candida* spp. and *Aspergillus* spp.

TREATMENT

General Approach to Treatment

Treatment of IE is complicated and difficult. Numerous factors involving vegetations influence the effectiveness of antimicrobial agents. The fibrin matrix of vegetations provides an environment where organisms are relatively free to replicate unimpeded, allowing the microbial density to reach very high concentrations (10^9–10^{10} CFU/g). Once organism density has reached this level, the majority of organisms are in a static growth phase. These factors hinder host defenses as well as the ability of antimicrobials to produce sufficient kill. This is often seen with β-lactams and glycopeptides as their effectiveness can be significantly diminished with increased bacterial inoculum and stationary growth phase of the bacteria. General recommendations encourage obtaining an infectious diseases/endocarditis team consult for all IE patients to aid in selection of empirical regimen, diagnosis, treatment duration, and management regardless of organism or disease severity.

KEY CONCEPT Selection of an appropriate antimicrobial agent must combine characteristics such as the ability to penetrate into the vegetation, the ability to achieve adequate drug concentrations, and the ability to be minimally affected by high bacterial inoculum to achieve adequate kill rates. **KEY CONCEPT** To accomplish this, parental, bactericidal antimicrobials are typically required to ensure optimal treatment, with an extended treatment course of 4 to 6 weeks (in most cases). Historically, parenteral therapy was recommended for the entire treatment duration. Patients would remain in the hospital minimally during the critical phase (initial 2 weeks) when complications are more frequent, then once clinically improved based on no systemic symptoms and negative follow-up blood cultures, therapy could be converted to daily administration of outpatient antimicrobial therapy (OPAT). However, OPAT may not be an option depending on factors such as lack of home healthcare access, transportation to outpatient infusion center or concern for central venous catheter in an injection drug user. Until recently, oral antibiotics were considered less reliable due to inconsistent GI absorption and potential subtherapeutic levels. However, a recent study, the POET trial (Partial Oral Treatment of Endocarditis) has lent support for transitioning to oral antibiotics as a safe and effective option for step-down therapy after receiving a minimum of 10 days of IV treatment and when giving a regimen consisting of at least two susceptible antibiotics in select patients with specific organisms and left-sided IE.[40] There are other studies in process to expand potential use of IV to oral antibiotics in IE. These include POET II (assessing shortened antibiotic therapy), RODEO-1 (left-sided IE due to susceptible staphylococci), and RODEO-2 (left-sided IE due to susceptible streptococci and enterococci).[41,42] However, based on current data, exploring use of early conversion to combination oral therapy with highly bioavailable agents may be an option in left-sided IE patients without significant cofounding factors to complete the treatment course. However, caution should be used as oral therapy is not suitable in many patients and consultation with the multidisciplinary endocarditis team is recommended to ensure selection of appropriate patient and treatment regimen/duration for this treatment option.

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Type II diabetes, hypertension, CKD stage 3, recurrent cellulitis, osteomyelitis of the right foot

Surgical History: None

FH: Mother has hypertension, CHF, dyslipidemia, and bipolar disorder, current age 68; father had a history of hypertension, ascites, cirrhosis, and end-stage liver disease, died at age 52.

SH: Currently living in his car. He admits to use of IV heroin but denied alcohol or tobacco usage.

Meds: Lisinopril 20 mg daily, insulin 70/30 50 units twice daily (previously on insulin glargine but unable to afford).

Allergies: Penicillin (rash) and trimethoprim/sulfamethoxazole (renal failure)

ROS: Ill appearing, weakness primarily to the left arm, shortness of breath, and generalized abdominal pain. Extremities with several mild hematomas and right foot with a chronic ulcer with some erythema and purulent drainage.

PE:

Weight: 188 lb **Height:** 5 ft 8 in.

VS: BP = 148/92 mm Hg, P = 98 beats/min, RR = 20 breaths/min, T = 39.6°C

Cardiovascular: Tachycardia, systolic murmur (not identified on previous admissions)

Abd: Soft, tender, guarded, nondistended; (+) bowel sounds

Labs: Within normal limits, except WBC = $22.8 \times 10^3/\mu L$ ($22.8 \times 10^9/L$), neutrophils = 86%, bands = 28%, SCr = 4.1 mg/dL (362.4 μmol/L), BUN = 62 mg/dL (22.1 mmol/L urea), ALT 168 U/L (2.8 μKat/L)

Given this additional information, what is your assessment of the patient's condition?

Do you have any other concerns based on the patient's presenting signs/symptoms?

What do you recommend for empiric treatment for this patient?

What other information or tests would be beneficial?

Nonpharmacologic Therapy

Surgery

Surgical intervention has become an integral therapy in combination with pharmacologic management of IE. Valve replacement is the predominant intervention and is used in almost one-half of all cases of IE.[1,37,43,44] Surgery is generally indicated if the patient has new or refractory congestive heart failure, significant valvular dysfunction, persistent infection despite antibiotics, more than one episode of serious emboli, large or mobile vegetations, mycotic aneurysm requiring resection, local complications (perivalvular or myocardial abscesses), PVE, or associated with a pathogen demonstrating higher antimicrobial resistance.[1,43,44] While timing of surgical intervention is still in question, patients with CHF or at high risk for emboli have improved outcomes with early surgery. Additionally, a patient's hemodynamic status (eg, blood pressure, heart rate, pulmonary artery pressure) should be assessed to determine when surgical intervention is warranted.[1] Despite appropriate medical management, a significant number of people who develop NVE require valve replacement surgery. Involvement of the aorta or development of IE complications is considered an indication for surgery in the majority of patients with PVE.[14,43,44] Based on the complexity of managing the needs (ie, medical, surgical, pharmacologic, and imaging) of IE patients, guidelines recommend utilizing a multidisciplinary group "endocarditis team." Subsequently, studies have now demonstrated positive outcomes including earlier surgical intervention, decreased length of hospital stay and antibiotic duration, and overall improved survival.[45,46]

Pharmacologic Therapy

Empirical Treatment

KEY CONCEPT The overall goal of therapy is to eradicate the infection and minimize/prevent any complications. Patients with suspected IE should be evaluated for risk factors that may provide some indication of the most likely causative organism. If no risk factors can be determined, empirical therapy should primarily cover Gram-positive bacterial organisms, specifically *S. aureus*, viridans group streptococci, and enterococci. Thus, vancomycin is a reasonable empiric therapy unless decreased local susceptibilities (mainly for enterococci) or patient concerns in which daptomycin would be more appropriate. If risk factors for other organisms are present, broaden coverage based on suspected pathogens. It is important to monitor the patient's response to therapy closely until cultures and susceptibilities are determined to ensure treatment is appropriately tailored to maximize patient outcome.

Organism Specific Treatment

The American Heart Association (AHA), as well as the European Society of Cardiology (ESC), has published guidelines for the management of IE, including specific treatment recommendations.[5,37] Both guidelines provide similar recommended treatment regimens (preferred antimicrobial agents and durations) for the most common organisms (streptococci, staphylococci, and enterococci) depending on whether the patient has NVE or PVE as listed in Tables 78–5 to 78–7. However, for more detailed information, refer to the complete guidelines.[5,37]

▶ *Streptococci*

The majority of viridans group streptococci and *S. gallolyticus* (*bovis*) remain very susceptible to penicillin. However, isolation of organisms with reduced penicillin susceptibilities is increasing; thus, antibiotic susceptibilities should be assessed to ensure the most appropriate treatment regimen. Owing to the similarities of these streptococci, most isolates have a penicillin MIC less than 0.12 mcg/mL (0.12 mg/L); therefore, penicillin G or ceftriaxone remain the preferred agents unless patients are unable to tolerate β-lactams or resistance is suspected. Typical length of treatment is 4 weeks and remains the most common duration. However, a shorter 2 week course may be employed for a patient with uncomplicated IE due to highly penicillin-susceptible strains with no extracardiac infection and creatinine clearance is greater than 20 mL/min/1.73 m^2 (0.19 mL/s/m^2). If the 2 week therapy is chosen, gentamicin should be added to the previous β-lactams for the entire course.

Patient Encounter, Part 3: Additional Laboratory and Diagnostic Tests

Preliminary Blood Cultures: Both sets (four out of four bottles) taken on admission in the emergency department are positive for Gram-positive cocci in clusters, coagulase-positive

Labs: CBC with differential and BMP obtained on day 4, all within normal limits excluding WBC = 21.2 × 10^3/μL (21.2 × 10^9/L), neutrophils = 82%, bands = 20%, SCr = 3.6 mg/dL (318.2 μmol/L), BUN = 78 mg/dL (27.9 mmol/L urea)

Echo: TTE revealed a large vegetation on the anterior mitral valve leaflet (2 × 2.5 cm) with moderate mitral valve regurgitation. The tricuspid valve was difficult to visualize but showed moderate regurgitation.

Given this additional information, would you make any changes in the assessment of your patient?

Would you adjust therapy at this time based on these new data?

Are you now able to determine treatment goals, including length of treatment?

What other information would you like to obtain?

When penicillin MICs for viridans group streptococci are greater than 0.12 mcg/mL (0.12 mg/L) but less than 0.5 mcg/mL (0.5 mg/L), antimicrobial duration should be increased to 4 weeks of penicillin G with gentamicin recommended during the first 2 weeks or ceftriaxone alone for 4 weeks. In patients with resistant strains of viridans group streptococci (MIC ≥ 0.5 mcg/mL [0.5 mg/L]), treatment should include antimicrobial agents utilized for enterococcal IE (precise agents determined by the susceptibility report) such as high-dose penicillin G or ceftriaxone combined with gentamicin. For any patient who is allergic or intolerant to β-lactams, vancomycin monotherapy is an alternative treatment option regardless of penicillin MIC.

Patients with PVE caused by viridans streptococci require treatment for 6 weeks with penicillin G or ceftriaxone in combination with gentamicin during the initial 2 weeks of therapy (if penicillin-susceptible), and with or without gentamicin over the entire 6 weeks (if less susceptible to penicillin, MIC > 0.12 mcg/mL [0.12 mg/L]). Vancomycin alone remains the primary alternative for β-lactam allergic patients.

Recommended therapies for viridans streptococci and *S. gallolyticus* (*bovis*) are summarized in Table 78–5.

▶ *Staphylococci*

It is important to determine (a) whether the isolate is methicillin-susceptible versus methicillin-resistant and (b) whether the

Table 78–5

Treatment Regimens for IE Caused by Viridans Group Streptococci and *S. gallolyticus (bovis)*

Regimen	Recommended Dose[a] and Route	Duration (weeks)	Comments
Native Valve IE caused by Highly Penicillin-Susceptible Strains, MIC ≤ 0.12 mcg/mL (≤ 0.12 mg/L)			
Penicillin G sodium[b]	2–3 million units IV every 4 hours	4	.
OR			
Ceftriaxone	2 g IV/IM every 24 hours	4	
Penicillin G sodium	2–3 million units IV every 4 hours	2	2-week regimen only recommended for uncomplicated NVE with creatinine clearance of > 20 mL/min/1.73 m^2 (0.19 mL/s/m^2); should not be used against *Abiotrophia, Granulicatella, or Gemella* spp. infection.
OR			
Ceftriaxone	2 g IV/IM every 24 hours	2	
PLUS			
Gentamicin[c]	3 mg/kg IV/IM once daily	2	If given as three divided doses, refer to Table 78–8 for synergistic dosing target concentrations; there are no optimal drug concentrations for single daily dosing.
OR			
Vancomycin	15 mg/kg every 12 hours	4	Should be used for patients unable to tolerate penicillin or ceftriaxone; refer to Table 78–8 for dosing target concentrations.
Native Valve IE caused by Relatively Penicillin-Resistant Strains, MIC > 0.12 to < 0.5 mcg/mL (> 0.12 to < 0.5 mg/L)			
Penicillin G sodium[b]	4 million units IV every 4 hours	4	If given as three divided doses, refer to Table 78–8 for synergistic dosing target concentrations; there are no optimal drug concentrations for single daily dosing.
PLUS			
Gentamicin[c]	3 mg/kg IV/IM once daily	2	
OR			
Ceftriaxone	2g IV/IM every 24 hours	4	If susceptible, ceftriaxone monotherapy may be considered.
Vancomycin	15 mg/kg every 12 hours	4	Should be used for patients unable to tolerate penicillin or ceftriaxone; refer to Table 78–8 for dosing target concentrations.
Prosthetic Valve or Other Prosthetic Material-related IE caused by Highly Penicillin-Susceptible Strains, MIC ≤ 0.12 mcg/mL (≤ 0.12 mg/L)			
Penicillin G sodium[b]	4 million units IV every 4 hours	6	
OR			
Ceftriaxone	2 g IV/IM every 24 hours	6	If given as three divided doses, refer to Table 78–8 for synergistic dosing target concentrations; there are no optimal drug concentrations for single daily dosing.
WITH OR WITHOUT			
Gentamicin[c,d]	3 mg/kg IV/IM once daily	2	
OR			
Vancomycin	15 mg/kg every 12 hours	6	Should be used for patients unable to tolerate penicillin or ceftriaxone; refer to Table 78–8 for dosing target concentrations.
Prosthetic Valve or Other Prosthetic Material-related IE caused by Relatively or Fully Penicillin-Resistant Strains, MIC > 0.12 mcg/mL (> 0.12 mg/L)			
Penicillin G sodium[b]	4 million units IV every 4 hours	6	
OR			
Ceftriaxone	2 g IV/IM every 24 hours	6	If given as three divided doses, refer to Table 78–8 for synergistic dosing target concentrations; there are no optimal drug concentrations for single daily dosing.
PLUS			
Gentamicin[c]	3 mg/kg IV/IM once daily	6	
OR			
Vancomycin	15 mg/kg every 12 hours	6	Should be used for patients unable to tolerate penicillin or ceftriaxone; refer to Table 78–8 for dosing target concentrations.

[a] Dose recommendations are based on patients with normal renal function. See Table 78–8 for additional dosing considerations.

[b] May give penicillin G sodium total daily dose as a continuous infusion. Ampicillin 2 g IV every 4 hours may be used as an alternative during shortage of penicillin.

[c] Avoid use of other potentially nephrotoxic drugs if receiving gentamicin therapy. Preferred given as a 3 mg/kg single dose, although may be administered in three divided doses.

[d] No benefit has shown combination therapy resulted in superior cure rates over monotherapy in PVE due to susceptible streptococci.

IM, intramuscular; IV, intravenous

Data from Refs. [1,5,6,37].

patient has a native versus prosthetic valve. For patients with NVE, methicillin-susceptible staphylococcal treatment should consist of a PRP or cefazolin, and for methicillin-resistant strains, therapy should consist of vancomycin or daptomycin (see Table 78–6). Duration for all therapies should be for 6 weeks. In patients with central nervous system (CNS) involvement (eg, brain abscess), use of PRP or vancomycin is recommended. If use of daptomycin is needed, consult with infectious diseases/endocarditis team is recommended to assist in optimal dosing.

For staphylococcal PVE, treatment length increases significantly, typically requiring a minimum of 6 weeks (see Table 78–6). For methicillin-sensitive staphylococci, a PRP should still be used, as well as vancomycin for methicillin-resistant staphylococci. Duration of therapy should be at least 6 weeks. However, with either regimen, addition of gentamicin (for synergy) for first 2 weeks and rifampin (to aid in preventing bacterial adherence to prosthetic devices given its ability to penetrate biofilms) for the entire length of treatment is recommended. Infectious diseases or

Table 78–6

Treatment Regimens for IE Caused by Staphylococci

Regimen	Recommended Dose[a] and Route	Duration (weeks)	Comments
Native Valve IE			
Oxacillin-Susceptible Strains			
Nafcillin or oxacillin	2 g IV every 4 hours	6	If unclear penicillin allergy, may perform skin testing.
Cefazolin	2 g IV every 8 hours	6	If anaphylactic to penicillin, recommend use of vancomycin instead of cefazolin.
Oxacillin-Resistant Strains			
Vancomycin	15 mg/kg every 12 hours	6	Refer to Table 78–8 for dosing target concentrations.
Daptomycin	≥ 8 mg/kg every 24 hours	6	
Prosthetic Valve IE			
Oxacillin-Susceptible Strains			
Nafcillin or oxacillin	2 g IV every 4 hours	≥ 6	Cefazolin may be used as an alternative to PRP.
PLUS			.
Rifampin	300 mg IV/PO every 8 hours	≥ 6	
PLUS			
Gentamicin	1 mg/kg IV/IM every 8 hours	2	Refer to Table 78–8 for synergistic dosing target concentrations.
Oxacillin-Resistant Strains			
Vancomycin	15 mg/kg every 12 hours	≥ 6	Refer to Table 78–8 for dosing target concentrations.
PLUS			
Rifampin	300 mg IV/PO every 8 hours	≥ 6	
PLUS			
Gentamicin	1 mg/kg IV/IM every 8 hours	2	Refer to Table 78–8 for synergistic dosing target concentrations.

[a] Dose recommendations are based on patients with normal renal function. See Table 78–8 for additional dosing considerations.

IM, intramuscular; IV, intravenous; PRP, penicillinase-resistant penicillin.

Data from Refs. [1,5,6,37].

Table 78–7

Treatment Regimens for IE Caused by Enterococci

Regimen	Recommended Dose[a] and Route	Duration (weeks)	Comments
Native Valve IE or PVE; Penicillin and Aminoglycoside[b] Susceptible; and Able to Tolerate β-lactam Therapy			
Ampicillin	2 g IV every 4 hours	4–6	NVE: if ≤ 3 months symptoms, 4-week therapy
OR			if > 3 months symptoms, 6-week therapy
Penicillin G sodium[c]	3–5 million units IV every 4 hours	4–6	PVE: 6-week therapy
PLUS			
Gentamicin	1 mg/kg IV/IM every 8 hours	4–6	
OR			
Dual *β-lactam*			Recommended for patients with impaired renal function (creatinine clearance < 50 mL/min/1.73 m^2 [0.48 mL/s/m^2]), or in patients who develop renal impairment or have toxicity secondary to gentamicin.
Ampicillin	2 g IV every 4 hours	6	
PLUS			
Ceftriaxone	2 g IV every 12 hours	6	
Native Valve IE or PVE; Penicillin Resistant; and Aminoglycoside Susceptible; or Unable to Tolerate β-lactams			
Vancomycin	15 mg/kg every 12 hours	6	If β-lactamase-producing strains and patient can tolerate a β-lactam antibiotic, ampicillin-sulbactam[d] plus gentamicin may be used.
PLUS			
Gentamicin	1 mg/kg IV/IM every 8 hours	6	
Native Valve IE or PVE; Penicillin, Aminoglycoside, and Vancomycin Resistant			
Daptomycin	10–12 mg/kg every 24 hours	> 6	
OR			
Linezolid	600 mg IV/PO every 12 hours	> 6	Bacteriostatic agent

[a] Dose recommendations are based on patients with normal renal function. See Table 78–8 for additional dosing considerations.

[b] For gentamicin-resistant strains, if streptomycin is susceptible, may substitute for gentamicin for each regimen listed (dose is 7.5 mg/kg IV or IM every 12 hours based on ideal body weight).

[c] May give penicillin G sodium total daily dose as a continuous infusion.

[d] Ampicillin-sulbactam dose is 3 g IV every 6 hours.

IM, intramuscular; IV, intravenous; PO, oral.

Data from Refs. [1,5,6,37].

endocarditis team consultation is recommended for all patients with *S. aureus* IE, irrespective of methicillin-susceptibility, due to an observed reduction in mortality associated with expert consultation in this patient population.[45,46]

Observed suboptimal outcomes in some cases of staphylococcal IE necessitates the expanded use of alternative therapies. Typically, standard therapy for MSSA is sufficient. However, for persistent MSSA bacteremia, combination β-lactams or use of alternative agents may be utilized. For MRSA, daptomycin is a reasonable alternative if the patient either has persistent bacteremia or the isolate has an elevated vancomycin MIC of 2 mcg/mL (2 mg/L), particularly if lack of clinical improvement noted. The approved daptomycin dosing for right-sided IE is 6 mg/kg/day (unless renal adjustments are necessary); however, guidelines recommend higher dosages of greater than or equal to 8 mg/kg.[5,25,37] Additionally, other antibiotics, such as ceftaroline, linezolid, telavancin, and long-acting lipoglycopeptides alone or in combination, have been used in patients with variable response rates.[32,47-50] These therapies often are reserved for patients who have been unresponsive to traditional therapy or for multidrug-resistant organisms, including those with reduced susceptibility to vancomycin.

▸ *Enterococci*

For enterococci, it is imperative to determine the specific species given significant differences in antibiotic susceptibility patterns between the two most common organisms (*E. faecalis* vs *E. faecium*). Historically, the mainstay of treatment for susceptible strains has been penicillin, ampicillin, or vancomycin, each combined with gentamicin for a total of 6 weeks. However, patients were often unable to tolerate or developed varying degrees of renal impairment (ie, toxicity). Therefore, the dual beta-lactam regimen, comprising ampicillin and ceftriaxone, is now commonly employed, particularly for *E. faecalis*.[5] As resistance develops to penicillin or ampicillin, vancomycin may provide adequate coverage. Once the isolate becomes resistant to vancomycin, daptomycin and linezolid are currently the most appropriate/viable treatment options. Refer to Table 78–7 for a summary of treatment regimens.

Treatment options for vancomycin-resistant enterococci (VRE) have not been well established. However, current recommendations for treating vancomycin-resistant enterococcal isolates include linezolid or daptomycin for a minimum of 6 weeks. The most likely species to develop vancomycin resistance is *E. faecium*, as *E. faecalis* infrequently develops multidrug resistance and ampicillin susceptibility is typically retained in this latter species. As per AHA IE guidelines, dosing for the recommended therapy is daptomycin 10 to 12 mg/kg/dose and linezolid 600 mg IV or orally every 12 hours. However, use of either agent has concerns. Linezolid is a bacteriostatic agent with potential for resistance development and/or increased likelihood of significant hematological side effects over a prolonged treatment course. Daptomycin is considered a bactericidal agent, but development of resistance is increasing; thus, dual therapy with β-lactams (eg, ampicillin or ceftaroline) has been shown to enhanced activity even for daptomycin nonsusceptible organisms. Synergistic combinations with gentamicin, rifampin, or tigecycline have also been utilized with variable results. Other potential agents include long-acting lipoglycopeptides (minimal data at this point) or quinupristin/dalfopristin (rarely used secondary to side effects and intrinsic resistance to *E. faecalis*).[48,50] Even with agents displaying susceptibility, combination therapy is often warranted; therefore, consultation with an infectious diseases specialist or endocarditis team is recommended if VRE is identified.

▸ *Gram-Negative Bacteria*

Identification of the exact pathogen is crucial in Gram-negative bacterial IE as treatment decisions depend on which organism is isolated. Therapy is usually targeted to the most susceptible antibiotics. Combination therapy is commonly used, usually with the addition of an aminoglycoside or fluoroquinolone. For example, *Pseudomonas* spp. are treated with an antipseudomonal β-lactam (eg, piperacillin/tazobactam, cefepime, meropenem) plus high-dose aminoglycoside (typically tobramycin 8 mg/kg/day).[1] However, exact dosing of antibiotics depends on the organism isolated. Length of treatment is usually a minimum of 6 to 8 weeks and often includes surgical intervention (ie, valve replacement surgery). Consultation with an infectious diseases specialist or endocarditis team is recommended.

▸ *HACEK Group*

The HACEK group bacteria are difficult to isolate, often leading to culture-negative IE. If one of these organisms is suspected, it is important to initiate appropriate empirical treatment. The preferred regimen is ceftriaxone (or another third- or fourth-generation cephalosporin), followed by ampicillin-sulbactam due to the increased occurrence of β-lactamase–producing strains. However, for patients who are intolerant of these treatments, fluoroquinolones may be used. The length of treatment for these organisms is typically 4 weeks (NVE) or 6 weeks (PVE).

▸ *Culture-Negative IE*

Treatment for culture-negative IE presents a significant dilemma. As outlined above, therapeutic regimens are usually guided by isolated organisms. When cultures fail to identify a specific organism, decisions regarding empiric treatment should cover the most common causative pathogens. Patient characteristics and risk factors aid in defining additional organisms requiring coverage.[5] Empiric regimens should also consider acute vs subacute presentation and NVE or PVE. The AHA recommends the following empiric regimens: vancomycin and cefepime (for NVE, acute presentation) plus rifampin and gentamicin (for early PVE, ≤ 1 year); vancomycin and ampicillin/sulbactam (for NVE, subacute presentation); or vancomycin plus ceftriaxone (for late PVE, > 1 year). If the patient is unresponsive to initial treatment, additional coverage for less common organisms becomes warranted. An infectious diseases specialist or endocarditis team should be consulted for the management of culture-negative IE.

▸ *Fungi*

Treatment of fungal IE is exceptionally difficult. There is a significant lack of evidence to identify the most appropriate therapy. Currently, amphotericin B is the most common treatment. However, valve replacement surgery is often considered a necessary adjunctive therapy in the majority of cases. Intravenous antifungal therapy requires high doses for a minimum of 6 weeks of treatment, often followed by life-long oral suppression therapy (ie, oral triazoles). Newer antifungals may be effective options, including echinocandins (eg, caspofungin) and voriconazole, depending on the organism and susceptibilities.[38]

Antimicrobial Dosing Considerations

The majority of antibiotic and antifungal agents used for the treatment of IE require dosing modifications based on renal or hepatic function. However, the most closely monitored are vancomycin and aminoglycosides. This is due in part because (a) therapeutic

Patient Encounter Part 4: Additional Laboratory

Susceptibility Report: *Staphylococcus aureus*

Drug	MIC (mg/L)	Interpretation
Ceftaroline	≤ 1	S
Clindamycin	≤ 0.25	S
Daptomycin	≤ 1	S
Erythromycin	> 8	R
Gentamicin	≤ 4	S
Linezolid	≤ 4	S
Oxacillin	≥ 4	R
Penicillin	≥ 8	R
Vancomycin	2	S
Tetracycline	8	I
Trimethoprim/ Sulfamethoxazole	≤ 0.5/9.5	S

Repeat blood cultures: Preliminary blood cultures from day 4—*Staphylococcus aureus*

Echo: TEE confirms large mitral valve vegetation (2.2 × 2.8 cm) and shows a 1.5 × 2 cm vegetation on the tricuspid valve

CT: Brain showed multiple low-density bilateral lesions of the temporal lobe, and right parietal lobe, suggestive of cerebral embolism. CT: Chest revealed multiple bilateral parenchymal nodular and wedge-shaped consolidations

VS Day 7: BP = 136/83 mm Hg, P = 85 beats/min, RR = 20 breaths/min, T = 38.9°C

Labs: CBC with differential and BMP obtained on day 7, all within normal limits excluding WBC = 19.7×10^3/μL (19.7×10^9/L), neutrophils = 78%, bands = 16%, SCr = 2.4 mg/dL (212.2 μmol/L), BUN 36 mg/dL (12.9 mmol/L urea)

Given this additional information, are there any changes in your assessment of the patient?

Do you need to adjust your treatment regimen based on these data?

What are your treatment goals, including nonpharmacologic therapy and length of treatment?

drug monitoring of serum concentrations is normally utilized to guide therapy, and (b) there is an increased likelihood of toxicity (ie, nephrotoxicity, ototoxicity) if the drug concentration is too high or adverse outcomes (ie, clinical failure or resistance development) if level is too low. Recently updated guidelines for vancomycin dosing for serious infections due to MRSA focused on utilization of area under the concentration–time curve (AUC)/MIC for the pharmacokinetic/pharmacodynamic (PK/PD) predictor of efficacy over use of trough concentrations.[26] This is particularly recommended for *S. aureus* isolates with an MIC of less than or equal to 1 mcg/mL (1 mg/L) as routine vancomycin dosing would obtain the recommended goal AUC/MIC of 400 to 600 based on assessment of vancomycin serum peak and trough concentrations. There are limited data on target AUC/MIC for *S. aureus* isolates with an MIC of 2 mcg/mL (2 mg/L) and use of alternative therapies may be considered, particularly if lack of clinical improvement is observed. Additionally, these vancomycin guidelines do not specify PK/PD parameters for streptococci or enterococci. The AHA specifies goal troughs of 10 to 15 and 10 to 20 mg/L (6.9-10.4 and 6.9-13.8 μmol/L). for streptococci and enterococci, respectively.[5] However, based on the complicated nature of IE, a goal trough of 15 to 20 mg/L (10.4-13.8 μmol/L) is typically employed. Other general dosing considerations are included in Table 78–8 for the most common drugs used in the treatment of IE. However, specific dosing adjustments for individual patients should be determined by referring to an appropriate drug dosing reference.

Prophylaxis

KEY CONCEPT Certain conditions have been associated more commonly with IE due to preexisting cardiac disease in the presence of a transient bacteremia. In an effort to prevent the development of IE, prophylactic treatment is generally considered appropriate for these at-risk patients. Although there are no well-controlled clinical studies of these recommendations, it is thought that if antibiotics are given just prior to a procedure, the number of bacteria may be decreased in the bloodstream and prevent the bacteria from adhering to the valves.

Cardiac conditions in which prophylaxis is reasonable include presence of prosthetic valves or material, prior IE, select forms of congenital heart disease, and cardiac transplant patients with cardiac valvulopathy (Table 78–9).[10] Although many patients have other cardiac dysfunction, only patients with these conditions are considered to be at a high risk of developing IE. No prophylaxis is advised in other patients.

Transient bacteremia may occur due to many types of dental and surgical procedures. However, the AHA guidelines significantly limit the types of procedures where prophylaxis is appropriate. Only dental procedures involving manipulation of gingival tissue or periapical region of teeth or perforation of the oral mucosa are considered to increase the likelihood that high-risk patients will develop IE.[10] Viridans group streptococci are the primary bacteria targeted for prophylaxis in this circumstance. On the other hand, prophylaxis should be given to patients undergoing GI or genitourinary (GU) surgeries that primarily targets enterococci.

The AHA guidelines include suggested antibiotic regimens for dental procedures for which prophylaxis is warranted.[10] Recommended regimens are summarized in Table 78–10. These guidelines recommend a single oral or intramuscular/intravenous dose initiated shortly before the procedure. A second prophylactic dose is not recommended. However, if an infection develops at the procedure site, additional antibiotics (ie, a therapeutic course) may be required.

Patient Encounter Part 5: Create a Care Plan

Based on this patient's information, create a care plan for the management of his IE. Be sure to include:

(a) A statement regarding treatment requirements and/or possible problems

(b) Goals of therapy

(c) A patient-specific plan, including preventive plans

(d) A follow-up plan to assess whether the goals have been met and to determine whether the patient experienced any adverse effects

Table 78–8

Dosage and Monitoring Considerations of Antibiotics for Treatment of IE[a]

Drug	Renal Adjustment	Hepatic Adjustment	Comments
Ampicillin	Required	None	Seizures most common AE if dosing not adjusted. Monitor for potential development of allergic interstitial nephritis (AIN).
Ampicillin/ Sulbactam	Required	None	Monitor for potential development of AIN.
Cefazolin	Required	None	Not recommended for IE with brain abscess due to insufficient penetration of blood–brain barrier (PRP preferred).
Ceftriaxone	If severe (see comment)	None	Do not exceed 2 g/day if patient has BOTH severe renal AND hepatic impairment
Daptomycin	Required	None	CPK should be monitored prior to and during therapy (at least weekly, and more frequently if increasing or on concomitant medications associated with muscle toxicity, particularly statins). Recommend to discontinue/switch therapy if patient symptomatic for myopathy when CPK is > 5 times upper limit of normal or if asymptomatic and CPK is > 10 times upper limit of normal.
Gentamicin	Required	None	Dosing should be based on ideal body weight; however, if significantly obese, use of adjusted body weight may be required to achieve target levels (listed below). Monitor therapeutic concentrations to guide dosage adjustments and target concentrations. Gentamicin: Only used as synergy (combination therapy) for Gram-positive bacteria. Target concentrations for synergy: peak 3–4 mcg/mL (3–4 mg/L; 6.3–8.4 μmol/L) and trough < 1 mcg/mL (1 mg/L; 2.1 μmol/L).
Linezolid	None	None	Metabolites may accumulate in severe renal impairment Monitor for hematologic AE, particularly severe thrombocytopenia Use in severe hepatic impairment not established
Nafcillin	None	If severe (see comment)	Adjustments necessary ONLY in patients with severe hepatic AND renal impairment. Monitor for potential development of AIN.
Oxacillin	If severe (see comment)	None	Monitor for potential development of AIN.
Penicillin G	Required	None	Dose increase dependent upon organism. Monitor for potential development of AIN.
Rifampin	None	Required	Assess other medications for potential interaction as rifampin a potent cytochrome P450 inducer. Inform patient of potential change in color of body fluids (ie, urine, sweat, and saliva) to orange, yellow, red, or brown.
Vancomycin	Required	None	Monitor therapeutic concentrations to guide dosage adjustments. For MRSA IE, recommend use of AUC/MIC with goal of 400–600 mg h/L (best estimation by calculation from serum peak and trough concentrations). For all other organisms, goal trough concentrations 10–20 mcg/mL (10–20 mg/L; 6.9-13.8 μmol/L) with some guidance suggesting higher levels of 15–20 mcg/mL (15–20 mg/L ; 10.4-13.8 μmol/L).
Newer and Salvage Drugs			
Ceftaroline	Required	None	Suggested dosages for off-label use in IE are higher than standard dosing (ie, 600 mg every 8 hours). Adjustments for off-labeled dosing should still be based on patient's CrCl (33%–67% reduction recommended).
Dalbavancin	Recommended	None	Half-life approximately 346 hours, dosing for IE not established.
Oritavancin	None	None	Half-life approximately 245 hours, dosing for IE not established.
Telavancin	Required	None	No therapeutic monitoring required for efficacy. Monitor for QTc prolongation and infusion-related reactions.
Streptomycin	Required	None	Used only as synergy (combination therapy) for Gram-positive bacteria if gentamicin resistance. Therapeutic concentrations vary for Gram-negative bacteria Monitor therapeutic concentrations to guide dosage adjustments Target concentrations for synergy: peak 20–35 mcg/mL (20–35 mg/L; 34–60 μmol/L) and trough < 10 mcg/mL (10 mg/L; 17 μmol/L)

[a] Gram-negative bacteria, fungal, or atypical treatments are not listed. It is suggested that an infectious diseases consultation be obtained if a patient has IE caused by one of these organisms due to the complexity and difficulty in managing these patients.

AE, adverse event; CPK, creatinine phosphokinase; CrCl, creatinine clearance.

Antimicrobial Stewardship in IE

Antimicrobial stewardship efforts in relation to IE should focus on recommendations which optimize antimicrobial management, including but not limited to, appropriate selection of empiric and definitive antimicrobial regimens, suggestion for infectious diseases/endocarditis team consultation, and ensuring adequate dosages for selected therapy. Once culture and susceptibility data are (if) available, the stewardship team can work with clinicians to tailor and maximize treatment of the patient. Patients with IE will require a prolonged treatment course; the stewardship team

Table 78–9

Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis for Which Prophylaxis with Dental Procedures Is Reasonable[a]

- Prosthetic cardiac valve or prosthetic material used for cardiac-valve repair
- Previous IE
- Congenital heart disease (CHD)[b]
  - Unrepaired cyanotic CHD, including palliative shunts and conduits
  - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure[c]
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
- Cardiac transplantation recipients who develop cardiac valvulopathy

[a] *All dental procedures* involving manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa are reasonable indications for prophylaxis in patients with the conditions listed above.

[b] Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.

[c] Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.

Data from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. Circulation. 2007;116:1736–1754. ©2007, American Heart Association, Inc.

can provide or assist in monitoring serum antibiotic concentrations (if patient is receiving vancomycin or an aminoglycoside) and pertinent laboratory values associated with side effects (such as creatine kinase increase with daptomycin and decreased platelets with linezolid). For institutions that have an "endocarditis team," a clinical pharmacist (infectious diseases or stewardship pharmacist preferred) should assist in managing therapy throughout treatment. Additionally, the stewardship team should be aware of potential patients requiring prophylaxis for IE and provide guidance/recommendations for antimicrobial coverage prior to inpatient surgical procedures or provide education on IE prevention prior to discharge. Other preventative measures, such as vaccinations, utilized for many infectious diseases have been investigated against organisms commonly causing IE; however, to date, none have come to fruition.[18]

OUTCOME EVALUATION

KEY CONCEPT Monitoring for successful therapy is critical for this serious infection to prevent complications, prevent development of resistance, and decrease mortality. Routine assessment of clinical signs and symptoms, as well as laboratory tests (eg, repeat blood cultures), microbiologic testing, and serum drug concentrations (if appropriate), must be performed.

Resolution of signs and symptoms typically occurs within a few days to a week in most cases. Monitor the patient's temperature daily for febrile episodes, as well as other vital signs, with expected normalization of values within 2 to 3 days of antimicrobial therapy initiation.[1] Persistent signs or symptoms could be indicative of inadequate treatment or source control and/or development of resistance.

Blood cultures are the primary laboratory evaluation to assess response to therapy. Collect and monitor blood cultures every 24 to 48 hours until bacteremia is cleared; with appropriate treatment, they should become negative within 3 to 7 days. Perform additional blood cultures if the patient appears unresponsive to current therapy or upon treatment completion to confirm eradication of infection. Evaluate all susceptibility testing reports to assess appropriateness of antimicrobial therapy.

Monitor the patient for potential development of side effects based on selected therapy. For patients receiving vancomycin and/or an aminoglycoside, collect and assess appropriate serum concentrations based on the causative organism, adjusting the dosage regimen if necessary. Refer to treatment and dosage consideration Tables 78–5 to 78–8 for therapeutic target goals.

Educate patients on the necessity of prophylactic antibiotics prior to major dental treatments or GI/GU surgeries to prevent

Table 78–10

Prophylactic Regimens for Dental Procedure

		Regimen: Single Dose 30–60 Minutes Before Procedure	
Situation	**Agent**	**Adults**	**Children**
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medications	Ampicillin or cefazolin or ceftriaxone	2 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin[a,b] or clindamycin or azithromycin or clarithromycin	2 g 600 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medications	Cefazolin or ceftriaxone[b] or clindamycin	1 g IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV

[a] Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.

[b] Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

IM, intramuscular.

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Patient Care Process

Collect Information:

- Perform a medication history review for prescription and nonprescription medications and herbal or dietary supplements.
- Determine allergies, including reaction, to medications, food, or material.
- Review medical and surgical history and findings of physical assessment.
- Review medical records and communicate with the patient to ascertain lifestyle habits, preferences and beliefs, goals for health and function, and socioeconomic factors affecting access to medication or other components of therapy.

Assess the Information:

- Determine whether patient has any risk factors for the development of IE utilizing modified Duke criteria (see Table 74–4).
- Review and document pertinent patient social, medical, and surgical history associated with development or identification of causative organisms of IE.
- Review physical exam and vital signs, relevant laboratory tests (ie, white blood cell count, differential, blood cultures), and diagnostic imaging (echocardiogram) as indicators of diagnosis and severity of the IE infection.
- Assess the empirical pharmacologic regimen for appropriate coverage of likely causative organisms, patient allergies, and potential adverse effects (eg, nephrotoxicity).
- Determine whether selected regimen is on institution's formulary. If not, is there a formulary alternative? If no alternative, is there anything specific to institution to utilize nonformulary agent?
- Determine if patient is receiving the appropriate therapy based on culture and sensitivities.

Develop a Care Plan:

- Once blood culture identification/susceptibility is reported, determine if patient is on appropriate antimicrobial therapy.
- Recommend change in therapy if the pathogen is not susceptible to current antimicrobial(s) or if patient not improving on current therapy (ie, resolution of bacteremia, afebrile, and decreasing white blood cell count).
- Determine whether drug doses are optimal for treatment but minimize development of adverse effects.
- Determine appropriate duration of treatment (timeframe based from first negative blood culture).
- Determine if lifestyle modifications are appropriate.

Implement the Care Plan:

- Educate the patients about the selected antimicrobial therapy and dosing, expected duration, possible adverse effects, and how to self-monitor for worsening of infection and adverse effects.
- Address any patient concerns about IE and its management.
- Discuss importance of lifestyle modifications if applicable.
- Determine if outpatient therapy is required and choose appropriate alternative if inpatient therapy not feasible based on frequency of dosages, lack of monitoring, or cost/insurance limitations.

Follow-Up: Monitor and Evaluate:

- Review medication efficacy and safety. Is the infection resolving? Is patient experiencing any adverse effects from their antimicrobial(s)? Are there any potential drug–drug interactions from this medication?
- Follow up with blood cultures (not needed unless clinical signs/symptoms of infection still present) and physical exam. Review medical history and any other pertinent laboratory tests and results of other diagnostic tests.
- Monitor vital signs/symptoms for return to baseline during each clinic follow-up over the duration of therapy. If continued to be abnormal, reassessment of therapy/other diagnostic testing is necessary.
- Once the infection has resolved, educate the patient on importance preventative antibiotics prior to future invasive dental procedures and to inform all healthcare providers including dentists of history of having IE.

recurrent infections. This is critical in patients with risk factors that predispose them to developing IE, such as prosthetic heart valves, other valvular defects, or previous IE.

Develop a follow-up plan to determine whether the patient has achieved a cure, which includes a clinical evaluation of signs/symptoms, repeat blood cultures, and possibly a repeat echocardiogram. Assess the patient for any adverse events throughout treatment course and at follow-up. Perform follow-up visit within a few weeks after the completion of therapy.

Abbreviations Introduced in This Chapter

AHA	American Heart Association
AIN	Allergic interstitial nephritis
AUC	Area under the concentration–time curve
CFU	Colony-forming units
CKD	Chronic kidney disease
CoNS	Coagulase-negative staphylococci
CNS	Central nervous system
CT	Computed tomography
CTA	Computed tomography angiography
ESR	Erythrocyte sedimentation rate
GI	Gastrointestinal
GU	Genitourinary
IE	Infective endocarditis
MIC	Minimum inhibitory concentration
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *S. aureus*
MSSA	Methicillin-sensitive *S. aureus*
NBTE	Nonbacterial thrombotic endocarditis
NVE	Native-valve endocarditis
PD	Pharmacodynamic
PET	Positron emission tomography

PK	Pharmacokinetic
PRP	Penicillinase-resistant penicillins (eg, nafcillin and oxacillin)
PVE	Prosthetic-valve endocarditis
TEE	Transesophageal echocardiogram
TPN	Total parenteral nutrition
TTE	Transthoracic echocardiogram
VRE	Vancomycin-resistant enterococci
WBC	White blood cell

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Tuberculosis

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Assess risk factors for developing an active tuberculosis (TB) infection.
2. Design appropriate antimicrobial regimens for the treatment of latent TB infection.
3. Design an appropriate therapeutic plan for a patient with active TB disease.
4. Distinguish among the diagnostic tests used for patients potentially infected with TB.
5. Determine appropriate monitoring parameters to evaluate the efficacy and safety of an active drug regimen for active TB.
6. Describe potential adverse reactions associated with TB medications.
7. Select patients for whom therapeutic drug monitoring (TDM) may be valuable and identify the necessary laboratory monitoring parameters for patients on anti-TB medications.

INTRODUCTION

Tuberculosis (TB) is one of the leading causes of death from infectious origin worldwide. In 2018, there were about 10 million new cases and an estimated 1.5 million deaths from TB reported.[1] Most deaths are preventable if appropriate access to health care for both diagnosis and treatment is available.

EPIDEMIOLOGY AND ETIOLOGY

KEY CONCEPT Roughly one-fourth of the world's population is infected with tuberculosis; TB and drug resistance is increasing in many areas.[1] The majority of cases worldwide are found in South-East Asia (44%) and Africa (24%). In the United States, about 13 million people have latent TB infection (LTBI), evidenced by a positive skin test (**purified protein derivative** [PPD]) with no concurrent signs or symptoms of disease. PPD is an antigen derived from *Mycobacterium tuberculosis* used to determine the presence of an immune response in patients with previous exposure.

In 2019, 8920 new TB cases were reported in the United States; a 1.1% decline from 2018.[2] The most recent data from the Centers for Disease Control and Prevention (CDC) indicate that TB deaths in the United States have decreased from 2016 by 2.5% in 2017.[3] (For details, visit the CDC website at www.cdc.gov/nchstp/tb.) TB is most prevalent in large urban areas and is exacerbated by crowded living conditions.[2] Those in close physical contact with patients that have active pulmonary TB are most likely to become infected.[2,3] TB cases in California, New York, Florida, and Texas accounted for over 40% of all cases in 2018.[2] These higher numbers may reflect the high-immigration rates into these states.[2] Mexico, the Philippines, Vietnam, India, and China account for the largest numbers of these immigrants.[2] People of Asian descent represent the largest proportion of TB cases as reported by race/ethnicity accounting for 35.3% of cases reported in 2018 followed by Hispanics (29%) non-Hispanic Black patients (19.9%), and non-Hispanic White patients (11.9%). When origin of birth is considered, reported cases among US-born persons are highest among non-Hispanic Black patients (35.7%) followed by non-Hispanic White patients (30.3%); and among non-US-born persons cases are highest among Asians (48.1%) followed by Hispanics (32%).[2,3] TB is more common among men and in those that are 25 to 44 years of age.[3]

Once infected, a person's lifetime risk of developing active TB is about 10%, with about half this risk during the first 2 years.[2-4] However, this risk is elevated in young children, the elderly, and immunocompromised patients. KEY CONCEPT Human immunodeficiency virus (HIV) is the most important risk factor for active TB because the immune deficit prevents patients from containing the initial infection.[1-4] HIV-infected patients with *M. tuberculosis* infection are roughly 100 times more likely to develop active TB than normal hosts.[1,3,4]

Etiology

TB is caused by *M. tuberculosis*, a rod-shaped thin aerobic bacterium. It presents either as LTBI or as progressive active disease.[4] The latter typically causes progressive destruction of the lungs, leading to death in most patients who do not receive treatment. *M. tuberculosis* are acid-fast bacilli (AFB). Acid-fast organisms are characterized by wax-like, nearly impermeable cells walls, which often do not stain with Gram stain and cannot be decolorized by acid alcohol. The cell wall contains a high amount of mycolic acids, long-chain fatty acids, and cell wall lipids that make the wall difficult to attack with conventional antibiotics. The acid-fast stain is a differential stain used to identify acid-fast organisms.

PATHOPHYSIOLOGY

Primary Infection

KEY CONCEPT *M. tuberculosis* is transmitted from person to person by coughing or by any other aerosol-producing activities such as sneezing.[4,5] This produces small particles called "droplet nuclei" that are suspended in the air for long periods of time. Primary infection usually results from inhaling droplet nuclei that contain *M. tuberculosis*.[4,5] The progression to clinical disease depends on three factors: (a) the number of *M. tuberculosis* organisms inhaled (infecting dose), (b) the virulence of these organisms, and (c) the host's cell-mediated immune response.[4,5] If pulmonary macrophages inhibit or kill the bacilli, the infection is aborted.[5] If not, *M. tuberculosis* eventually spreads throughout the body through the bloodstream.[4,5] *M. tuberculosis* most commonly infects the posterior apical region of the lungs, where conditions are most favorable for its survival.

T lymphocytes become activated over the course of 3 to 4 weeks, producing interferon-γ (IFN-γ) and other cytokines. These stimulate microbicidal macrophages to surround the tuberculous foci and form **granulomas** to prevent further spread.[5] A granuloma is a nodular aggregation of mononuclear inflammatory cells formed when the immune system attempts to wall off foreign substances. At this point, the infection is largely under control, and bacillary replication falls off dramatically. Any remaining mycobacteria are believed to reside primarily within granulomas or within macrophages that have avoided detection and lysis, which account for the occurance of latent TB. Over 1 to 3 months, tissue hypersensitivity occurs, resulting in a positive PPD.[4,5] Approximately 95% of individuals with an intact immune system will enter into this latent phase. **KEY CONCEPT** Progressive primary disease occurs in roughly 5% of patients, especially children, the elderly, and immunocompromised patients.[6,7] This presents as a progressively worsening pneumonia and frequently spreads, leading to meningitis and other severe forms of TB, often before positive skin test (often called PPD) or IFN-γ release assays (IGRAs).[6]

Reactivation Disease

About 10% of infected patients develop reactivation TB, with half occurring in the first 2 years after infection.[4] Reactivation TB results when a previously "dormant" focus is reactivated and causes disease. Progression involves the development of caseating granulomas as a result of a vigorous immune response. Liquefaction then leads to local spread, and a pulmonary cavity results. This provides a portal to the airways and subsequently ambient air that enhances person-to-person spread. Bacterial counts in the cavities can be as high as 10^8/mL (10^{11}/L) of cavitary fluid.[4,5] Prior to the chemotherapy era, pulmonary TB usually was associated with hypoxia, respiratory acidosis, and eventually death related to asphyxia; a fate that remains all too common in poor countries where patients do not have access to effective therapy.

Extrapulmonary and Miliary Tuberculosis

Caseating granulomas, regardless of location, can spread tubercle bacilli and cause symptoms.[4] Because of muted or altered symptoms, the diagnosis of TB is difficult and often delayed in immunocompromised hosts.[4,5] HIV-infected patients may present with only extrapulmonary TB, which is uncommon in HIV-negative persons. A widely disseminated form of the disease called *miliary TB* can occur, particularly in children and immunocompromised hosts. This can be rapidly fatal and immediate treatment is required.[5]

Influence of HIV Infection on Pathogenesis

As CD4$^+$ lymphocytes multiply in response to the mycobacterial infection, HIV multiplies within these cells and selectively destroys them, gradually eliminating the TB-fighting lymphocytes.[7,8] HIV-positive patients often have negative PPD and fail to produce **cavitary lesions**, and fever may be absent. Cavitary lesions are present in a wide variety of pathological processes involving the lung and are observed radiographically as gas or fluid filled areas of the lung in the center of a nodule. Approximately 5% of HIV-infected patients with pulmonary TB who are not being treated effectively with antiretroviral medications will have positive results on acid-fast staining, yet have a normal chest radiograph. Patients coinfected with HIV and TB have a substantially higher risk of early mortality compared with HIV-negative patients with TB.[9,10]

CLINICAL PRESENTATION AND DIAGNOSIS

Culture and Susceptibility Testing

KEY CONCEPT Microscopic examination of infected material ("**sputum smear**" of material on a glass slide) is the most rapid and readily available test to detect AFB in clinical specimens. Three sputum specimens should be collected in patients suspected of pulmonary TB to increase the likelihood of finding AFB. *The sensitivity of the sputum smear is only about 45% and less for HIV-infected patients, so culture-based TB diagnosis is the current gold standard.*[4,11,12] Unfortunately, culture is much slower due to the roughly 20-hour doubling time of the bacilli. Furthermore, microscopic examination for AFB through sputum smear alone cannot determine which of over 100 mycobacterial species is present.[13] Depending on the presence of epidemiological risk factors, the usual practice is to isolate the patient and treat empirically until the presence of *M. tuberculosis* is confirmed by nucleic acid amplification (NAA) or positive culture.

Antimicrobial susceptibility testing is essential for directing proper treatment. One common method utilizing solid growth media, known as the *proportion method,* takes 3 to 8 weeks to produce results. Growth in liquid media is faster and can detect live mycobacteria in about 2 weeks.[11,12] Rapid-identification tests include NAA tests utilizing the polymerase chain reaction (PCR)[13-15]. NAA tests have been approved for use in the United States to detect *M. tuberculosis* in respiratory secretions. These tests are highly sensitive and specific for smear-positive patients and somewhat less sensitive in smear-negative patients but only need as few as 1 to 10 organisms/mL (10^3–10^4/L) to give a positive result.[13-16] The Cepheid MTB/RIF Assay performed on the Xpert System is a qualitative test designed for the rapid detection of *M. tuberculosis* and rifampin resistance.[17,18] Results are available in hours and the time for diagnosis and treatment initiation can be significantly shortened. These tests are particularly useful in limited resource settings.[19] DNA fingerprinting is performed to assist surveillance programs and contact investigations. Various techniques are employed including restriction fragment length polymorphism (RFLP) analysis, spoligotyping, and mycobacterial interspersed repeat units. These techniques exploit conserved fragments in the TB genome that change gradually over time and allow investigators to determine if strains are related to one another. Strains that are related to one another are referred to as clusters. Clusters generally indicate recent transmission and are then targeted for interventions by TB programs.[20,21]

Clinical Presentation

Fever, night sweats, weight loss, fatigue, and a productive cough are the classic symptoms of TB.[4,5] Onset may be gradual, and the diagnosis is easily missed if the symptoms are muted due to compromised immune system.[4,5] Progressive pulmonary disease leads to cavitary lesions visible on X-ray. Physical examination is nonspecific but may be consistent with pneumonia. Dullness to chest percussion, rales, and increased vocal **fremitus** may be observed on examination. Laboratory data often are uninformative, but a modest increase in the white blood cell (WBC) count with a lymphocytic predominance can be seen. Frequently, however, the physical examination is largely unremarkable.

Atypical presentations are common in patients coinfected with HIV.[4,5,9] Symptoms for these patients range from classic pulmonary to muted and nonspecific. Extrapulmonary TB typically presents either as a slowly progressive decline in the effected organ's function or commonly as a mass lesion. Lymphadenopathy is relatively common.[5,6] Abnormal behavior, headaches, or convulsions suggest tuberculous meningitis, although other acute central nervous system (CNS) infections must be excluded.[4,5]

Multidrug-resistant TB (MDR-TB) remains a public health concern. In 2017, the WHO estimated approximately 600,000 cases of TB worldwide with resistance to rifampicin, of which 82% had MDR-TB.[22] There are a number of laboratory tools available for the diagnosis of MDR-TB, including phenotypic culture-based drug susceptibility testing as well as molecular methods.[23] The Xpert MTB/RFI assay was approved by the Food and Drug Administration (FDA) in 2013. Other assays have not yet been approved for use in the United States, but several validated tests (line-probe assays, molecular beacons, and DNA sequencing) are being used. Molecular testing may be useful in patients with a high risk of having MDR-TB, very ill patients who are not improving with standard first-line therapy, and for outbreak investigations.[24]

The Elderly

Positive PPD test, fevers, night sweats, sputum production, or hemoptysis may be absent in the elderly population, making TB hard to distinguish from other bacterial and viral infections, as well as chronic lung diseases.[4,23] In contrast, mental status changes are twice as common in the elderly, and CNS disease must be considered when TB is entertained. Mortality is six times higher in the elderly, in part owing to delays in diagnosis.[4,23,25]

Children

TB in children may present as atypical bacterial pneumonia and often involves the lower and middle lobes.[4,6,26] Extrapulmonary TB is more common in children.

Prevention

The Bacille Calmette–Guérin (BCG) is a vaccine made from strains of tubercle bacilii and is used to produce immunity against human TB. It is administered in countries where TB remains common and appears to stimulate children's immune systems to ward off the most serious forms of the disease. In fact, BCG is most effective in reducing infant mortality from TB meningitis and miliary disease. BCG does not block infection, and these same children often experience reactivation TB as young adults.[26]

Skin Testing

TB skin testing with PPD (commercially available as Tubersol or Aplisol) is one of the oldest diagnostic tests still in clinical use.[4,6,8] Also known as the tuberculin skin test, the product is injected into the skin (not subcutaneously) with a fine (27-ga) needle, a technique referred to as the Mantoux method and produces a small, raised, blanched wheal to be read by an experienced professional in 48 to 72 hours. The chance of a false-negative result is increased when the patient is immunosuppressed. The CDC does not recommend the routine use of anergy panels to determine if a patient's T-cell immune system reacts to common antigens.[8,27]

Criteria for interpretation are listed in Table 79–1 and the summary of recommendations is found in Table 79-2.[6]

The "booster effect" occurs in patients who do not respond to an initial PPD test but show a positive reaction if retested 1 to

Table 79–1

Criteria for Tuberculin Positivity, by Risk Group[6]

Reaction ≥ 5 mm of Induration	Reaction ≥ 10 mm of Induration	Reaction ≥ 15 mm of Induration
HIV-infected persons	Recent immigrants (ie, within the last 5 years) from high-prevalence countries	Persons with no risk factors for TB
A recent contact of a person with TB disease	Injection drug users	
Fibrotic changes on chest radiograph consistent with prior TB	Residents and employees[a] of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with AIDS, and homeless shelters	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of 15 mg/day or more of prednisone for 1 month or longer, taking TNF-α antagonists)[b]	Mycobacteriology laboratory personnel, persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders, other specific malignancies, gastrectomy, and jejunoileal bypass Children younger than 5 years of age or infants, children, and adolescents exposed to adults at high risk	

Interpretation of IGRA Results

The interpretation of IGRAs is based on the amount of IFN-γ, in T-SPOT TB. Laboratories should provide both the qualitative and quantitative results.

- Qualitative results are reported positive, negative, indeterminate, or borderline.
- Quantitative results are reported as numerical values that include a response to the TB antigen and two controls, nil and mitogen. Quantitative results may be useful for clinical decision-making in individual cases, in combination with risk factors.

[a] For persons who are otherwise at low risk and are tested at the start of employment, a reaction of 15 mm or more of induration is considered positive.

[b] Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

Data from Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: diagnosis of tuberculosis in children and adults. CID. 2017;64(1):111–115.

Table 79–2

Summary of Recommendations for Testing for Latent Tuberculosis Infection (LTBI)

Group	Testing Strategy	Considerations
Likely to be Infected **High** Risk of Progression (TST ≥ 5 mM)	**Adults** **Acceptable:** IGRA or TST Consider dual testing where a positive result from either result would be considered **positive** **Children ≤ 5 years of age** **Preferred:** TST **Acceptable:** IGRA or TST Consider dual testing where a positive result from either would be considered **positive**[a]	Prevalence of BCG vaccination Expertise of staff and/or laboratory Test availability Patient perceptions Staff perceptions Programmatic concerns
Likely to be Infected **Low** to **Intermediate** Risk of Progression (TST ≥ 10 mM)	**Preferred:** IGRA where available **Acceptable:** IGRA or TST	
Unlikely to be Infected (TST >15 mM)	**Testing for LTBI is not recommended** **If necessary:** **Preferred:** IGRA where available **Acceptable:** IGRA or TST **For serial testing:** **Acceptable:** IGRA or TST Consider repeat or dual testing where a negative result from either would be considered **negative**[b]	

[a] Performing a second diagnostic test when the initial test is negative is a strategy to increase sensitivity.

[b] Performing a confirmatory test following an initial positive result is based upon both the evidence that false positive results are common among individuals who are likely to be infected with TB. A second test is presumed to help identify false-positive results.

Modified from Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: diagnosis of tuberculosis in children and adults. CID. 2017;64(1):111–115.

3 weeks later.[6,24,27] In order to reduce the likelihood that a boosted reaction is misinterpreted as a new infection, the two-step method is recommended at the time of initial testing for individuals such as health care workers or nursing home residents who may be tested periodically. If the first PPD test is negative, repeat the test in 1 to 3 weeks. If the second test is positive, it is most commonly a boosted reaction, and the person should be classified as previously infected.

Newer Diagnostic Tests

The development of blood tests and IGRAs that have replaced the PPD test in the United States for individuals 5 years and older who meet the following criteria: likely to be infected with *M. tuberculosis*; low or intermediate risk of disease progression; testing for LTBI is warranted; and have history of BCG vaccine or unlikely to return to have PPD read.[6,27] These newer methods measure the release of IFN-γ in blood in response to TB antigens. The two TB blood tests approved in the United States are: the QuantiFERON-TB Gold In-Tube test (QFT-GIT) and the T-SPOT TB test (T-Spot).[27] The sensitivity of IGRAs ranges from 80% to 90%, and specificity of 95% for diagnosis of latent TB. Recent evidence suggests that prior placement of PPD can boost an IGRA. The boosting effect may wane after several months.[8,27] The IGRAs do not cause the booster phenomenon and are unaffected by BCG or infection by most non-TB mycobacteria. Results of the IGRAs are available in less than 24 hours, versus the 3 days required for the traditional PPD test. Data are limited for use of IGRAs in children younger than 5 years of age, persons recently exposed to TB, health care workers, and immunodeficient patients.[27] KEY CONCEPT The CDC has endorsed the use of IGRA tests in all circumstances where the PPD is used. IGRAs are approved for the diagnosis of LTBI in HIV-infected patients, but sensitivity is diminished.[27] Testing with both PPD and IGRA generally is not recommended but may be useful in certain situations (eg, if the initial PPD test is negative and the risk for infection, clinical suspicion, or the risk for poor outcome is high; or if the initial PPD test is positive and additional evidence of infection is required; or the patient has a low risk of infection or progression).[27,28] IGRAs, and the PPD, should not be used to rule in or rule out the diagnosis of active TB disease.[28]

Patient Encounter Part 1

HPI: RG is a 46-year-old man who presents to the medical clinic complaining of a 2-month history of a persistent cough that has become productive over the past 3 weeks. He also complains of fever, night sweats, malaise, and a 6-kg (13-lb) weight loss over the past 2 months.

PMH: HIV positive; Hypertension (HTN) × 5 years—not well controlled.

FH: Mother, age 82, alive and well, lives with RG. Father died of alcoholic liver disease 10 years ago. One brother, age 53, lives with the patient, currently undergoing chemotherapy treatment for lung cancer.

SH: Born and raised in Florida. Single. He occasionly smokes marijuana and drinks 1 to 2 glasses of wine daily. He owns his own import/export business and travels internationally to Central and South America.

Meds: Lisinopril 20 mg daily; amlodipine 5 mg daily; Atripla one daily. Patient reports that he tries to be compliant with his therapies and takes them regularly except when he travels he often forgets to take his medication.

What factors place this patient at increased risk for acquiring TB?

TREATMENT

General Approaches to Treatment

The primary treatment approach is the use of antimicrobials active against *M. tuberculosis*. For LTBI, monotherapy can be used only for patients with evidence of a positive PPD test or positive IGRA in the absence of signs or symptoms of disease. Once active disease is present, typically *four medications* must be used simultaneously from the start treatment.[4,5,8,27] The shortest duration of treatment is 4 months in the unusual case of smear- and culture-negative clinical cases of pulmonary TB, and up to 2 years of treatment may be necessary for advanced cases of MDR-TB.[27,29]

Directly observed treatment (DOT) is a method used to ensure adherence in which patients are directly observed by a health care worker while taking their anti-TB medication.[30] Case management interventions such as patient education, counseling, home visits, integration, and coordination of care with specialists as well as incentives and enablers during treatment of patients with TB disease are also encouraged. These are examples a cost-effective ways to ensure completion of treatment.

Desired Outcomes

Steps should be taken to (a) prevent the spread of TB (respiratory isolation); (b) find where TB has already spread (contact

Patient Encounter Part 2

VS: BP 142/82 mm Hg, P 90 beats/min, RR 18 breaths/min, T 38°C (100.4°F), O_2 sat 82% (0.82) on room air, Wt 51 kg (112 lb), Ht 5′8″ (173 cm)

HEENT: PERRLA; EOMI

Neck: Supple; no lymphadenopathy, bruits, or JVD; no thyromegaly

Chest: Diffuse rhonchi, decreased breath sounds on left

CV: RRR; no murmurs, rubs, gallops

Abd: (+) BS; nontender, nondistended

Neuro: A&O × 3

Laboratory Values (US Units)

Lab	Normal	Lab	Normal
Na 139 mEq/L	135–145 mEq/L	Hgb 13.5 g/dL	13.5–17.5 g/dL
K 3.9 mEq/L	3.5–5 mEq/L	Hct 40%	40%–54%
Cl 98 mEq/L	95–105 mEq/L	RBC 4.6×10^6 mm^3	$4.6–6.0 \times 10^6$ mm^3
CO_2 38 mEq/L	22–30 mEq/L	WBC 4.0×10^3 mm^3	$4.0–10 \times 10^3$ mm^3
BUN 20 mg/dL	5–25 mg/dL	PMN 51%	50%–65%
SCr 1.0 mg/dL	0.8–1.3 mg/dL	Lymph 25%	25%–35%
Gluc 150 mg/dL	< 140 mg/dL	Mono 2%	2%–6%
AST 36 IU/L	5–40 IU/L		
ALT 28 IU/L	5–35 IU/L	CD4 count 350 cells/mm^3	>500 cells/mm^3
Tbili 1 mg/dL	0.1–1.2 mg/dL		
PT 10 seconds	10–12 seconds		

Laboratory Values (SI Units)

Lab	Normal	Lab	Normal
Na 139 mmol/L	135–145 mmol/L	Hgb 135 g/L or 8.38 mmol/L	135–175 g/L or 8.38–10.86 mmol/L
K 3.9 mmol/L	3.5–5 mmol/L	Hct 0.40 vol fraction	0.40–0.54 vol fraction
Cl 98 mmol/L	95–105 mmol/L	RBC 4.6×10^{12}/L	$4.6–6.0 \times 10^{12}$/L
CO_2 38 mmol/L	22–30 mmol/L	WBC 4.0×10^9/L	$4.0–10.0 \times 10^9$/L
BUN 7.1 mmol/L	1.8–8.9 mmol/L	PMN 0.51	0.50–0.65
SCr 88 μmol/L	71–115 μmol/L	Lymph 0.25	0.25–0.35
Gluc 8.3 mmol/L	< 7.8 mmol/L	Mono 0.02	0.02–0.06
AST 0.60 μkat/L	0.08–0.67 μkat/L		
ALT 0.47 μkat/L	0.08–0.58 μkat/L		
Tbili 17.1 μmol/L	1.7–20.5 μmol/L		
PT 10 seconds	10–12 seconds		

CXR: Bilateral upper lobe infiltrates with cavitary lesions on left; small left pneumothorax

Clinical Course: The patient was admitted and placed on respiratory isolation. Three separate sputum AFB stain specimens were reported to contain 3+ AFB. IFN-γ was sent and a PPD tuberculin skin test was placed. Sputum samples were sent for AFB, fungi, and bacterial cultures and sensitivities. IFN-γ test resulted positive and after 48 hours, the PPD skin test was read as a 7-mm area of induration.

Assessment: Active pulmonary TB; pneumothorax.

Which signs, symptoms, and other findings are consistent with active TB infection?

How might HIV-positive patients present differently as compared to HIV-negative patients?

investigation); and (c) return the patient to a state of normal weight and well-being. Items (a) and (b) are performed by public health departments. Clinicians involved in the treatment of TB should verify that the local health department has notified of all new cases of TB.[8]

Pharmacologic Therapy

Treating LTBI

KEY CONCEPT The CDC and National Tuberculosis Controllers Association recommend rifampin-based regimens for the treatment of LTBI presumed to be susceptible to isoniazid or rifampin.[31] The regimens include rifampin daily for 4 months, rifampin and isoniazid daily for 3 months, or rifapentine and isoniazid once weekly for 3 months. In some instances, isoniazid may be used as an alternative for a 6- or 9-month duration of treatment. Isoniazid monotherapy regimens are associated with lower treatment completion and more adverse effects. However, isoniazid monotherapy is still the preferred regimen for the treatment of LTBI in patients with HIV infection.[32] Pyridoxine (25–50 mg/day in adults) can reduce the risk of peripheral neuropathy associated with isoniazid.[8,31,33] Treatment of LTBI reduces a person's lifetime risk of active TB from about 10% to about 1%.[8,28,31] The combination of pyrazinamide and rifampin is no longer recommended.[31,34,35] Most isoniazid resistance cases are reported amongst non-US-born individuals, and in 2018 the multidrug resistance rate reported in the United States was 1.5%.[2,3] When resistance to isoniazid and rifampin is suspected, there is no regimen proven to be effective.[33] Options for treatment of drug-resistant TB are based on suspected patterns for drug resistance and may include a fluoroquinolone.[36] Note that patients with LTBI are not infectious and there is no isolate on which to perform susceptibility testing. Susceptibility patterns must be inferred based on the most likely source of infection.

Treating Active Disease

In the United States, TB patients can receive free treatment through local health departments. Treating active TB disease requires combination chemotherapy. **KEY CONCEPT** A four-drugs treatment regimen is started with the first-line drugs for the treatment of active disease: isoniazid, rifampin, pyrazinamide, and ethambutol. Isoniazid and rifampin should always be included in the medication regimen to prevent potential drug resistance.[8,33] Drug susceptibility testing should be done on the initial isolate for all patients.[8,33] Susceptibility testing should be repeated if the patient remains culture-positive 8 weeks or more into therapy.[29]

The standard TB treatment regimen for susceptible TB is isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for 4 months, for a total of 6 months of treatment.[8,33] Extending the treatment duration to 9 months is recommended for patients at a greater risk of failure and relapse, including those with cavitary lesions on initial chest radiograph and positive cultures at the completion of the initial 2-month phase of treatment, as well as for patients treated initially without pyrazinamide. Ideally, treatment should be continued for at least 6 months from the time that patients convert to a negative culture.[8,33] When the patients' sputum smears convert to negative, the risk of infecting others is greatly reduced, but it is not zero.[33] Such patients can be removed from respiratory isolation if they are responding clinically. The decision to discontinue isolation should be done by medical providers experienced in TB control. Table 79–4 shows the recommended treatment regimens. Daily dosing rather than intermittent dosing is preferred; but intermittent dosing can be considered in patients with low risk of relapse and negative HIV test results. DOT is essential for more difficult to treat patients such as patients who are nonadherent, drug resistant, or with certain comorbidities.[30,34] Doses missed during an intermittent TB regimen decrease the efficacy of the regimen and increase the relapse rate.

Table 79–3

Recommendations for Regimens to Treat Latent Tuberculosis Infection[31]

Preferred Regimens
3 months isoniazid plus rifapentine given once weekly
4 months rifampin given daily
3 months isoniazid plus rifampin given daily

Adjustments to the regimen should be based on susceptibility data.[16,33] Drug resistance should be suspected in patients who have been treated previously for TB. **KEY CONCEPT** If adjustments are needed based on suspected resistance, two or more drugs with in vitro activity against the patient's isolate and that were not used previously should be added to the regimen.[16,33] Due to the risk of further drug resistance, it is critical to avoid adding only a single drug to a failing regimen.[29,33] When isoniazid and rifampin cannot be used, either because of drug resistance or intolerance, treatment durations typically become 2 years or more, regardless of immune status.[16,33] TB specialists should be consulted regarding cases of drug-resistant TB, or whenever treatment is uncertain.[33] Therapeutic drug monitoring (TDM) can direct dosing for such patients.[37] One of the proven reasons for treatment failure is malabsorption of orally administered drugs.[33,37]

Special Populations

Treatment for extrapulmonary TB is the same as for pulmonary disease. Unless contraindicated, corticosteroid treatment also should be added to the treatment regimen of TB meningitis and pericarditis. Patients with CNS TB usually are treated for 12 months.[4,33] Isoniazid and pyrazinamide cross the blood–brain barrier well, but rifampin and ethambutol tend to have low CNS penetration. TB osteomyelitis typically is treated for 9 months, occasionally with surgical débridement.[4,33] TB of the soft tissues can be treated with conventional regimens.[4,33] Patients with diabetes mellitus have been shown to have low 2-hour peak serum concentrations of antimicrobials. TDM can be considered to optimize treatment response.[38] TB in children may be treated with regimens similar to those used in adults, typically for 6 months. Some physicians extend treatment to 9 months for infants, and for those who are slow to respond or who have severe disease.[6,7,33] Pediatric doses of isoniazid and rifampin on a milligram-per-kilogram basis are higher than those used in adults (Table 79–5).[33] Pregnant women receive the usual treatment of isoniazid, rifampin, and ethambutol for 9 months.[29,33] Pyrazinamide has not been studied in large numbers of pregnant women, but anecdotal data suggest that it may be safe.[33,39] The clinician should always determine risk versus benefit and determine if a drug is safe to administer in pregnancy.

Human Immunodeficiency Virus

HIV-infected adults may receive a 6-month total treatment regimen with isoniazid, a rifamycin, pyrazinamide, and ethambutol for the first 2 months followed by isoniazid and a rifamycin for 4 months.[33,40] Some clinicians recommend extending treatment to 9 months. Rifabutin is used to reduce drug interactions with protease inhibitors and some nonnucleoside reverse transcriptase inhibitors. Integrated antiretroviral therapy (ART) is superior

Table 79–4

Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms[33]

	Initial Phase		Continuation Phase		
Regimen	**Drugs**	**Interval and Doses[a] (Minimal Duration)**	**Drugs[b]**	**Interval and Doses[b] (Minimal Duration)**	**Comments[c,d]**
1	Isoniazid Rifampin Pyrazinamide Ethambutol	7 days/week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks)[c]	Isoniazid/Rifampin	7 days/week for 126 doses (18 weeks) or 5 days/week for 90 doses (18 weeks)[c]	This is the preferred regimen for patient with newly diagnosed pulmonary tuberculosis
2	Isoniazid Rifampin Pyrazinamide Ethambutol	7 days/week for 56 doses or 5 days/ week for 40 doses (8 weeks)	Isoniazid/Rifampin	Three times weekly for 54 doses (18 weeks)[d]	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve
3	Isoniazid Rifampin Pyrazinamide Ethambutol	Three times weekly for 24 doses (8 weeks)	Isoniazid/Rifampin	Three times weekly for 54 doses (18 weeks)	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance
4	Isoniazid Rifampin Ethambutol Pyrazinamide	7 days/week for 14 doses then twice weekly for 12 doses[e]	Isoniazid/Rifampin	Twice weekly for 36 doses (18 weeks)	Do not use twice weekly regimens in HIV-infected patients or patients with smear positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which in inferior

[a] Other combinations may be appropriate in certain circumstances; additional details are provided in the section "Recommended Treatment Regimens."

[b] When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice. DOT should be used when drugs are administered < 7 days/week.

[c] Based on expert opinion, patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week) continuation phase.

[d] Pyridoxine (vitamin B6), 25–50 mg/day, is given with INH to all persons at risk of neuropathy (eg, pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.

[e] Alternatively, some US tuberculosis control programs have administered intensive-phase regimens 5 days/week for 15 doses (3 weeks), then twice weekly for 12 dose.

DOT, directly observed therapy; EMB, ethambutol; HIV, human immunodeficiency virus; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin.

Data from Centers for Disease Control and Prevention. Treatment of Tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America. CID. 2016:63;853–867.

to sequential ART in the treatment of naïve HIV-seropositive patients with TB.[41] The optimal timing of integrated HIV and TB therapy is influenced by the patient's immune status.[41] It is recommended to start integrated ART therapy 2 to 8 weeks after initiating anti-TB therapy in patients with CD4 cell counts less than 50/mm^3.[41] TB-HIV experts should manage such patients. Highly intermittent regimens (twice or once weekly) are not recommended for HIV-positive TB patients.[33,40] Some patients with acquired immunodeficiency syndrome (AIDS) malabsorb their oral medications, and drug interactions are common. Thus, TDM may be useful in these cases.[29,33,37]

For complete recommendations on management of TB and HIV visit the CDC website: www.cdc.gov/tb/publications/guidelines/HIV_AIDS.htm.

▶ *Multidrug-Resistant TB*

MDR-TB is caused by *M. tuberculosis* that is resistant to at least isoniazid and rifampin. If drug-resistant TB is suspected, the empiric regimen should be modified based on patterns of suspected resistance. Once susceptibilities are confirmed, regimens can be modified appropriately. Five drugs are recommended during the initial phase of treatment followed by four drugs in the continuation phase.[42] Patients with MDR-TB are at a high risk of failure and should be treated by specialists or centers with experience treating drug-resistant TB. For effective treatment of MDR-TB a 5 to 7 month intensive phase after culture conversion is recommended followed by a 15- to 21-month total treatment duration.[42] Even longer durations are recommended for patients with extensively drug-resistant TB (XDR-TB). Of note, the WHO recommendations differ slightly with regard to treatment durations. The treatment of MDR-TB is evolving with the introduction of the "BPaL" regimen, consisting of bedaquiline (which has a partially active M2 metabolite), pretomanid, and linezolid for 6 months. As new drugs are approved, MDR-TB treatments will be revised.

▶ *Renal Failure*

Isoniazid and rifampin usually do not require dose modification in renal failure.[29] Pyrazinamide and ethambutol typically are

Table 79–5

Antituberculosis Drugs for Adults and Children[33]

Drug	Daily Doses[a,b,c]	Adverse Effects	Monitoring
Isoniazid	*Adults*: 5 mg/kg *Children*: 10–15 mg/kg	Asymptomatic elevation of aminotransferases, clinical hepatitis, fatal hepatitis, peripheral neurotoxicity, CNS system effects, lupus-like syndrome, hypersensitivity, monoamine poisoning, diarrhea	LFT monthly in patients who have preexisting liver disease or who develop abnormal liver function that does not require discontinuation of drug Dosage adjustments may be necessary in patients receiving anticonvulsants or warfarin
Rifampin[d]	*Adults*: 10 mg/kg *Children*: 10–20 mg/kg	Cutaneous reactions, GI reactions (nausea, anorexia, abdominal pain), flu-like syndrome, hepatotoxicity, severe immunologic reactions, orange discoloration of bodily fluids (sputum, urine, sweat, tears), drug interactions owing to induction of hepatic microsomal enzymes	Rifampin causes many drug interactions. For a complete list of drug interactions and effects, refer to CDC website: www.cdc.gov/nchstp/tb/tb
Rifabutin[d]	*Adults*: 5 mg/kg *Children*: Appropriate dosing unknown	Hematologic toxicity, uveitis, GI symptoms, polyarthralgias, hepatotoxicity, pseudojaundice (skin discoloration with normal bilirubin), rash, flu-like syndrome, orange discoloration of bodily fluids (sputum, urine, sweat, tears)	Drug interactions are less problematic than rifampin
Rifapentine[d]	*Adults*: 10 mg/kg (continuation phase) dosed weekly *Children*: The drug is not approved for use in children < 12 yr	Similar to those associated with rifampin	Drug interactions are being investigated and are likely similar to rifampin
Pyrazinamide	*Adults*: Based on IBW: 40–55 kg: 1000 mg; 56–75 kg: 1500 mg; 76–90 kg: 2000 mg *Children*: 30–40 mg/kg	Hepatotoxicity, GI symptoms (nausea, vomiting), nongouty polyarthralgia, asymptomatic hyperuricemia, acute gouty arthritis, transient morbilliform rash, dermatitis	Serum uric acid can serve as a surrogate marker for compliance LFTs in patients with underlying liver disease
Ethambutol[e]	*Adults*: Based on IBW: 40–55 kg: 800 mg; 56–75 kg: 1200 mg; 76–90 kg: 1600 mg *Children*[c]: 15–25 mg/kg	Retrobulbar neuritis, peripheral neuritis, cutaneous reactions	Baseline visual acuity testing and testing of color discrimination Monthly testing of visual acuity and color discrimination in patients taking > 15–20 mg/kg, renal insufficiency, or receiving the drug for > 2 months
Cycloserine[f]	*Adults*: 10–15 mg/kg *Children*: 15–20 mg/kg	CNS effects	Monthly assessments of neuropsychiatric status Serum concentration may be necessary until appropriate dose is established
Ethionamide[g]	*Adults*: 15–20 mg/kg *Children*: 15–20 mg/kg	GI effects, hepatotoxicity, neurotoxicity, endocrine effects	Baseline LFTs Monthly LFTs if underlying liver disease is present TSH at baseline and monthly intervals
Streptomycin	*Adults*[h] *Children*: 15–20 mg/kg	Ototoxicity, neurotoxicity, nephrotoxicity	Baseline audiogram, vestibular testing, Romberg testing and SCr Monthly assessments of renal function and auditory or vestibular symptoms
Amikacin/kanamycin	*Adults*[h] *Children*: 15–20 mg/kg/day	Ototoxicity, nephrotoxicity	Baseline audiogram, vestibular testing, Romberg testing and SCr Monthly assessments of renal function and auditory or vestibular symptoms
Capreomycin	*Adults*[h] *Children*: 15–20 mg/kg	Nephrotoxicity, ototoxicity	Baseline audiogram, vestibular testing, Romberg testing and SCr Monthly assessments of renal function and auditory or vestibular symptoms Baseline and monthly serum K^+ and Mg^{2+}

(Continued)

Table 79–5

Antituberculosis Drugs for Adults and Children[33] (*Continued*)

Drug	Daily Doses[a,b,c]	Adverse Effects	Monitoring
p-Aminosalicylic acid (PAS)	*Adults*: 8–12 g/day in two or three doses *Children*: 200–300 mg/kg/day in two to four divided doses	Hepatotoxicity, GI distress, malabsorption syndrome, hypothyroidism, coagulopathy	Baseline LFTs and TSH TSH every 3 months
Levofloxacin[i]	Adults: 500–1000 mg daily *Children*: Not recommended	GI disturbance, neurologic effects	No specific monitoring recommended
Moxifloxacin[j]	*Adults*: 400 mg daily *Children*: Not recommended		
Bedaquiline	*Adults:* Weeks 1–2: 400 mg daily Weeks 3–24: 200 mg three times weekly *Children:* Not recommended	GI disturbances, dizziness, headache, rash, arthralgia	Serum K, Ca, Mg ECG at baseline, weeks 2, 12, 24 Weekly ECG for persons taking other QTc prolonging drugs, history of arrhythmias, hypothyroidism, uncompensated heart failure, or have serum K, Ca, or Mg below normal limits

[a] Dose per weight is based on ideal body weight. Children weighing > 40 kg should be dosed as adults.

[b] For purposes of this document adult dosing begins at age 15 years.

[c] The authors of this chapter do not agree with the use of maximum doses, since this arbitrarily caps doses for patients who otherwise might need larger doses. These maximum doses were not based on prospective studies in large or overweight individuals and do not consider patients with documented malabsorption of their medications. Clinical judgment should be used in such circumstances.

[d] Higher doses of rifampin and rifapentine are being studied. Rifabutin dose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors.

[e] The drug can likely be used safely in older children but should be used with caution in children < 5 years of age, in whom visual acuity cannot be monitored. In younger children, ethambutol at the dose of 15 mg/kg/day can be used if there is suspected or proven resistance to isoniazid or rifampin.

[f] It should be noted that, although this is the dose recommended generally, most clinicians with experience using cycloserine indicate that it is unusual for patients to be able to tolerate this amount. Doses are often divided. Serum concentration measurements are often useful in determining the optimal dose for a given patient.

[g] Doses are often divided. The single daily dose can be given at bedtime or with the main meal.

[h] Dose: 15 mg/kg/day, and 10 mg/kg in persons older than 59 years of age. Usual dose: 750–1000 mg administered intramuscularly or intravenously, given as a single dose 5–7 days/week and reduced to two or three times per week after the first 2–4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.

[i] The long-term (more than several weeks) use of levofloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. However, most experts agree that the drug should be considered for children with tuberculosis caused by organisms resistant to both isoniazid and rifampin. The optimal dose is not known.

[j] The long-term (more than several weeks) use of moxifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.

Data from Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016;63(7):853–867.

reduced to three times weekly to avoid accumulation of the parent drug (ethambutol) or metabolites (pyrazinamide).[43] Renally cleared TB drugs include the aminoglycosides (typically amikacin), ethambutol, cycloserine, and levofloxacin.[44,45] Linezolid also has significant renal clearance. With renal impairment, dosing intervals need to be extended for these drugs. TB drugs should be administered after hemodialysis, and in this case three-times weekly regimens may be more convenient. Serum concentration monitoring should be performed for cycloserine and ethambutol to avoid dose-related toxicities in renal failure patients.[43,44]

▸ *Hepatic Failure*

Hepatically cleared TB drugs include isoniazid, rifampin, pyrazinamide, ethionamide, and *p*-aminosalicylic acid.[29] Bedaquiline and pretomanid also are hepatically cleared. Ciprofloxacin and moxifloxacin are about 50% cleared by the liver. Isoniazid, rifampin, pyrazinamide, and to a lesser degree ethionamide, *p*-aminosalicylic acid, and rarely ethambutol may cause hepatotoxicity.[29] These patients require close monitoring, and serum concentration monitoring may be the most accurate way to dose them.[37]

Patient Encounter Part 3

Based on the information provided, what are the goals of therapy for this patient?

Select and recommend a therapeutic plan for treatment of this patient's TB infection. What drugs, dose, schedule, and duration of therapy are best for this patient?

Who else should be tested? How should any contacts infected by this patient be evaluated and treated?

▸ *TB Drugs*

Detailed information regarding TB drugs can be accessed at the following references.[29,33,37] A summary is provided in Table 79–5.[33] Isoniazid, rifampin, ethambutol and pyrazinamide are the key drugs. Other drugs are used in selected circumstances. Quinolones eventually may be used as first-line drugs but currently are not.[45,46] In 2012, the FDA approved bedaquiline for the treatment of MDR-TB.[47] Bedaquiline may be used in adults with confirmed pulmonary MDR-TB when an effective treatment regimen cannot otherwise be provided.[48] It should be used with three or more drugs that are active against the patient's isolate. Bedaquiline carries a black-box warning due to prolongation of QTc interval. Baseline and follow-up electrocardiograms are recommended. For treatment of XDR-TB, other new therapies drugs such as pretomanid have been approved for use in combination with bedaquiline and linezolid.[49] Additional second-line options available in the United States include imipenem, meropenem, with clavulanate (as found in amoxicillin/clavulanate) used to protect either carbapenem from MTB's beta-lactamase.

OUTCOME EVALUATION

Effectiveness of TB therapy is determined by AFB smears and cultures. Sputum samples should be sent for AFB staining and microscopic examination (sputum smears) every 1 to 2 weeks until two consecutive smears are negative. This provides early evidence of a response to treatment.[33] Once on maintenance therapy, *sputum cultures* can be performed monthly until two consecutive cultures are negative, which generally occurs over 2 to 3 months. If sputum cultures continue to be positive after 2 months, repeat drug susceptibility testing and check serum concentrations of the drugs.

Patient Encounter Part 4

Based on the information provided, which clinical and laboratory parameters should be monitored in this patient to determine efficacy and avoid toxicity?

Is this patient a candidate for therapeutic drug monitoring? Why or why not?

KEY CONCEPT Nonadherence is a significant problem in the treatment of TB.[33,34,49] DOT should be used because it is difficult to determine which patients will be noncompliant with the complex regimen.[33,34,49] DOT also provides increased opportunities to observe the patient for any apparent toxicities, thus improving overall care.[49] DOT now can be performed using video or wireless methods, as well as in-person observation.

Patient weight should be monitored in addition to radiographic and bacteriological testing. Serum chemistries, including blood urea nitrogen (BUN), creatinine, aspartate transaminase (AST),

Patient Care Process

Collect Information:

- Obtain a thorough medical, social, and medication history. (Medical risk factors, eg, immunocompromised and living conditions.)
- Obtain necessary laboratory tests, cultures, and radiology to determine active infection. (Collect appropriate samples for smears and cultures, tuberculin skin test/interferon γ.)
- Review physical assessment findings.
- Speak with the patient, obtain risk factors for infection and developing active TB (travel, living conditions, immune status, etc).

Assess the Information:

- Assess the patient's risk factors and signs and symptoms to determine whether the patient might be infected with TB.
- Assess potential for risk of transmission
- Assess immune status
- Based on physical examination, medical history, laboratory tests and cultures, and X-rays, determine whether the patient has an active TB infection.
- Assess the efficacy, safety, and patient adherence of required pharmacotherapy.
- Identify any significant adverse drug effects or interactions.

Develop a Care Plan:

- Isolate the patient with active disease to prevent the spread of the disease.
- Select and recommend appropriate antituberculosis treatment. Consider susceptibility, HIV status, drug interactions, type of TB infection, etc.
- Choose medication doses that are optimal for the patient. Consider renal function, liver function, potential for drug interactions etc.
- Consider DOT.
- Identify the index case that infected the patient, identify all persons infected by both the index case and the new case of TB, and the complete appropriate treatments for those individuals.

Implement the Care Plan:

- Provide education and review drugs, duration, dose, frequency, and side effects of selected medications.
- Educate the patient about the importance of compliance with the regimen and the risks of noncompliance.
- Ensure adherence to the treatment regimen by the patient.

Follow-up: Monitor and Evaluate:

- Follow up at required intervals to obtain AFB stains to evaluate the effectiveness of treatment.
- Review susceptibilities when available and modify treatment regimen as determined by susceptibility results.

Review patient adherence to treatment plan

- Continue treatment for at least 6 months from the time that the patient converts to a negative culture.
- Consider TDM if no clinical improvement or if risk of inadequate absorption, elimination, or drug interactions.

and alanine transaminase (ALT) and a complete blood count with platelets at baseline and periodically, thereafter, should be checked depending on the presence of other factors that may increase the likelihood of toxicity (eg, advanced age, alcohol abuse, and pregnancy).[33] Suspect hepatotoxicity in patients whose transaminases exceed five times the upper limit of normal (ULN), or whose total bilirubin exceeds 3 mg/dL (51 μmol/L), and in patients with symptoms such as nausea, vomiting, and jaundice with liver enzyme elevations of more than three times ULN. At this point, discontinue the offending agents. Typically, all TB drugs are stopped, followed by the sequential reintroduction of the drugs, along with frequent testing of liver enzymes. This usually is successful in identifying the offending agent; other agents may be continued.[33]

Therapeutic Drug Monitoring

TDM is the use of serum drug concentrations to optimize therapy.[33,37] Patients with uncomplicated, drug-susceptible TB generally do well. Pharmacokinetic variability of anti-TB drugs can contribute to poor outcomes despite adherence. TDM can be used to shorten the time to response and to treatment completion. The evidence to support the use of TDM in the treatment of TB is growing.[37] TDM can assist in patients failing appropriate DOT (no clinical improvement after 2–4 weeks or smear-positive after 4–6 weeks). Patients with AIDS, diabetes, impaired renal clearance, and various GI disorders often fail to absorb or eliminate these drugs properly and are also candidates for TDM. Drug concentrations in patients with hepatic or renal disease should be monitored, given their potential for toxicities. In the treatment of MDR-TB, TDM may be particularly useful.[29] Finally, TDM of the TB and HIV drugs is perhaps the most logical way to untangle the complex drug interactions. For a complete list of drug interactions, visit the CDC website: www.cdc.gov/tb/publications/guidelines/TB_HIV_DRUGS/default.htm.[50] In particular, interactions between the rifamycins (eg, rifampin, rifapentine, and rifabutin) and the HIV protease inhibitors and nonnucleoside reverse transcriptase inhibitors are common and require dose and frequency modifications in many cases. Because these are constantly being updated, the preceding link is an excellent way to keep up with frequent changes.

Abbreviations Introduced in This Chapter

AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine transaminase
ART	Antiretroviral therapy
AST	Aspartate transaminase
BCG	Bacille Calmette–Guérin
CDC	Centers for Disease Control and Prevention
CNS	Central nervous system
DOT	Directly observed therapy
HIV	Human immunodeficiency virus
HTN	Hypertension
IGRA	Interferon-γ release assay
IFN	Interferon
LTBI	Latent tuberculosis infection
MDR-TB	Multidrug-resistant tuberculosis
NIDDM	Noninsulin-dependent diabetes mellitus
PCR	Polymerase chain reaction
PPD	Purified protein derivative
RFLP	Restriction fragment length polymorphism
TB	Tuberculosis
TDM	Therapeutic drug monitoring
ULN	Upper limit of normal
WBC	White blood cell
XDR-TB	Extremely drug-resistant tuberculosis

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80

Gastrointestinal Infections

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the epidemiology and clinical presentation of commonly encountered gastrointestinal (GI) infections.
2. Summarize common risk factors associated with the development of a GI infection.
3. Given a patient with a GI infection, develop an individualized treatment plan.
4. Outline the impact of widespread antimicrobial resistance on current treatment recommendations for GI infections.
5. Discuss the effect of host immunosuppression on the risk of disease complications and treatment strategies associated with GI infections.
6. Educate patients on appropriate prevention measures of GI infections, including vaccinations.

INTRODUCTION

With suggested prevalence approaching one episode per person per year in resource-rich settings, and greater prevalence in low- and middle-income countries, most readers will have personal experience with gastrointestinal (GI) infections.[1] Culprits in GI infections comprise a diverse group of microorganisms, including bacteria, viruses, and protozoans. Corresponding clinical presentations are also nuanced, but acute diarrheal illness is a common unifying theme. Syndromes of acute diarrhea or vomiting are described by the overarching term, gastroenteritis. Diarrhea, in turn, is most commonly defined as greater than three loose stools in a 24-hour period.

A useful way to broadly classify GI infections is to divide them into inflammatory or noninflammatory categories. Inflammatory diarrhea is caused by invasive or cytotoxin-producing bacteria, or in some cases by amoebae (eg, *Entamoeba histolytica*), which damage the intestinal mucosa. Characteristics of GI infections caused by these organisms include frequent, painful, small-volume bowel movements containing blood and mucus. Fever is another common, though not universal, symptom. Syndromes of inflammatory diarrhea are also frequently referred to as dysentery. Pathogens implicated in inflammatory GI infections are listed in Table 80–1.

Noninflammatory GI infections are often caused by viruses but may also be associated with protozoans and enterotoxin-producing bacteria. Rather than tissue destruction, noninflammatory diarrhea is differentiated by disruption of the intestinal processes of absorption or secretion. This difference in pathophysiology explains the contrasting clinical characteristics of large-volume, watery diarrhea associated with abdominal cramping or vomiting. Individuals with noninflammatory GI infections are often normothermic or have only mild fever.

A thorough patient history may yield further clinical clues, leading the clinician to suspect involvement of a particular pathogen even prior to diagnostic testing. Examples of patient risk factors or exposures associated with specific organisms are listed in Table 80–2. These may include ingestion of contaminated food or water, animal exposures, recent antibiotic therapy, or immunocompromising conditions.

KEY CONCEPT While risk factors and implicated pathogens are varied, rehydration is the foundation of therapy for those suffering from dehydration due to GI infections, with oral rehydration therapy (ORT) preferred when possible (Table 80–3). Indication for antimicrobial therapy is dependent on many factors (to be discussed further in the following sections), including severity of illness and suspected pathogen.

INFLAMMATORY GASTROINTESTINAL INFECTIONS

SHIGELLA

Epidemiology

Shigella causes bacillary dysentery, which refers to diarrheal stool containing pus and blood. Shigellosis is endemic in most developing countries and is the most important cause of bloody diarrhea worldwide. It is estimated to cause between 80 and 160 million cases and 270,000 deaths each year, the majority of which occur in children less than 5 years old.[2,3] There are approximately 500,000 infections each year in the United States; it is a particular problem in daycare centers and in areas with crowded living conditions or poor sanitation. Most cases of shigellosis are transmitted through the fecal–oral route. Activities that may lead to shigellosis include handling diapers, ingesting pool water, or consuming vegetables from a sewage-contaminated field. *Shigella* transmission from contaminated food and water, although less common, is associated with large outbreaks.

Pathogenesis

Shigella organisms are nonmotile, nonlactose-fermenting, gram-negative rods and are members of the Enterobacteriaceae family.

Table 80–1

Gastrointestinal Pathogens Causing Acute Diarrhea

Mechanism	Location	Illness	Stool Findings	Examples of Pathogens Involved
Noninflammatory (enterotoxin)	Proximal small bowel	Watery diarrhea	No fecal leukocytes; mild or no increase in fecal lactoferrin	*Vibrio cholerae*, enterotoxigenic *Escherichia coli* (LT and/or ST), enteroaggregative *E. coli, Clostridium perfringens, Bacillus cereus, Staphylococcus aureus, Aeromonas hydrophila, Plesiomonas shigelloides*, rotavirus, norovirus, enteric adenoviruses, *Giardia lamblia, Cryptosporidium* spp., *Cyclospora* spp., microsporidia
Inflammatory (invasion or cytotoxin)	Colon or distal small bowel	Dysentery or inflammatory diarrhea	Fecal polymorphonuclear leukocytes; substantial increase in fecal lactoferrin	*Shigella* spp., *Salmonella* spp., *Campylobacter jejuni*, enterohemorrhagic *E. coli*, enteroinvasive *E. coli, Yersinia enterocolitica, Listeria monocytogenes, Vibrio parahaemolyticus, Clostridioides difficile, A. hydrophila, P. shigelloides, Entamoeba histolytica, Klebsiella oxytoca*
Penetrating	Distal small bowel	Enteric fever	Fecal mononuclear leukocytes	*Salmonella* Typhi, *Y. enterocolitica*

Abbreviations: LT, heat-labile enterotoxin; ST, heat-stable enterotoxin.

Table 80–2

Exposure or Condition Associated With Pathogens Causing Diarrhea

Exposure or Condition	Pathogen(s)
Foodborne	
Foodborne outbreaks in hotels, cruise ships, resorts, restaurants, catered events	Norovirus, nontyphoidal *Salmonella*, *Clostridium perfringens*, *Bacillus cereus*, *Staphylococcus aureus*, *Campylobacter* spp, ETEC, STEC, *Listeria*, *Shigella*, *Cyclospora cayetanensis*, *Cryptosporidium* spp
Consumption of unpasteurized milk or dairy products	*Salmonella*, *Campylobacter*, *Yersinia enterocolitica*, *S. aureus* toxin, *Cryptosporidium*, and STEC. *Listeria* is infrequently associated with diarrhea, *Brucella* (goat milk cheese), *Mycobacterium bovis*, *Coxiella burnetii*
Consumption of raw or undercooked meat or poultry	STEC (beef), *C. perfringens* (beef, poultry), *Salmonella* (poultry), *Campylobacter* (poultry), *Yersinia* (pork, chitterlings), *S. aureus* (poultry), and *Trichinella* spp (pork, wild game meat)
Consumption of fruits or unpasteurized fruit juices, vegetables, leafy greens, and sprouts	STEC, nontyphoidal *Salmonella*, *Cyclospora*, *Cryptosporidium*, norovirus, hepatitis A, and *Listeria monocytogenes*
Consumption of undercooked eggs	*Salmonella*, *Shigella* (egg salad)
Consumption of raw shellfish	*Vibrio* species, norovirus, hepatitis A, *Plesiomonas*
Exposure or contact	
Swimming in or drinking untreated fresh water	*Campylobacter*, *Cryptosporidium*, *Giardia*, *Shigella*, *Salmonella*, STEC, *Plesiomonas shigelloides*
Swimming in recreational water facility with treated water	*Cryptosporidium* and other potentially waterborne pathogens when disinfectant concentrations are inadequately maintained
Healthcare, long-term care, prison exposure, or employment	Norovirus, *Clostridioides difficile*, *Shigella*, *Cryptosporidium*, *Giardia*, STEC, rotavirus
Child care center attendance or employment	Rotavirus, *Cryptosporidium*, *Giardia*, *Shigella*, STEC
Recent antimicrobial therapy	*C. difficile*, multidrug-resistant *Salmonella*
Travel to resource-challenged countries	*Escherichia coli* (enteroaggregative, enterotoxigenic, enteroinvasive), *Shigella*, Typhi and nontyphoidal *Salmonella*, *Campylobacter*, *Vibrio cholerae*, *Entamoeba histolytica*, *Giardia*, *Blastocystis*, *Cyclospora*, *Cystoisospora*, *Cryptosporidium*
Exposure to house pets with diarrhea	*Campylobacter*, *Yersinia*
Exposure to pig feces in certain parts of the world	*Balantidium coli*
Contact with young poultry or reptiles	Nontyphoidal *Salmonella*
Visiting a farm or petting zoo	STEC, *Cryptosporidium*, *Campylobacter*
Exposure or condition	
Age group	Rotavirus (6–18 months of age), nontyphoidal *Salmonella* (infants from birth to 3 months of age and adults >50 years with a history of atherosclerosis), *Shigella* (1–7 years of age), *Campylobacter* (young adults)
Underlying immunocompromising condition	Nontyphoidal *Salmonella*, *Cryptosporidium*, *Campylobacter*, *Shigella*, *Yersinia*
Hemochromatosis or hemoglobinopathy	*Y. enterocolitica*, *Salmonella*
AIDS, immunosuppressive therapies	*Cryptosporidium*, *Cyclospora*, *Cystoisospora*, microsporidia, *Mycobacterium avium*–intercellulare complex, cytomegalovirus
Anal-genital, oral-anal, or digital-anal contact	*Shigella*, *Salmonella*, *Campylobacter*, *E. histolytica*, *Giardia lamblia*, *Cryptosporidium* as well as sexually transmitted infections

Abbreviations: ETEC, enterotoxigenic *Escherichia coli*; STEC, Shiga toxin–producing *Escherichia coli*.

Table 80–3

Clinical Assessment of Degree of Dehydration in Children Based on Percentage of Body Weight Loss

Variable	Mild (3%–5%)	Moderate (6%–9%)	Severe (10% or More)
Blood pressure	Normal	Normal	Normal to reduced
Quality of pulses	Normal	Normal to slightly decreased	Moderately decreased
Heart rate	Normal	Increased	Increased (bradycardia in severe cases)
Skin turgor	Normal	Decreased	Decreased
Fontanelle	Normal	Sunken	Sunken
Mucous membranes	Slightly dry	Dry	Dry
Eyes	Normal	Sunken orbits/decreased tears	Deeply sunken orbits/decreased tears
Extremities	Warm, normal capillary refill	Delayed capillary refill	Cool, mottled
Mental status	Normal	Normal to listless	Normal to lethargic to comatose
Urine output	Slightly decreased	< 1 mL/kg/hour	< 1 mL/kg/hour
Thirst	Slightly increased	Moderately increased	Very thirsty
Fluid replacement	ORT 50 mL/kg over 2–4 hours	ORT 100 mL/kg over 2–4 hours	Lactated Ringer 40 mL/kg in 15–30 minutes, then 20–40 mL/kg if skin turgor, alertness, and pulse have not returned to normal *or* lactated Ringer or normal saline 20 mL/kg, repeat if necessary, and then replace water and electrolyte deficits over 1–2 days, followed by ORT 100 mL/kg over 4 hours

From Martin S, Jung R. Gastrointestinal infections and enterotoxigenic poisonings. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill; 2014:1951–1967.

They are separated into four serogroups (A, B, C, and D), with *Shigella sonnei* (serogroup D) responsible for most shigellosis cases in the United States.[3] Infection with *Shigella* occurs after ingestion of as few as 10 to 100 organisms, which may explain the ease of person-to-person spread. Symptoms develop about 1 to 2 days after contracting the bacteria.[4]

Shigella strains invade intestinal epithelial cells, with subsequent multiplication, inflammation, and destruction. This organism only rarely invades the bloodstream; however, bacteremia can occur in malnourished children and immunocompromised patients and is associated with a mortality rate as high as 20%.[9]

Treatment and Monitoring

In April 2017 and June 2018, the CDC issued health advisories describing the emergence of *Shigella* strains with elevated MIC values for ciprofloxacin in the United States.[5,6] The CDC no longer recommends that antibiotics be routinely prescribed for *Shigella* infections. Antibiotic therapy should be reserved for patients who develop severe illness (eg, invasive disease, hospitalization), are immunocompromised, or when public health officials advise treatment in an outbreak situation (eg, day care, food handlers, nursing homes).[3,5] Although treatment can shorten the duration of symptoms by 1 to 2 days, shigellosis is generally a self-limited infection, and unnecessary treatment with antibiotics promotes further resistance. Empiric therapy for *Shigella* should be considered for immunocompetent patients with documented fever, abdominal pain, bloody diarrhea, and bacillary dysentery (frequent scant bloody stools, fever, abdominal cramps, tenesmus).[7] Azithromycin, fluoroquinolones, and ceftriaxone are considered first-line therapy for the treatment of shigellosis in adults. If treatment failure from any agent is suspected, an infectious diseases specialist should be consulted to identify an appropriate antibiotic. Due to concerns for resistance, patients with travel-related shigellosis should be treated empirically with first-line therapy until antimicrobial susceptibility data are available. In children, oral azithromycin or parenteral ceftriaxone are considered preferable to fluoroquinolones for first-line therapy. Antimotility medications (eg, loperamide) are not recommended as they can worsen symptoms. All shigellosis cases should be reported to the local health department.[5]

Clinical Presentation and Diagnosis of Shigellosis

- Biphasic illness
  - Early—high fever, watery diarrhea without blood
  - Later—after approximately 48 hours, colitis develops with urgency, **tenesmus**, and **dysentery**
    - Low-grade fever
    - More frequent small-volume stools ("fractional stools")
    - Vomiting (35%)
- Complications of shigellosis
  - **Proctitis** or rectal prolapse—more common in infants and young children
  - Intestinal obstruction
  - Colonic perforation
  - Bacteremia—more common in children
  - Metabolic disturbances
  - Neurologic disease—most commonly seizures (approximately 10% of patients)
  - Hemolytic–uremic syndrome (HUS)
- Microscopic examination of stool is extremely useful and reveals multiple polymorphonuclear leukocytes and red blood cells (RBCs). Diagnosis is usually confirmed by stool culture

SALMONELLA

Epidemiology

Salmonella are gram-negative facultative rods that cause a wide variety of disease manifestations. *Salmonella enterica* (serotypes Typhi and Paratyphi A and B) cause typhoid (or enteric) fever. Although typhoid fever is now a rare disease in the United States with approximately 350 culture-confirmed cases reported per year, these infections cause an estimated 30 million cases and 215,000 deaths annually worldwide.[8,9] Typhoid fever is most commonly acquired from water or food contaminated by feces from an infected person. The incubation period is 6 to 30 days; illness onset is insidious with gradually increasing fatigue and fever. Nontyphoidal *Salmonella* (NTS) are important causes of reportable food-borne infection. There are an estimated 1.35 million cases of NTS illness annually in the United States, and almost 153 million worldwide.[9,10] Annual mortality rates are 420 and 57,000, respectively. The highest incidence is in those younger than 1 year of age, older than 65 years of age, or those with HIV/AIDS. Foods commonly associated with infection include raw meat, poultry, eggs, dairy, and unwashed fruit and vegetables.[11,12] Exotic pets, especially reptiles, are an increasing source of human salmonellosis. NTS strains may also result in bacteremia and focal disease, such as endovascular infections, osteomyelitis, meningitis, and septic arthritis.[9,12] Recurrent *Salmonella* bacteremia is an AIDS-defining illness.

Risk factors for salmonellosis include extremes of age, malnutrition, immunosuppression, and genetic factors.[12,13] Proper food handling and storage can help prevent *Salmonella* gastroenteritis. Effective handwashing is important, especially when handling eggs and poultry.

Clinical Presentation and Diagnosis of Salmonellosis

Gastroenteritis

- Onset 8 to 48 hours after ingestion of contaminated food
- Fever, diarrhea, and cramping
- Stools are loose, moderate volume, and without blood
- Headache, myalgias, and other systemic symptoms can occur
- Certain underlying conditions (eg, AIDS, inflammatory bowel disease, and prior gastric surgery) predispose the patient to more severe disease

Enteric Fever

- Febrile illness 5 to 21 days after ingestion of contaminated food or water, which may be persistent and high grade. A relative bradycardia may be noted at the fever peak.
- Chills, diaphoresis, headache, anorexia, cough, weakness, sore throat, dizziness, muscle pain, and diarrhea may be present before onset of fever
- Rose spots, a coated tongue, and/or hepatosplenomegaly may be noted
- Intestinal hemorrhage or perforation, leukopenia, anemia, and subclinical disseminated intravascular coagulopathy may occur
- Culture of stool, blood, or bone marrow for *Salmonella* species is helpful

Treatment and Monitoring

▶ *Gastroenteritis*

Gastroenteritis from NTS is usually self-limited, and antibiotics have no proven value in uncomplicated patients.[7,9] Patients respond well to ORT. Symptoms typically diminish in 3 to 7 days without sequelae. Antibiotic use may result in a higher rate of chronic carriage and relapse. Antimicrobial use should be limited to preemptive therapy among patients at higher risk of extraintestinal spread or invasive disease. These include neonates (up to 3 months of age), persons over 65 years old, those with atherosclerosis, immunocompromised patients, or patients with cardiac or significant joint disease.[7] Antibiotic options should be based on susceptibility information and include ceftriaxone, ciprofloxacin, trimethoprim/sulfamethoxazole, or amoxicillin. Antimotility agents should not be used.

▶ *Enteric Fever*

Treatment of enteric fever with antibiotics can shorten the clinical course and reduce the risk of death.[9,14] The current drug of choice for typhoid fever in adults is a fluoroquinolone, such as ciprofloxacin; however, ceftriaxone should be considered in patients with invasive disease or those who are at risk of a fluoroquinolone-resistant infection. Azithromycin or ceftriaxone are preferred in children. The recommended adult dose of ciprofloxacin for uncomplicated typhoid fever is 500 mg orally twice daily for 5 to 7 days; however, decreased susceptibility to ciprofloxacin is a significant problem in many parts of the world. In the United States, *Salmonella* spp. with decreased ciprofloxacin susceptibility are associated with travel to Southeast Asia.[11] If ciprofloxacin resistance is suspected or confirmed, ceftriaxone may be used; however, this agent may be less suitable in some low- and middle-income countries due to cost and route of administration. Azithromycin is an effective alternative for uncomplicated typhoid fever.[12,13] Of note, patients may continue to have fever for up to 3 to 5 days after initiating antibiotic therapy.

Two unconjugated typhoid vaccines are available for use in the United States; however, neither is licensed by the FDA for the prevention of paratyphoid fever. Both vaccines provide 50% to 80% efficacy against *Salmonella* serotype Typhi infection but offer no protection against Paratyphi infection. Immunization is recommended for travelers going to endemic areas such as Latin America, Asia, and Africa; household contacts of chronic carriers; and laboratory personnel who frequently work with *Salmonella* serotype Typhi.[14] Vaccination is increasingly important for travelers to consider since the growth of multidrug-resistant strains of *Salmonella* serotype Typhi have become common in many regions.

▶ *Bacteremia and Focal Infections*

Due to concern for resistance, treatment of *Salmonella* bacteremia or focal infections should be initiated with both a third-generation cephalosporin (eg, ceftriaxone) and a fluoroquinolone (eg, levofloxacin, ciprofloxacin).[12] Once susceptibilities are determined, therapy can be streamlined to a single, narrow-spectrum agent. If there is no evidence of an endovascular infection, therapy for bacteremia should continue for 7 to 14 days. For patients with suspected meningitis, high-dose ceftriaxone is preferred because of its optimal penetration of the blood–CSF barrier. Osteomyelitis and joint infections, often associated with sickle cell anemia, are difficult to eradicate and require longer durations of antimicrobial therapy (at least 4–6 weeks).

Patient Encounter 1

A 20-year-old man with a medical history significant for sickle cell anemia presents to his local emergency department (ED) with a 2-day history of episodes of fever and chills. He also reports a 2-week history of pain and loss of range of motion in his right knee. When asked about medication allergies, he reports a reaction of GI upset to amoxicillin–clavulanate. Upon admission, the physician inquires about pets in the home. The patient reports he has a pet box turtle which has been with him since childhood. STAT blood cultures are positive for nontyphoidal *Salmonella* (NTS).

What risk factors are present in this patient that may have predisposed him to developing Salmonella bacteremia and probable joint infection?

What empiric therapy would you recommend? Are there any special considerations regarding duration of therapy?

CAMPYLOBACTER

Epidemiology

Campylobacter jejuni is the most commonly identified cause of bacterial gastroenteritis worldwide. In the United States, this organism accounts for an estimated 1.5 million infections, 13,000 hospitalizations, and 100 deaths annually.[16] Risk factors for *Campylobacter* infection include consumption of contaminated foods of animal origin, especially undercooked poultry or other foods that are cross-contaminated by raw poultry meat during food preparation; unpasteurized milk; contaminated water; foreign travel; contact with farm animals and pets; and the use of antimicrobial therapy.[17] People should be instructed to wash their hands after contact with raw meats and animals.

In developed countries, there are two distinct age peaks for Campylobacter infection: younger than 1 year of age and 15 to 44 years of age, with a mild male predominance. In developing countries, *Campylobacter*-associated diarrhea is primarily a pediatric disease.

Pathophysiology

Campylobacter spp. are gram-negative bacilli that have a curved or spiral shape. *Campylobacters* are sensitive to stomach acidity; as a result, diseases or medications that buffer gastric acidity may increase the risk of infection. The infectious inoculum for *C. jejuni* is low, similar to that for *Salmonella* spp. After an incubation period, infection is established in the jejunum, ileum, colon, and rectum.

Clinical Presentation and Diagnosis of Campylobacteriosis

- Incubation period of 1 to 7 days.
- A brief prodrome of fever, headache, and myalgias is followed by crampy abdominal pain, a high fever, and several bowel movements per day, which may be watery or bloody.
- The abdominal pain and tenderness may be localized, and pain in the right lower quadrant may mimic acute appendicitis. Abdominal pain is more prevalent in *Campylobacter* infection than in either *Shigella* or *Salmonella* infections.
- Tenesmus occurs in approximately 25% of patients.
- Fecal leukocytes and red blood cells (RBCs) are detected in the stools of 75% of infected individuals. Diagnosis of *Campylobacter* is established by stool culture.

Treatment

Effective fluid and electrolyte replacement is the cornerstone of therapy for patients with *Campylobacter* infection.[7,17] In most cases, this can be accomplished with the use of oral glucose–electrolyte solutions. Antibiotic therapy is not needed in most patients who are immunocompetent since the disease is self-limiting, lasting a week or less. Antibiotics should be considered in patients with high fevers, symptoms lasting longer than 1 week, pregnancy, extraintestinal infection, or immunocompromising conditions.

Azithromycin is the recommended first-line drug (500 mg orally daily for 3 days) for the treatment of *Campylobacter* infections.[7,17] A fluoroquinolone (ciprofloxacin 500 mg orally twice daily for 5–7 days) may also be considered; however, the widespread use of these agents in food animals has resulted in fluoroquinolone-resistant *Campylobacter* strains worldwide. Choice of agent may depend on travel history and risk of resistance in certain countries. *Campylobacter fetus* is the most commonly identified species in patients with bacteremia, which primarily occurs in patients who are elderly or immunocompromised.[17] In addition, focal infections such as cellulitis, vascular infections, meningitis, and abscesses may be present. For these serious infections, treatment with a third-generation cephalosporin, gentamicin, ampicillin, or a carbapenem is recommended.[19] Antimotility agents should be avoided because they may prolong the duration of symptoms and have been associated with worse outcomes. Postinfectious complications associated with *Campylobacter* infection can include reactive arthritis, irritable bowel syndrome (IBS), and Guillain–Barré syndrome (GBS).

ENTEROHEMORRHAGIC *ESCHERICHIA COLI*

Epidemiology

KEY CONCEPT Blood in the stool indicates the possibility of inflammatory mucosal disease of the colon such as enterohemorrhagic *Escherichia coli* (EHEC), a pathogenic subgroup of Shiga toxin–producing *E. coli* (STEC) and an important cause of bloody diarrhea in the United States. Acute hemorrhagic colitis has been primarily associated with the O157:H7 serotype.[18] This serotype is responsible for large outbreaks of infection, has higher rates of complications, and appears to be more pathogenic than non-EHEC STEC strains. The spectrum of disease associated with *E. coli* O157:H7 includes bloody diarrhea, which is seen in up to 95% of patients; nonbloody diarrhea; hemolytic–uremic syndrome (HUS); and thrombotic thrombocytopenic purpura (TTP).[19]

An estimated 265,000 STEC infections occur each year in the United States.[20] Serotype O157:H7 causes about one-third of these infections. Very young children and the elderly are more likely to develop severe illness and HUS; however, healthy older children and young adults can also become seriously ill.[18] Outbreaks of diarrhea due to *E. coli* O157:H7 and other STECs have occurred following ingestion of contaminated beef, unpasteurized milk, vegetables (eg, alfalfa sprouts, coleslaw, and lettuce), and apple juice. The most important reservoir for *E. coli* O157:H7 is the GI tract of cattle. Person-to-person transmission also occurs, and swimming in infant pools or contaminated lakes or drinking contaminated municipal water are additional risk

Clinical Presentation and Diagnosis of EHEC

- Incubation period of 3 to 5 days
- Bloody stools
- Leukocytosis is often present; fever is frequently absent
- Abdominal tenderness
- HUS in 2% to 10% of patients (especially children 1–5 years of age and the elderly in nursing homes); develops on average 1 week after the onset of diarrhea

factors. The incidence of diagnosed *E. coli* O157:H7 infections in the United States is greater among rural populations and usually occurs in summer and autumn months.

Pathophysiology

The infectious inoculum of EHEC is very low, between 1 and 100 colony-forming units (CFUs). The major virulence factor for EHEC is the production of two Shiga-like cytotoxins (Shiga toxin [Stx] I and II), which are responsible for vascular damage and systemic effects such as HUS. Adhesion mediates initial attachment of EHEC to intestinal epithelial cells. Following attachment, these organisms produce lesions on individual intestinal epithelial cells in the small or large intestine resulting in diarrhea.

Treatment

The only recommended treatment of EHEC infection is supportive, including fluid and electrolyte replacement, usually in the form of ORT.[7,18] Most illnesses resolve in 5 to 7 days. Patients should be monitored for the development of HUS.[19] Antibiotics are currently contraindicated because they can induce the expression and release of toxin. Antimotility agents should be avoided because they delay clearance of the pathogen and toxin, which increases the risk of systemic complications. The incidence of HUS has declined in recent years and nonsteroidal anti-inflammatory drugs (NSAIDs) are increasingly recognized as an important contributor to acute kidney injury in infected children, especially if volume depleted.

Prevention of EHEC infection is especially important because no therapeutic interventions are available to lessen the risk of the development of HUS. Hamburgers should be cooked thoroughly until the temperature of the thickest part of the patty is 72°C. All surfaces and utensils that contact raw meat should be washed thoroughly before reuse. Fruits and vegetables should be washed thoroughly, especially those that will not be cooked. Handwashing is also very important and should include the supervision of handwashing by children in daycare centers.

CLOSTRIDIOIDES DIFFICILE

Epidemiology

Clostridioides difficile (*C. difficile; formerly Clostridium difficile*) infection (CDI) is the most common healthcare-associated infection and the primary cause of hospital-acquired infectious diarrhea. In 2017, an estimated 223,900 cases of CDI occurred in hospitalized patients, which led to 12,800 deaths and attributable healthcare costs of $1 billion.[10] Strategies to reduce CDI have led to decreases in healthcare-associated cases; however, community-associated cases have not decreased. Patients with community-associated CDI are often younger, lack traditional risk factors, and generally have less severe disease compared with those with hospital-acquired infections.[21] Common risk factors for hospital-acquired CDI include increasing age, severe underlying illness, intensive care unit admission, gastric acid suppression, and exposure to antimicrobials, especially broad-spectrum, multiple-drug regimens. **KEY CONCEPT** Healthcare-associated CDI is almost always associated with antimicrobial use; therefore, unnecessary and inappropriate antibiotic therapy should be avoided. Key strategies to reduce the incidence of CDI include improving antibiotic use via antimicrobial stewardship as well as infection prevention and control procedures. These include, but are not limited to, handwashing with soap and water and healthcare facility cleaning and disinfection. Clindamycin, fluoroquinolones, cephalosporins, carbapenems, and penicillins are antibiotics most commonly associated with CDI; however, almost all antibiotics except aminoglycosides have been implicated.[22]

Pathophysiology

C. difficile, a Gram-positive, spore-forming anaerobe, is spread by the fecal–oral route, and patient-to-patient spread is an important mode of transmission within the hospital.[23] The organism is ingested either as the vegetative form or spores, which can survive for long periods in the environment and can traverse the acidic stomach. In the small intestine, spores germinate into the vegetative form. Once the GI tract is colonized with spores, disruption of the gut flora, which occurs with antibiotic therapy, allows *C. difficile* to proliferate. Toxin production is essential for the disease to occur and is responsible for the inflammation, fluid and mucus secretion, and mucosal damage that lead to diarrhea or colitis. After treatment, up to 30% of patients will develop recurrence of diarrhea and require retreatment. The risk of recurrence increases with each subsequent episode. Multiple risk factors have been linked to recurrent CDI, including impaired adaptive host response, particularly to the *C. difficile* toxins, infection with unique strains associated with epidemic outbreaks, lack of diversity in the patient's gut microbiome, and repeat or continued exposure to antimicrobials.

Treatment

Patients who develop CDI while receiving an antibiotic should have the antibiotic discontinued, if possible.[23] The use of concurrent antibiotics during CDI therapy, or soon thereafter, lowers the chances of a clinical cure and increases the risk of recurrence.[24] If antimicrobial therapy must continue, an attempt should be made to switch the patient to an agent with a lower risk of CDI.[22] Clinical practice guidelines recommend that initial antimicrobial therapy should be based on the severity of illness and whether it is an initial episode, first recurrence, or two or more recurrences.[25] Severe disease is defined as either a white blood cell count greater than 15,000 cells/mL or serum creatinine greater than 1.5 mg/dL. The clinical definition of fulminant disease is a patient with CDI who presents with hypotension or shock, ileus, or megacolon.

Oral vancomycin (125 mg orally four times daily for 10 days or 10mg/kg/dose four times daily for children) or fidaxomicin (200 mg orally twice daily for 10 days) are recommended as first-line drug therapy for the treatment of an initial episode of nonsevere or severe CDI.[23] Metronidazole (500 mg orally three times daily for 10 days or 7.5 mg/kg/dose every 6 hours for children) is no longer considered first line and should only be considered in patients with nonsevere disease, and access to vancomycin or fidaxomicin is limited.[25] For the treatment of fulminant CDI, a higher dose of vancomycin (500 mg orally by mouth or via nasogastric tube four times daily) may be combined with IV metronidazole (500 mg every 8 hours). Vancomycin may be given as

Clinical Presentation and Diagnosis of CDI

- Symptoms can start as early as the first day of antimicrobial therapy or several weeks after antibiotic therapy is completed
- Asymptomatic carriage
- Diarrhea:
  - Acute watery diarrhea with lower abdominal pain, low-grade fever, and mild or absent leukocytosis
  - Mild, with only three or four loose watery stools per day
- *C. difficile* toxins are present in stool, but sigmoidoscopic examination is normal
- Colitis:
  - Profuse, watery diarrhea with 5 to 15 bowel movements per day, abdominal pain, abdominal distention, nausea, and anorexia
  - Left or right lower quadrant abdominal pain and cramps that are relieved by passage of diarrhea
  - Dehydration and low-grade fever
  - Sigmoidoscopic examination may reveal a nonspecific diffuse or patchy erythematous colitis with or without pseudomembranes
- Toxic megacolon: Suggested by acute dilation of the colon to a diameter greater than 6 cm, associated systemic toxicity, and the absence of mechanical obstruction. It carries a high mortality rate
- Fulminant colitis: Acute abdomen and systemic symptoms such as fever, tachycardia, dehydration, and hypotension. Some patients have marked leukocytosis (up to 40×10^3 white blood cells/mm^3 [40×10^9/L]). Diarrhea is usually prominent but may not occur in patients with paralytic ileus and toxic megacolon.
- Recurrent disease:
  - Risk factors include increased age, recent abdominal surgery, increased number of *C. difficile* diarrheal episodes, and leukocytosis
  - About 10% to 30% of patients develop a second episode of CDI within 2 months of the initial diagnosis
- In most cases, *C. difficile* toxin testing of an unformed stool specimen effectively establishes the diagnosis. It should be noted that three or more loose stools without alternative explanation, including laxative use in the preceding 48 hours, should be documented prior to obtaining *C. difficile* testing. Stool culture is the most sensitive test, but it is not clinically practical due to slow turnaround time. Enzyme immunoassay (EIA) testing for toxin A and B is rapid, but less sensitive, and no longer routinely used as a standalone test. Many labs now use newer tests, such as EIA detection of glutamate dehydrogenase (GDH) combined with an EIA toxin test or nucleic acid amplification test (NAAT). In some cases, a two- or three-step method, using a combination of NAAT plus EIA and/or GDH, is used to improve positive predictive value. Leukocytosis, hypoalbuminemia, and fecal leukocytes are nonspecific but suggestive of *C. difficile* infection
- In selected patients, sigmoidoscopy, colonoscopy, or abdominal CT scan can provide useful diagnostic information

a retention enema (500 mg in 100 mL of normal saline every 6 hours) if an ileus is present. The use of antimotility agents (eg, loperamide, diphenoxylate/atropine) should be avoided in most cases due to the concern for precipitating toxic megacolon. Surgical intervention may be lifesaving, particularly in cases complicated by toxic megacolon or colonic perforation.

The recurrence rate after an initial episode of CDI is approximately 10% to 30%, with the highest risk within the first 2 weeks.[25] Continuous use of acid suppression therapies or reexposure to antimicrobial agents increases the risk of CDI recurrences.[26] Although there are no differences in initial clinical cure, fidaxomicin has been shown to decrease the risk of recurrence

Patient Encounter 2

A 65-year-old woman with a history of breast cancer (diagnosed 15 years ago; currently in remission) and hypertension presents to the hospital complaining of abdominal discomfort and acute diarrhea for the last 3 days. Over the last 24 hours, she states she has had at least 6 bouts of loose, watery diarrhea. She thought it might be due to "something she ate," but it has begun to concern her because it does not seem to be going away. Upon chart review, you note that she was recently admitted to the hospital 2 weeks ago for a urinary tract infection. She received intravenous antibiotic therapy (ceftriaxone) for 3 days and was subsequently discharged on an additional 7 days of oral therapy (ciprofloxacin). She also received pantoprazole at that time for "stress ulcer prophylaxis," which was continued at discharge with an outpatient prescription. During this admission, she is noted to be afebrile, her white blood cell count is 12,800 cells/mL, and her serum creatinine is 1.3 mg/dL (99.2 μmol/L), which is stable upon comparison with her previous hospital admission. Due to her recent history of antibiotic use and new-onset diarrhea, a stool sample is sent to the microbiology lab for a *C. difficile* toxin PCR. Home medications include amlodipine 10mg orally once daily and pantoprazole 40 mg orally once daily.

Should this patient be given loperamide (Imodium) to decrease her diarrhea while the C. difficile toxin PCR is pending?

The C. difficile toxin PCR report comes back from the lab and is positive. What antimicrobial therapy should you recommend for this patient?

What is the recommended duration of therapy for her CDI?

Would you recommend any changes to her current medications?

Assuming this patient is successfully treated for her CDI, what is the risk of the infection recurring? If it does recur, what antimicrobial agent should be recommended to treat the first recurrence?

Table 80–4

Agents Responsible for Acute Viral Gastroenteritis and Diarrhea

Virus	Peak Age	Peak Time	Duration	Transmission	Symptoms
Rotavirus	6 months–2 years	Winter	3–8 days	Fecal–oral, water, food	Diarrhea, vomiting, fever, abdominal pain
Enteric adenovirus	< 2 years	Year-round	7–9 days	Fecal–oral	Diarrhea, respiratory symptoms, vomiting, fever
Astrovirus	< 7 years	Winter	1–4 days	Fecal–oral, water, shellfish	Vomiting, diarrhea, fever, abdominal pain
Noroviruses	> 5 years	Variable	12–24 hours	Fecal–oral, food, aerosol	Nausea, vomiting, diarrhea, abdominal cramps, headache, fever, chills, myalgia

Modified from Martin S, Jung R. Gastrointestinal infections and enterotoxigenic poisonings. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 8th ed. New York, NY: McGraw-Hill; 2011:1951–1967.

compared or oral vancomycin in patients. This decrease comes at a higher acquisition cost. Patients with recurrent CDI may be treated with either a prolonged taper or pulsed dosing of oral vancomycin administered over 2 to 8 weeks or fidaxomicin for 10 days. Patients with multiple recurrent CDI, refractory to vancomycin and fidaxomcin, may be a candidate for fecal microbiota transplantation. Fecal microbiota transplantation (FMT) has a reported efficacy of about 90% in preventing recurrent CDI and should be considered in patients with multiple recurrent episodes of CDI.[25] In 2016, the FDA approved bezlotoxumab, a human monoclonal antibody that binds to *C. difficile* toxin B, to reduce recurrence of CDI in patients at high risk of recurrence. This drug is administered as a single infusion (10 mg/kg), but it is important to note it is not an antibacterial drug and must be used in conjunction with antibacterial drug treatment.[27] Rifaximin, administered directly following a course of metronidazole or vancomycin, may be an option for the prevention of recurrent episodes of CDI in some patients.

Strict infection control measures, including contact precautions, should be instituted for all patients with CDI. Environmental cleaning with chlorine-containing agents should be used to eliminate *C. difficile* spores. Because alcohol is ineffective in killing spores, it is essential that healthcare workers wash their hands with soap and water rather than using alcohol-based hand sanitizers. Meticulous handwashing is the single most important strategy to decrease the patient-to-patient transmission of *C. difficile*. Although some systematic reviews have concluded that the use of probiotics may help prevent CDIs,[28] randomized controlled trials (RCTs) have failed to do so.[29] Probiotics should not be recommended for the prevention of CDI in hospitalized patients without additional evidence from RCTs.

NONINFLAMMATORY GASTROINTESTINAL INFECTIONS

Though the syndrome of profuse watery diarrhea they cause is usually self-limited, pathogens causing noninflammatory GI infections accounted for more than 1.3 million deaths worldwide in 2015 and were the fourth leading cause of death in children less than 5 years of age.[30] **KEY CONCEPT** Of these pathogens, viruses are the most common cause of noninflammatory gastroenteritis. Many viruses are implicated, including noroviruses, rotaviruses, astroviruses, enteric adenoviruses, and coronaviruses (Table 80–4). This section will focus on two of the most common, noroviruses and rotaviruses. *Cryptosporidium*, a common protozoan cause of noninflammatory GI infections, and enterotoxin-producing bacterial pathogens will also be highlighted.

NOROVIRUS

It is estimated, on average, a resident of the United States will experience five norovirus episodes in their lifetime.[31] Noroviruses are the most common cause of epidemic diarrheal illness, accounting for one-third of viral gastroenteritis in the United States and 90% of viral gastroenteritis outbreaks worldwide.[32] The ability of this group of viruses to survive extremes of temperature and many common chlorine or alcohol-based cleaning products explains their tendency to cause not only sporadic cases, but also epidemics. Outbreaks may occur in healthcare settings

Clinical Presentation and Diagnosis of Norovirus Infection

- Symptom onset may be rapid or gradual
- Abdominal cramping and nausea are common first symptoms
- Moderate, nonbloody diarrhea (up to four to eight stools per day)
- Low-grade fever present in approximately 50% of cases
- Other manifestations may include headache, malaise, and myalgias
- Symptoms typically last 48 to 72 hours and are usually self-limiting
- Those less than 5 or greater than 85 years of age or individuals with immunocompromising conditions may have more severe disease
- Often a clinical diagnosis is done based on history and symptoms, though definitive diagnosis can be made by polymerase chain reaction (PCR) of the stool

Clinical Presentation and Diagnosis of Rotavirus Infection

- Incubation period of 2 days
- 2- to 3-day **prodrome** of fever and vomiting
- Profuse diarrhea without blood or leukocytes (up to 10–20 stools per day)
- Severe dehydration
- Anorexia
- Fever may be present
- Presentation in adults may vary from asymptomatic to nonspecific symptoms of headache, malaise, and chills to severe diarrhea, nausea, and vomiting
- Diagnosis can be made by polymerase chain reaction (PCR) of the stool

or in the community—particulary in close-proximity groups (cruise ships, day cares, etc)—and are most frequent in the winter months. Transmission is multifaceted with viral spread possible through contaminated food or water, person-to-person contact, or through contaminated surfaces or objects (ie, *fomites*). Person-to-person spread via the fecal–oral route is thought to be the most common mode of transmission.

There is no current targeted antiviral therapy against noroviruses. Subsequently, as with many other causes of gastroenteritis, rehydration therapy and other symptomatic management for pain or nausea are the foundations of treatment. There is lack of evidence to support the use of antimotility agents for norovirus infection, and these should generally be avoided in pediatric and elderly populations due to potential for adverse effects. When possible, immunocompromised patients with severe disease may need to undergo lightening of their immunosuppression.

ROTAVIRUS

Rotavirus is the leading cause of childhood gastroenteritis and death worldwide, with an estimated 128,500 attributable deaths in 2016.[33] Highest mortality rates are reported in the very young and in resource-limited settings. Most infections occur in children between 6 months and 2 years of age, and typically during the winter season, though adults may be infected as well. Almost all children will experience at least one episode of rotavirus infection before 5 years of age. Person-to-person transmission occurs through the fecal–oral route.

The mechanism of diarrhea has not been clearly elucidated, but theories include a reduction in the absorptive surface along with impaired absorption owing to cellular damage, enterotoxigenic effects of a rotavirus protein, and stimulation of the enteric nervous system.

The cornerstone of rotavirus treatment is supportive care and rehydration with ORT or IV fluids. Antimotility and antisecretory agents should not be used owing to their potential side effects in children and the self-limited nature of the disease. **KEY CONCEPT** Two oral rotavirus vaccines are currently approved by the FDA, *RotaTeq* and *Rotarix*. Since their introduction in 2006, these vaccines have reduced diarrhea-related healthcare use in children by as much as 80% and have conferred protection on unvaccinated children (herd immunity). This reduction in healthcare usage has resulted in an estimated annual savings of 121 to 231 million USD.[34] The CDC Advisory Committee on Immunization Practices recommends vaccination at 2, 4, and 6 months for *RotaTeq* and 2 and 4 months for *Rotarix*. There is a small risk of **intussusception** from rotavirus vaccination within a week or 2 of the first two doses. This risk is estimated to be between 1 in 20,000 and 1 in 100,000 infants who receive the vaccine.[35]

CRYPTOSPORIDIUM

Epidemiology

Cryptosporidiosis has been recognized as a human disease since the 1970s, with increasing importance in the 1980s and 1990s because of its association with HIV/AIDS as an opportunistic

Clinical Presentation and Diagnosis of Cryptosporidiosis

General

- 7- to 10-day incubation period
- Profuse, watery diarrhea with mucus but not blood or leukocytes that lasts for approximately 2 weeks
- Nausea, vomiting, fever, and abdominal cramps may accompany the diarrhea
- Simplest method of diagnosis is detection of oocysts by modified acid-fast staining of a stool specimen. Standard ova and parasite test does not include *Cryptosporidium*

Immunocompetent

- May manifest as asymptomatic disease, acute diarrhea, or persistent diarrhea lasting for several weeks
- Usually self-limiting

Immunocompromised

- May manifest as asymptomatic disease, chronic diarrhea lasting at least 2 months, or fulminant infection with at least 2 L of watery stool per day
- In HIV-infected individuals, asymptomatic disease is more common in those with a $CD4^+$ cell count greater than 200 cells/mm^3 (200×10^6/L), and fulminant infection is more common in those with a $CD4^+$ cell count of less than 50 cells/mm^3 (50×10^6/L)

Patient Encounter 3

A young woman comes into your pharmacy to pick up a pediatric oral electrolyte solution recommended by her child's doctor for her 2-year-old's mild dehydration. Her child has been ill with gastroenteritis for the last week. About a week and half prior to the onset of symptoms, the family had visited a water park, and she had played with the toddler in the kiddie pools. She describes the child's bowel movements as large-volume and watery. According to the local news, the water park has been temporarily closed due to an outbreak of similar symptoms in other children. The mother wants to know if there are any medications that could be used to treat her child besides the oral rehydration therapy.

Based on the history of illness, including recent exposures, what organism is a likely pathogen causing the child's gastroenteritis?

What discussion points could you include in your conversation with the mother regarding indication for antimicrobial treatment of this pathogen?

What counseling points would be important to include regarding potential duration of illness and measures to prevent autoinfection?

infection. *Cryptosporidium* is now recognized as a major cause of diarrhea in children, especially those less than 2 years old[36] and has been linked with childhood malnutrition and death in resource-limited settings. Studies using PCR and antigen detection have identified *Cryptosporidium* in 15% to 25% of children with diarrhea, which is often prolonged (7–14 days) or persistent (> 14 days).[37] Incident rates have also increased in the United States, which is partially attributed to recreational water park outbreaks and likely reflects increased use of communal swimming venues (eg, lakes, swimming pools, and water parks) by young children.[38] Cryptosporidiosis is spread person to person, usually via the fecal–oral route; by animals, particularly cattle and sheep; and through the environment, especially water.

Pathophysiology

Cryptosporidium is an intracellular protozoan parasite that is capable of completing its entire life cycle within one host. Humans become infected upon ingestion of the oocysts, and autoinfection and persistent infections are possible owing to repeated life cycles within the GI tract. As few as 10 to 100 oocysts can cause infection.

Treatment

In general, immunocompetent persons and those with asymptomatic infection do not require antimicrobial therapy. In patients with HIV/AIDS, the optimal therapy is restoration of immune function through the use of antiretroviral therapy (ART). For persons in whom antimicrobial therapy is deemed necessary or patients living with HIV/AIDS in whom ART is ineffective, a combination of an antimicrobial and an antidiarrheal agent is recommended.[37]

Nitazoxanide is the only FDA-approved agent for the treatment of cryptosporidiosis in adults and children 1 year and older. This agent has demonstrated efficacy in cryptosporidiosis (eg, higher rates of diarrhea resolution and oocyst-free stools compared to placebo) in immunocompetent persons and patients living with HIV/AIDS. Patients who are infected with both HIV and *Cryptosporidium* usually require longer therapy durations and higher doses than immunocompetent patients. An alternative agent that may be considered is paromomycin, a nonabsorbable aminoglycoside, though evidence of its long-term success in patients is limited.[37]

ENTEROTOXIN-PRODUCING BACTERIA AND FOOD POISONING

Each year in the United States, approximately 76 million food-borne illnesses occur, leading to 325,000 hospitalizations and more than 5000 deaths. Many bacterial and viral pathogens that have been discussed previously in this chapter (eg, *Salmonella*, *Shigella*, *Campylobacter*, *E. coli*, and noroviruses) can cause food poisoning. Other bacteria that can cause food-borne illness include *Staphylococcus aureus*, *C. perfringens*, *Clostridium botulinum*, and *Bacillus cereus* (Table 80–5). Food poisoning should be suspected if at least two individuals present with similar symptoms after the ingestion of a common food in the prior 72 hours.

Table 80–5

Food Poisonings

Organism	Onset (Hours)	Associated Foods	Duration	Symptoms	Treatment
Staphylococcus aureus	1–6	Salad, pastries, ham, poultry	12 hours	Nausea, vomiting	Supportive
Bacillus cereus—emetic	0.5–6	Rice, noodles, pasta, pastries	24 hours	Vomiting	Supportive
Bacillus cereus—diarrheal	8–16	Meats, vegetables, soups, sauces, milk products	24 hours	Diarrhea, abdominal pain	Supportive
Clostridium perfringens (type A)	8–12	Meats, poultry	24 hours	Nausea; abdominal cramps; profuse, watery diarrhea	Supportive
Clostridium botulinum	18–24	Canned fruits, vegetables, meats, honey, salsa, relish	Weeks	Acute GI symptoms followed by symmetric, descending, flaccid paralysis; death is possible	Supportive (including mechanical ventilation); trivalent antitoxin

Patient Care Process

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements.
- Identify allergies or rashes to medications and other substances.
- Review the medical history and physical assessment findings. In a child, immunization records are especially important.
- Speak with the patient to assess cultural beliefs, health goals, or socioeconomic factors that may affect medication access, vaccination, and other aspects of care.

Assess the Information:

- Determine if the patient is taking any substance that could interact with prescription medications (eg, vitamins, OTC medications, herbals, probiotics).
- Based on medical history, determine if the patient has risk factors for GI disorders, such as diarrhea and *C. difficile* colitis.
- Based on physical examination and review of systems, identify signs or symptoms associated with diarrhea or possible *C. difficile* infection.
- Determine the patient's weight history and determine if weight loss has occurred.
- Determine the cause of any weight loss (eg, anorexia, dehydration, insufficient calories).
- Determine adherence to current medication regimen.
- Identify potential adverse drug events or drug interactions with medication regimen.
- Review current evidence-based guideline recommendations.

Develop a Care Plan:

- Evaluate drug therapy options based on the patient's diagnosis.
- Discuss treatment options with the prescriber.
- Determine whether immunizations are needed in the near future.

Implement the Care Plan:

- Determine if the patient has insurance coverage, if applicable, and if recommended agents are included in the health system's formulary.
- Educate the patient about changes in drug therapy, appropriate administration of medications, potential adverse effects associated with the new antibiotic, and how to manage and report adverse effects that may occur.
- Dialogue with patient about concerns or past problems taking medications; suggest possible solutions.
- Indicate what actions to take if the patient vomits the dose or forgets to take a dose.
- Counsel patient on the recognition of symptoms of *C. difficile* infection, serious diarrhea, and dehydration, and actions to take if these occur, including notification of the patient's primary care physician.
- Discuss importance of taking the medications as prescribed as well as importance of routine vaccinations.

Follow-up: Monitor and Evaluate:

- Follow up assessing for symptoms of chronic diarrhea.

Abbreviations Introduced in This Chapter

CDC	Centers for Disease Control and Prevention
CDI	*Clostridioides difficile* infection
CFUs	Colony-forming units
EHEC	Enterohemorrhagic *Escherichia coli*
ESBL	Extended-spectrum beta-lactamase
FMT	Fecal microbiota transplantation
HUS	Hemolytic–uremic syndrome
ORT	Oral rehydration therapy
MIC	Minimum inhibitory concentration
NSAID	Nonsteroidal anti-inflammatory drug
NTS	Nontyphoidal *Salmonella*
PPI	Proton pump inhibitor
STEC	Shiga toxin–producing *E. coli*
TTP	Thrombotic thrombocytopenic purpura
WHO	World Health Organization

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Intra-Abdominal Infections

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Define and differentiate between primary and secondary intra-abdominal infections (IAIs).
2. Describe the microbiology typically seen with primary and secondary IAIs.
3. Describe the clinical presentation typically seen with primary and secondary IAIs.
4. Describe the role of culture and susceptibility information for diagnosis and treatment of IAIs.
5. Recommend the most appropriate drug and nondrug measures to treat IAIs.
6. Recommend an appropriate antimicrobial regimen for treatment of primary and secondary IAIs.
7. Describe the patient-assessment process during the treatment of IAIs.
8. Introduce the concepts of antimicrobial stewardship programs (ASPs) and antimicrobial de-escalation as it pertains to the treatment of IAIs.

INTRODUCTION

Intra-abdominal infections (IAIs) are those contained within the peritoneal cavity or retroperitoneal space. The peritoneal cavity extends from the undersurface of the diaphragm to the floor of the pelvis and contains the stomach, small bowel, large bowel, liver, gallbladder, and spleen. The duodenum, pancreas, kidneys, adrenal glands, great vessels (aorta and vena cava), and most mesenteric vascular structures reside in the retroperitoneum, which is the anatomical space in the abdominal cavity behind the peritoneum. IAIs may be generalized or localized. Localized IAIs may be contained within visceral structures, such as the liver, gallbladder, spleen, pancreas, kidney, or female reproductive organs. Two generalized types of IAI are discussed throughout this chapter: peritonitis and abscess. **Peritonitis** is defined as the acute inflammatory response of the peritoneal lining to microorganisms, chemicals, irradiation, or foreign-body injury.

An **abscess** is a purulent collection of fluid separated from surrounding tissue by a wall consisting of inflammatory cells and adjacent organs. It usually contains necrotic debris, bacteria, and inflammatory cells. Peritonitis and abscess differ considerably in presentation and approach to treatment.

EPIDEMIOLOGY AND ETIOLOGY

Peritonitis may be classified as primary, secondary, or tertiary. Primary peritonitis, also called spontaneous bacterial peritonitis, is an infection of the peritoneal cavity without an evident source of bacteria from the abdomen.[1,2] In secondary peritonitis, a focal disease process is evident within the abdomen. Secondary peritonitis may involve perforation of the gastrointestinal (GI) tract (possibly due to ulceration, ischemia, or obstruction), postoperative peritonitis, or posttraumatic peritonitis (eg, blunt or penetrating trauma). Tertiary peritonitis occurs in critically ill patients and is an infection that persists or recurs at least 48 hours after apparently adequate management of primary or secondary peritonitis. Factors related to the development of tertiary peritonitis are not well described although it is more often associated with opportunistic and nosocomial pathogens.

- **KEY CONCEPT** Most IAIs are secondary infections that are caused by a defect in the GI tract that must be treated by surgical drainage, resection, and/or repair. The prevalence of primary peritonitis is 10% to 30% in hospitalized patients with alcoholic cirrhosis.[3] Patients undergoing continuous ambulatory peritoneal dialysis (CAPD) average one episode of peritonitis every 2 years.[4] The majority of these are related directly to the peritoneal dialysis (PD) rather than nondialysis-related intra-abdominal or systemic processes. Secondary peritonitis may be caused by perforation of a peptic ulcer, traumatic perforation of the stomach, small or large bowel, uterus, or urinary bladder. It may also be caused by appendicitis, pancreatitis, diverticulitis, bowel infarction, inflammatory bowel disease, cholecystitis, operative contamination of the peritoneum, or diseases of the female genital tract such as septic abortion, postoperative uterine infection, endometritis, or salpingitis. Appendicitis is one of the most common causes of IAI.[5]

Primary peritonitis in adults occurs most commonly in association with alcoholic cirrhosis, especially in the end stage, or with ascites caused by postnecrotic cirrhosis, chronic active hepatitis, acute viral hepatitis, congestive heart failure, malignancy, systemic lupus erythematosus, and nephrotic syndrome. It also may result from the use of a peritoneal catheter for dialysis with renal failure or central nervous system (CNS) ventriculoperitoneal shunting for hydrocephalus. Abscesses are the result of chronic inflammation and may occur without preceding generalized peritonitis. They may be located within the peritoneal cavity or in a visceral organ and may vary in size, taking a few weeks to years to form.

Patient Encounter 1, Part 1

A 47-year-old female with a history of COPD, cirrhosis, and atrial fibrillation presents to the emergency room with chief complaints of worsening breathing and a weight gain of 10 kg over the last month. Her current medications are: spironolactone 25 mg orally daily, prednisone 25 mg orally daily, lactulose 30 mL orally titrated at home to 1 to 2 bowel movements per day, budesonide–formoterol (160–4.5 mcg/puff) inhaler two puffs inhaled twice daily, diazepam 5 mg orally twice daily, and apixaban 5 mg orally twice daily. The patient only speaks fluent Russian as her main language and no English.

PMH: COPD, cirrhosis, atrial fibrillation

Meds: Obtained from patient's outpatient pharmacy: Spironolactone 25 mg orally daily, prednisone 25 mg orally daily, lactulose 30 mL orally titrated at home to 1 to 2 bowel movements per day, budesonide–formoterol inhaler two puffs inhaled twice daily, diazepam 5 mg orally twice daily, and apixaban 5 mg orally twice daily

SOC: Divorced, occasional cannabis use

PE:

Abdomen soft and distended, positive bowel sounds with 2 days of loose stools. Neuro exam—patient is altered and not able to speak coherently and has asterixis, Skin—spider angiomas and jaundiced. Rest of the physical examination is noncontributory.

VS: T 101.3°F (38.0°C), BP 90/65 mm Hg, P 135 beats/min, RR 16 breaths/min, Wt 170 lb (67.7 kg), Ht 5′2″ (175 cm)

Labs: Hct 14.0% (0.140), Hgb 6.2 g/dL (62 g/L; 3.8 mmol/L), WBC 20 × 10^3/mm^3 (20 × 10^9/L), serum creatinine 1.4 mg/dL (123 μmol/L), BUN 20 mg/dL (7.14 mmol/L), Na 125 mEq/L (125 mmol/L), K 4.2 mEq/L (4.9 mmol/L), Cl 98 mEq/L (98 mmol/L), CO_2 22 mEq/L (22 mmol/L), total bilirubin 2.2 mg/dL (37.6 μmol/L), aPTT 40.0 seconds, INR—2.2, albumin 2.4 g/dL, ammonia 24.3 umol/L, estimated CrCl from the Cockcroft–Gault formula (40 mL/min)

1. *Discuss the diagnostic approach which should be taken in this patient in order to elucidate a diagnosis.*
2. *What are the top three diagnoses that could be made for this patient?*
3. *Based on your assessment of her medication history, are there any of her medications that could be potentiating her clinical condition? If so, which ones should be held or discontinued on hospital admission and transfer to the GI service?*
4. *What pharmacotherapeutic treatments should the pharmacy clinician focus on?*

PATHOPHYSIOLOGY

IAI results from bacterial entry into the peritoneal or retroperitoneal spaces or from bacterial collections within intra-abdominal organs. In primary peritonitis, bacteria may enter the abdomen via multiple mechanisms (ie, via the bloodstream or lymphatic system, by transmigration through the bowel wall, and through an indwelling PD catheter or ventriculoperitoneal catheter). **Hematogenous** bacterial spread (through the bloodstream) occurs more frequently with tuberculosis peritonitis or peritonitis associated with cirrhotic ascites. When peritonitis results from PD, skin-surface flora are introduced via the peritoneal catheter. In secondary peritonitis, bacteria most often enter the peritoneum or retroperitoneum as a result of perforation of the GI or female genital tracts caused by diseases or traumatic injuries, or via the fallopian tubes in females.

If bacteria that enter the abdomen are not contained by cellular and humoral defense mechanisms, bacterial dissemination occurs throughout the peritoneal cavity, resulting in peritonitis. This is more likely to occur in the presence of a foreign body, hematoma, necrotic tissue, large bacterial inoculum, continuing bacterial contamination, and contamination involving a mixture of synergistic organisms.

The fluid and protein shift into the abdomen (called **third spacing**) may be so dramatic that circulating blood volume is decreased, which causes decreased cardiac output and hypovolemic shock. Fluid shifts into the peritoneum occur secondary to inflammatory processes and leaky capillaries, as well as sepsis (Chapter 84). Accompanying fever, vomiting, or diarrhea may worsen the fluid imbalance. A reflex sympathetic response, manifested by sweating, tachycardia, and vasoconstriction, may be evident. With an inflamed peritoneum, bacteria and endotoxins are absorbed easily into the bloodstream (**translocation**), and this may result in septic shock (Chapter 84).[1] Other foreign substances present in the peritoneal cavity potentiate peritonitis notably feces, dead tissue, barium from medical imaging procedures, mucus, bile, and blood.

Many of the manifestations of IAIs, particularly peritonitis, result from cytokine activity. Inflammatory cytokines are produced by macrophages and neutrophils in response to bacteria and bacterial products or to tissue injury, resulting from the surgical incisions.[1] The outer membrane components of Gram-negative and Gram-positive organisms contribute to the cascade of proinflammatory cytokines, ultimately leading to end-organ dysfunction (lungs, heart, kidneys) and septic shock (Chapter 84).[6] Peritonitis may result in death because of the effects on major organ systems.

An abscess occurs if peritoneal contamination is localized but bacterial elimination is incomplete. The location of the abscess often is related to the site of primary disease. For example, abscesses resulting from appendicitis tend to appear in the right lower quadrant or the pelvis; those resulting from diverticulitis tend to appear in the left lower quadrant or pelvis. A mature abscess may have a fibrinous capsule that isolates bacteria and the liquid core from antimicrobials and immunologic defenses. In such cases, surgical drainage is the only effective therapy.

Microbiology of Intra-Abdominal Infection

KEY CONCEPT Primary bacterial peritonitis is often caused by a single organism. When peritonitis occurs in association with cirrhotic ascites, *Escherichia coli* and *Klebsiella* are isolated most frequently.[8] Other potential pathogens are *Haemophilus pneumoniae, Pseudomonas*, anaerobes, and *Streptococcus pneumoniae*.[9] Occasionally, primary peritonitis may be caused by *Mycobacterium tuberculosis*. In children, the pathogen is usually

Patient Encounter 2, Part 1

A 69-year-old man with a history of diabetes complicated by neuropathic pain, hypertension, hyperlipidemia, and ESRD on three times weekly hemodialysis presents to the dialysis center at the outpatient clinic with a 2-day history of high fevers and worsening "gut" pain. His surgical history comprises a bowel resection (5 years ago), an AV fistula graft for long-term hemodialysis plans (2 years ago). He was recently discharged from the inpatient medicine service last month with a methicillin-resistant Staphylococcus epidermidis bacteremia and GI bleed.

PMH: Diabetes with neuropathic pain, hypertension, hyperlipidemia, ESRD (oliguric)

Meds: Metformin 500 mg orally twice daily, atorvastatin 80 mg orally daily, gabapentin 300 mg orally daily, nephrocaps one capsule daily, calcium acetate 1334 mg orally daily with each meal, ferrous sulfate 325 mg orally twice daily, pantoprazole 40 mg orally daily, clonidine 0.2 mg orally three times daily, amlodipine 10 mg orally daily, valsartan 160 mg orally daily

SOC: Married, some alcohol, and no smoking, or illicit drugs

PE:

The patient is experiencing abdominal tenderness and on pain scale of 1 to 10 (endorses 7). He also had one bloody stool per rectum over the last 72 hours.

VS: T 102°F (38.9°C), BP 120/75 mm Hg, P 90 beats/min, RR 16 breaths/min, Wt 260 lb (dry weight on admission [118 kg]), Ht 6′ 4″ (193 cm)

Labs: Na 140 mEq/L (140 mmol/L), K 4 mEq/L (4 mmol/L), Cl 99 mEq/L (95 mmol/L), CO$_2$ 25 mEq/L (25 mmol/L), glucose 300 mg/dL (4.68 mmol/L), BUN 80 mg/dL (28.6 mmol/L), serum creatinine 8 mg/dL (707 μmol/L), glucose 300 mg/dL (4.68 mmol/L), total bilirubin 1 mg/dL (17.1 μmol/L), lactate 5.5 mg/dL (0.60 mmol/L), Hct 24% (0.24), Hgb 8 g/dL (80 g/L; 4.96 mmol/L), WBC 25 × 10^3/mm^3 (25 × 10^9/L), procalcitonin 10 mcg/L

1. *What test(s) or lab(s) should be done to ascertain the cause of his new possible pending hospital admission from the clinic?*
2. *Which monitoring parameters should be monitored in the next 24 to 72 hours?*
3. *What pharmacological treatments (fluids, antibiotics, and doses) and potential toxicities can occur with this initial plan?*
4. *List the top four to five most likely organisms and resistance patterns that can result from overuse of antimicrobials for intra-abdominal processes.*

S. pneumoniae or a Group A *Streptococcus, E. coli,* or *Bacteroides* species.[4,7] Peritonitis in patients undergoing PD is caused most often by common skin organisms ranging from *Staphylococcus aureus* to *Staphylococcus epidermidis*.[10]

KEY CONCEPT Because of the diverse bacteria present in the GI tract, secondary IAIs are often polymicrobial.[2,11]

Bacterial Synergism and Other Factors

A combination of aerobic and anaerobic organisms appears to increase the severity of infection (synergism). Facultative bacteria (eg, *E. coli*) may provide an environment conducive to the growth of anaerobic bacteria.[2] Although many bacteria isolated in mixed infections are nonpathogenic by themselves, their presence may be essential for the pathogenicity of the bacterial mixture.[3]

Complicating the clinical picture for treatment are polymicrobial IAIs with certain bacterial species being isolated, such as *Enterococci* or *Pseudomonas aeruginosa*. Targeting these organisms may be necessary in some patients to avoid treatment failure or mortality, especially if they are immunocompromised.[12]

CLINICAL PRESENTATION AND DIAGNOSIS

IAIs have a wide spectrum of clinical features. Patients with primary and secondary peritonitis present quite differently. Peritonitis is usually easier to detect and diagnose. Intra-abdominal abscess, on the other hand, may continue unrecognized for long periods of time because the infection is walled off and does not elicit the same host immune response as primary peritonitis.

Clinical Presentation of Primary Peritonitis

General

Patients may not be in acute distress, particularly with peritoneal dialysis (PD)-related peritonitis.

Symptoms

Patients may complain of nausea, vomiting (sometimes with diarrhea), and abdominal tenderness.

Signs

- Temperature may range from only mildly elevated to significantly elevated. In patients undergoing PD, temperature may not be elevated.
- Bowel sounds may be hypoactive.
- Cirrhotic patients may have worsening encephalopathy.
- There may be cloudy dialysate fluid with PD.

Laboratory Tests

- The WBC may range from mildly elevated to significantly elevated.
- Ascitic fluid usually contains more than 0.25 × 10^3/mm^3 (0.25 × 10^9/L) leukocytes, and bacteria may be evident on Gram stain of a centrifuged specimen.

Other Diagnostic Tests

- Culture of peritoneal dialysate or ascitic fluid should be positive.

Table 81–1

Likely Intra-Abdominal Pathogens

Type of Infection	Aerobes	Anaerobes
Primary (Spontaneous) Bacterial Peritonitis		
Children	Group A *Streptococcus, Escherichia coli*, pneumococci	—
Cirrhosis	*E. coli, Klebsiella*, pneumococci (many others)	—
Peritoneal dialysis	*Staphylococcus, Streptococcus, E. coli, Klebsiella, Pseudomonas*	—
Secondary Bacterial Peritonitis		
Gastroduodenal	*Streptococcus, E. coli*	—
Biliary tract	*E. coli, Klebsiella, Enterococci*	*Clostridium* or *Bacteroides* (infrequent)
Small or large bowel	*E. coli, Klebsiella, Proteus*	*B. fragilis* and other *Bacteroides, Clostridium*
Appendicitis	*E. coli, Pseudomonas*	*Bacteroides*
Abscesses	*E. coli, Klebsiella, Streptococcus, Enterococci*	*B. fragilis* and other *Bacteroides, Clostridium,* anaerobic cocci
Liver	*E. coli, Klebsiella, Streptococcus, Enterococci, Staphylococcus,* amoeba	*Bacteroides* (infrequent)
Spleen	*Staphylococcus, Streptococcus, E. coli, Salmonella*	

Patients with abscesses may present with symptoms that are indolent. The epidemiology and treatment of primary peritonitis are summarized in Tables 81–1 and 81–2.

PREVENTION AND TREATMENT

For patients that are presenting for elective general surgery and nonemergent surgical procedures, best practice for the prevention of IAI constitutes perioperative antimicrobial prophylaxis. Dependent on the length of the surgery, intraoperative administration of antibiotics may be required. Evidence also strongly recommends discontinuation of perioperative of antibiotics at the 24-hour time frame for antimicrobial stewardship (Chapter 69).[13] The primary goals of treatment are correction of the intra-abdominal disease processes or injuries that have caused infection and drainage of collections (**source control**) of purulent material (**abscess**). A secondary goal is to resolve the infection without major organ system complications (eg, pulmonary, hepatic, cardiovascular, or renal failure) or adverse drug effects. Ideally, the patient should be discharged from the hospital with full function for self-care and routine daily activities.

General Approach to Treatment

The treatment of IAI most often requires the coordinated use of four major modalities: (a) prompt drainage, (b) support of vital functions, (c) appropriate antimicrobial therapy to treat infection not eradicated by surgery,[14] and (d) antimicrobial stewardship principles (Chapter 69).[15,16] For most cases of primary peritonitis,

Table 81–2

Recommended Agents for the Treatment of Community-Acquired Intra-Abdominal Infections in Adults

Agents Recommended for Mild-to-Moderate Infections	Agents Recommended for High-Risk or High-Severity Infections[f]
Single Agent	
Cefoxitin[a]	Piperacillin–tazobactam
Moxifloxacin[b]	Imipenem–cilastatin[c], meropenem[c], doripenem[c]
Ertapenem[c]	
Combination Regimens	
Cefazolin[a], cefuroxime[a], ceftriaxone, cefotaxime (each in combination with metronidazole)	Cefepime, ceftazidime, ceftazidime/avibactam[d], or ceftolozane/tazobactam[e] (each in combination with metronidazole)
Ciprofloxacin[b] or levofloxacin[b] (each in combination with metronidazole)	Ciprofloxacin[b] or levofloxacin[b] (each in combination with metronidazole)

[a] Empiric first- and second-generation cephalosporin use should be avoided unless local antibiograms show > 80%–90% susceptibility of *Escherichia coli* to these agents.

[b] Use of quinolones may be associated with treatment failure due to increasing resistance of enteric pathogens including *E. coli*. Empiric quinolone use should be avoided unless local antibiograms show > 80%–90% susceptibility of *E. coli* to quinolones.

[c] Carbapenems should typically be reserved for settings where there is a high risk of resistance to other agents (ie, extended-spectrum β-lactamase [ESBL]-producing pathogens).

[d] Ceftazidime/avibactam should be reserved for patients infected with *Enterobacteriaceae* that are resistant to all other β-lactams including carbapenems, and in particular, *Klebsiella pneumoniae* carbapenemase (KPC)-producing pathogens.

[e] Ceftolozane/tazobactam should be reserved for patients infected with Gram-negative bacteria that are resistant to all other β-lactams. Ceftolozane/tazobactam may have activity against multi-drug resistant *Pseudomonas*; however, susceptibility must be confirmed.

[f] High-severity is defined as patients suffering from septic shock requiring vasopressors and intensive care unit admission.

Reproduced, with permission, from Gross AE, Olsen KM. Intra-abdominal infections. In: DiPiro JT, Yee GC, Posey M, et al., eds. Pharmacotherapy: A Pathophysiologic Approach. 11th ed. New York, NY: McGraw-Hill; 2019.

drainage procedures may not be required, and antimicrobial agents become the mainstay of therapy. Antimicrobials are an important adjunct to drainage procedures in the treatment of secondary IAIs. However, the use of antimicrobial agents without surgical intervention, especially in secondary peritonitis, is usually inadequate.

KEY CONCEPT In the early phase of serious IAIs, attention should be given to preserving major organ system function. A common cause of early death is hypovolemic shock caused by inadequate intravascular volume expansion and tissue perfusion. With generalized peritonitis, large volumes of intravenous (IV) fluids are required to maintain intravascular volume, improve cardiovascular function, and ensure adequate tissue perfusion and oxygenation. Adequate urine output should also be maintained to ensure appropriate fluid resuscitation and to preserve renal function.

An additional important component of therapy is nutrition. IAIs often involve the GI tract directly or disrupt its function (paralytic ileus). The return of GI motility may take days, weeks, and occasionally, months. In the interim, enteral or parenteral nutrition, as indicated, facilitates improved immune function and wound healing to ensure recovery.

Clinical Presentation of Secondary Peritonitis

General

Patients may be in acute distress.

Symptoms

- Patients may complain of nausea, vomiting, and generalized abdominal pain.
- Patients may demonstrate abdominal guarding and rigidity.

Signs

- Sweating, tachypnea, and tachycardia are present.
- Temperature is normal initially, then may increase to 100 to 102°F (37.8–38.9°C) within the first few hours; temperature may continue to rise for the next several hours.
- Hypotension and shock may develop if intravascular volume is not restored.
- Decreased urine output may develop secondary to dehydration or intravascular volume depletion.
- Bowel sounds are faint initially and eventually cease.

Laboratory Tests

- The WBC count is typically high (WBCs 15–20 × 10^3/mm^3 [15–20 × 10^9/L]), with neutrophils predominating and an elevated percentage of immature neutrophils (bands).
- The hematocrit and blood urea nitrogen increase because of dehydration.
- Hyperventilation and vomiting result in early alkalosis, which changes to acidosis and lactic academia due to reduced intravascular volume and diminished tissue perfusion.

Other Diagnostic Tests

Abdominal radiographs may be useful because free air in the abdomen (indicating intestinal perforation) or distension of the small or large bowel is often evident.

Nonpharmacologic Therapy

▶ Drainage Procedures

Primary peritonitis is treated with antimicrobials and rarely requires drainage. Secondary peritonitis requires surgical removal of the inflamed or gangrenous tissue to prevent further bacterial contamination. If the surgical procedure is suboptimal, attempts are made to provide drainage of the infected or gangrenous structures.

The drainage of purulent material is the critical component of management of an intra-abdominal abscess. This may be performed surgically or with percutaneous image-guided techniques.[16] Without adequate drainage of the abscess, antimicrobial therapy and fluid resuscitation can be expected to fail. In addition, some of the most valuable microbiologic information may be obtained at the time of percutaneous or operative abscess drainage.

▶ Fluid Therapy

In patients with peritonitis, hypovolemia is often accompanied by acidosis, and large volumes of a balanced crystalloid IV solution, such as Lactated Ringer's, may be required initially to restore intravascular volume. Maintenance fluids should be instituted (after intravascular volume is restored) with 0.9% sodium chloride and potassium chloride (20 mEq/L [20 mmol/L]) or 5% dextrose and 0.45% sodium chloride with potassium chloride (20 mEq/L [20 mmol/L]). The administration rate should be based on estimated daily fluid loss through urine and nasogastric suction, including 0.5 to 1.0 L for insensible fluid loss. Aggressive fluid therapy often must be continued in the postoperative period because fluid will continue to sequester in the peritoneal cavity, bowel wall, and lumen.

Pharmacologic Therapy

▶ Antimicrobial Therapy

The goals of antimicrobial therapy are as follows:

- To control bacteremia and prevent the establishment of metastatic foci of infection
- To reduce suppurative complications after bacterial contamination
- To prevent local spread of existing infection
- To de-escalate antimicrobials as soon as pathogens are identified and culture and sensitivity data are reported

KEY CONCEPT An empirical antimicrobial regimen should be started as soon as the presence of IAI is suspected and before identification of the infecting organisms is complete. Therapy must be initiated based on the likely pathogens, which vary depending on the site of IAI, the underlying disease process, and individual history of previous organisms. Cultures of metastatic IAI sites generally are not useful for directing antimicrobial therapy. Table 81–1 lists the likely pathogens against which antimicrobial agents should be directed.

▶ Antimicrobial Experience

Important findings from clinical trials regarding selection of antimicrobials for IAIs are as follows:

- Antimicrobial regimens for secondary IAIs should cover a broad spectrum of aerobic and anaerobic bacteria from the GI tract. It is believed that the overuse of antimicrobials has contributed to the development of IAIs with carbapenem-resistant *Enterobacteriaceae* (CRE), *Pseudomonas*, and

Patient Encounter 1, Part 2: Physical Examination and Diagnostic Tests

PE:

The patient is experiencing more pain (8/10 pain scale), and the attending physician decides to perform an invasive test.

Ascitic fluid analysis is reported as follows: hazy yellow color with 3225/mm^3 (3.225 × 10^9/L) WBC, (40% [0.40] neutrophils, 5% [0.05] lymphocytes, 55% [0.55] macrophages). Urinalysis is not significant because the patient is oliguric. Other physical examination findings are nonsignificant.

VS: As noted previously

Labs: As noted previously

Serum: As noted previously

KUB: Negative findings

DPL (diagnostic peritoneal lavage): 3225/mm^3 (3225 × 10^9/L)

Microbiological cultures: 2/2 bottles from the blood positive for Gram-positive pairs in chains and Gram-negative bacilli.

1. *Discuss the most appropriate pharmacologic course of treatment, outlining medications, dosing, and monitoring parameters.*
2. *List the goals of treatment and follow-up plan that should be developed by the clinician to ensure positive patient outcomes.*

PE:

The patient is becoming more obtunded 24 hours into the hospital course, so it is difficult to determine her degree of pain. The attending physician decides to perform an invasive test(s).

Ascitic fluid analysis is reported as follows: moderate bloody turbid color with 1,036/mm^3 (1.036 × 10^9/L) WBC, (44% [0.44] neutrophils, 5% [0.05] mesothelial cells, 51% [0.51] macrophages), RBC 19,182/mm^3 ANC 456 units/mm^3. Other physical examination findings are nonsignificant, except for asterixis (similar to initial presentation).

VS: As noted previously

Labs: As noted previously

Serum: As noted previously

KUB: Distended loops of bowel

DPL (diagnostic peritoneal lavage): WBC 1,036/mm^3 (1.036 × 10^9/L), RBC 19,182/mm^3 (19,182 × 10^9)

Microbiological cultures: 2/2 bottles from the blood are positive for Gram-negative bacilli.

1. *Discuss the most appropriate pharmacologic course of treatment, outlining medications, dosing, and monitoring parameters.*
2. *List the goals of treatment and follow-up plan that should be developed by the clinician to ensure positive patient outcomes.*
3. *Based on the fact that this patient speaks Russian, how can the pharmacist on the multidisciplinary team bridge the gaps of educating the patient on their diagnosis, medical/surgical care, and medication education?*

Acinetobacter spp., as well as greater prevalence of methicillin-resistant *S. aureus* (MRSA), *Candida* spp., and *Enterococcus* IAIs. This has made drug selection a challenge.[18,19]

Patient Encounter 2, Part 2

The patient's clinical status worsens over the next 24 hours requiring the patient to be intubated with high Fi02 requirements; vasopressors being initiated (norepinephrine and vasopressin); 2 L of Lactated Ringer's being administered; and stat antimicrobial coverage being initiated. Neurologically, the patient is more obtunded and has a Richmond Agitation Sedation Score (RASS) of −5 indicating near coma (despite no sedation or analgesia post intubation).

1. *What are your next steps in terms of a care plan as well as monitoring parameters for this patient?*
2. *If the patient's blood cultures (2/2 bottles) reveal both a Pseudomonas aeruginosa and Enterococcus spp., what new agents could be used and what treatment duration should you use?*
3. *If this is an intra-abdominal infectious process, what should be the nonpharmacological treatment plan and goals and the pharmacological plans and goals for this patient?*

- Single-agent regimens (such as antianaerobic cephalosporins, extended-spectrum penicillins with β-lactamase inhibitors, or carbapenems) are as effective with fewer adverse effects as combinations of aminoglycosides (more adverse reactions) or fluoroquinolones (more incidences of *Clostridium difficile*) with antianaerobic agents. This is also true for antimicrobial treatment of acute bacterial contamination from penetrating abdominal trauma.
- Antimicrobial stewardship efforts in the treatment of IAIs show promise to curb antimicrobial overuse that contributes to multidrug-resistant (MDR) organisms, without affecting positive outcomes.[20] Strategies utilized by antimicrobial stewardship programs (ASPs) are impactful on antimicrobial use when they incorporate institution-specific antibiograms, utilize national guidelines for treatment, and proactively target adherence with education to prescribers for IAIs (Chapter 69).[18]
- Metronidazole in combination with either certain cephalosporins or fluoroquinolones (ciprofloxacin, levofloxacin) is considered effective empiric antimicrobial regimens for mild–moderate infections and high-risk or high-severity infections.
- Oral alternatives (such as moxifloxacin; the combination of levofloxacin or ciprofloxacin plus metronidazole; or amoxicillin-clavulanate) can be considered if patients can be transitioned. (after susceptibility results and clinical improvements are noted).

- Results from recent trials suggest that a 4-day duration of therapy is acceptable for most patients with IAIs with adequate source control.[21,22]
- New agents for the treatment of MDR Gram-negative bacilli for complicated IAIs have recently been approved. Ceftolozane is a novel cephalosporin with the β-lactamase inhibitor tazobactam that confers enhanced activity against both *P. aeruginosa* and MDR Gram-negative bacilli. Ceftazidime–avibactam is another combination antibiotic (β-lactam/β-lactamase inhibitor) and treatment option in complicated IAIs (*Klebsiella pneumoniae* CRE). Both new antibiotics have been studied in combination with metronidazole. Another new broad spectrum fluorocycline antibiotic, eravacycline, is approved for complicated IAIs, specifically due to CRE bacteria but lacks *P. aeruginosa* coverage.[23] ASPs will need to ensure proper use of these agents to limit resistance as much as possible.[24-28]
- IAIs present in many different ways and with a wide spectrum of severity. The antibiotic regimen employed and the duration of treatment depend on the specific clinical circumstances (ie, the nature of the underlying disease process and the condition of the patient).

Recommendations

KEY CONCEPT For most IAIs, the antimicrobial regimen should be effective against both aerobic and anaerobic bacteria.[16] Although it is impossible to provide antimicrobial activity against every possible pathogen, agents with activity against enteric Gram-negative bacilli, such as *E. coli* and *Klebsiella* spp., and anaerobes, such as *Bacteroides fragilis* and *Clostridia* spp., should be administered.

Table 81–2 presents the recommended agents for treatment of community-acquired and complicated IAIs from the Infectious Diseases Society of America and the Surgical Infection Society.[29] These recommendations were formulated using an evidence-based approach. Most community-acquired infections are "mild-to-moderate," whereas healthcare-associated infections tend to be more severe and difficult to treat. Table 81–3 presents guidelines for treatment and alternative regimens for specific situations. These are general guidelines; there are many factors that cannot be incorporated into such a table.

Aminoglycosides (with nephrotoxicity and ototoxicity being a concern) and clindamycin have been relegated to secondary or tertiary options for the treatment of IAIs. Metronidazole is the agent of choice for *B. fragilis*; but antianaerobic cephalosporins, such as cefoxitin, cefotetan, or ceftizoxime, and combinations of extended-spectrum penicillins with β-lactamase inhibitors would be suitable alternatives. Preemptive antifungal therapy may be indicated with either an azole antifungal (fluconazole) or an echinocandin (caspofungin or micafungin) in patients who are immunocompromised or postsurgical with recurrent infection. These patients are more likely to develop a fungus secondary to risk factors such as being on broad-spectrum antimicrobials, having central lines, and being on parenteral nutrition.

In immunocompromised patients or patients with valvular heart disease or a prosthetic heart valve, there is justification to provide specific antimicrobial activity against *Enterococci*. Ampicillin or other penicillins are active against *Enterococci* (eg, penicillin and piperacillin) and should be used in patients at high risk of IAI, patients with persistent or recurrent IAI, or patients who are immunosuppressed, such as after organ transplantation. Ampicillin remains the drug of choice for this indication because it is most active in vitro against *Enterococci* and is relatively inexpensive. Vancomycin is active against most *Enterococci*; however, resistance is increasing.

Intraperitoneal (IP) administration of antibiotics is preferred over IV therapy in the treatment of peritonitis that occurs in patients undergoing CAPD.[30] The International Society of Peritoneal Dialysis guidelines for the diagnosis and pharmacotherapy of PD-associated infections provide dosing recommendations for intermittent and continuous therapy based on the modality of dialysis (CAPD or automated peritoneal dialysis [APD]) and the extent of the patient's residual renal function.[10]

KEY CONCEPT Antimicrobial agents effective against both Gram-positive and Gram-negative organisms should be used for initial IP empirical therapy for peritonitis in PD patients. The most important factors to take into consideration for initial antimicrobial selection are the dialysis center's and the patient's history of infecting organisms and their susceptibilities. The use of cefazolin (loading dose [LD] 500 mg/L, maintenance dose [MD] 125 mg/L) plus ceftazidime (LD 500 mg/L, MD 125 mg/L) or cefepime (LD 250–500 mg/L, MD 100–125 mg/L) or gentamicin (LD 8 mg/L, MD 4 mg/L) or tobramycin (LD 3 mg/kg, MD 0.3 mg/kg) is suitable for initial two-drug combination empirical therapy. If patients are allergic to cephalosporin antibiotics, vancomycin (LD 30 mg/kg, MD 1.5 mg/kg/bag) or an aminoglycoside should be substituted. Aztreonam (LD 1000 mg/L, MD 250 mg/L) is an alternative to ceftazidime or cefepime in this patient population. Another option is monotherapy with imipenem–cilastatin (LD 250 mg/L, MD 50 mg/L) or cefepime. Antimicrobial doses should be increased empirically by 25% in patients with residual renal function (> 100 mL/day urine output).[10] Repeat dialysis effluent cell counts and cultures should be done after at least 3 to 5 days of antimicrobial therapy, which should continue for at least a 14- to 28-day treatment course dependent on the microorganism identified. The reader is referred to these guidelines for additional information.[10]

After acute bacterial contamination, such as with abdominal trauma where GI contents contaminate the peritoneum, combination antimicrobial regimens are not required. If the patient is seen soon after injury (within 2 hours) and surgical measures are instituted promptly, antianaerobic cephalosporins (eg, cefoxitin or cefotetan) or extended-spectrum penicillins are effective in preventing most infectious complications. Antimicrobials should be administered as soon as possible after injury.[30]

For appendicitis, the antimicrobial regimen used should depend on the appearance of the appendix at the time of operation, which may be normal, inflamed, gangrenous, or perforated. Because the condition of the appendix is unknown preoperatively, it is advisable to begin antimicrobial agents before the appendectomy is performed. Reasonable regimens would be antianaerobic cephalosporins or, if the patient is seriously ill and on vasopressors in the intensive care unit (Chapter 84), a carbapenem or β-lactam–β-lactamase-inhibitor combination that are more broad spectrum in their scope. If, at operation, the appendix were normal or inflamed, postoperative antimicrobials would not be required. If the appendix is gangrenous or perforated, a treatment course of 4 days with the agents listed in Table 81–2 is appropriate.

KEY CONCEPT Acute intra-abdominal contamination, such as after a traumatic injury, may be treated with a short course (24 hours) of antimicrobials if therapy is begun quickly.[29] For established infections (ie, peritonitis or intra-abdominal abscess), an antimicrobial course limited to 4 days is justified. Under certain

Table 81–3

Guidelines for Empiric Antimicrobial Agents for Intra-Abdominal Infections[10,29]

	Primary Agents	Alternatives
Primary (Spontaneous) Bacterial Peritonitis		
Cirrhosis	Ceftriaxone, cefotaxime	1. Piperacillin–tazobactam, carbapenems 2. Aztreonam combined with an agent active against *Streptococcus* spp. (eg, vancomycin) or quinolones with significant *Streptococcus* spp. activity (levofloxacin, moxifloxacin)
Peritoneal dialysis	Initial empiric regimens should be active against both Gram-positive (including *Staphylococcus aureus*) and Gram-negative pathogens: Gram-positive agent (first-generation cephalosporin or vancomycin) plus a Gram-negative agent (third-generation cephalosporin or aminoglycoside)	1. Cefepime or carbapenems may be used alone 2. Aztreonam or an aminoglycoside may be used in place of ceftazidime or cefepime as long as combined with a Gram-positive agent 3. Quinolones may be used in place of Gram-negative agents if local susceptibilities allow
	1. *Staphylococcus* spp.: oxacillin/nafcillin or first-generation cephalosporin	1. Vancomycin should be used if concern for methicillin-resistant *Staphylococcus* spp. 2. Add rifampin for 5–7 days with vancomycin to reduce the risk for relapsing or repeat methicillin-resistant *S. aureus* peritonitis
	2. *Streptococcus* or *Enterococcus*: ampicillin	1. An aminoglycoside may be added for *Enterococcus* spp. 2. Linezolid, daptomycin, or quinupristin/dalfopristin should be used to treat vancomycin-resistant *Enterococcus* spp. not susceptible to ampicillin.
	3. Aerobic Gram-negative bacilli: ceftazidime or cefepime	1. The regimen should be based on in vitro sensitivity tests.
	4. *Pseudomonas aeruginosa*: two agents with differing mechanisms of action, such as an oral quinolone plus ceftazidime, cefepime, gentamicin, or a carbapenem	
Secondary Bacterial Peritonitis		
Perforated peptic ulcer	First-generation cephalosporins	1. Ceftriaxone, cefotaxime, or antianaerobic cephalosporins[a]
Other	Third- or fourth-generation cephalosporin with metronidazole, piperacillin–tazobactam or carbapenem	1. Ciprofloxacin[b] or levofloxacin[b] each with metronidazole, or moxifloxacin[b] alone 2. Aztreonam with vancomycin and metronidazole 3. Antianaerobic cephalosporins[a]
Abscess		
General	Third- or fourth-generation cephalosporin with metronidazole, piperacillin–tazobactam	1. Imipenem-cilastatin, meropenem, doripenem, or ertapenem 2. Ciprofloxacin[b] or levofloxacin[b] each with metronidazole or moxifloxacin alone
Liver	As above	Use metronidazole if amoebic liver abscess is suspected
Spleen	Ceftriaxone or cefotaxime	Moxifloxacin[b] or levofloxacin[b]
Other Intra-Abdominal Infections		
Appendicitis	Same management as for community-acquired complicated intra-abdominal infections as listed in Table 81–2	
Community-Acquired Acute Cholecystitis	Ceftriaxone or cefotaxime	Severe infection, piperacillin/tazobactam, antipseudomonal carbapenem, aztreonam with metronidazole
Cholangitis	Ceftriaxone or cefotaxime each with or without metronidazole	Vancomycin with aztreonam with or without metronidazole
Acute Contamination from Abdominal Trauma	Anti-anaerobic cephalosporins[a] or metronidazole with either ceftriaxone or cefotaxime	1. Piperacillin/tazobactam or a carbapenem 2. Ciprofloxacin[b] or levofloxacin[b] each with metronidazole or moxifloxacin alone

[a] Cefoxitin or cefotetan; these agents should be avoided empirically unless local antibiograms show > 80%–90% susceptibility of *Escherichia coli* to these agents.

[b] Use of quinolones may be associated with treatment failure due to increasing resistance of enteric pathogens including *E. coli*. Empiric quinolone use should be avoided unless local antibiograms show > 80%–90% susceptibility of *E. coli* to quinolones.

conditions, therapy for longer than 4 days would be justified (eg, poor response, resistant organism identified, or failure to control the source of infection). For some abscesses, such as pyogenic liver abscess, antimicrobials may be required for a month or longer because of resistance increasing after initial antimicrobial treatment.

OUTCOME EVALUATION

Whether diagnosed with primary or secondary peritonitis, monitor the patient for relief of symptoms. Once antimicrobials are initiated, and the other important therapies described earlier are used, most patients should improve within 2 to 3 days. Successful antimicrobial therapy with resolution of infection will result in decreased pain, manifested as resolution of abdominal guarding and decreased use of pain medications over time. The patient should not appear in distress, with the exception of recognized discomfort and pain from incisions, drains, and a nasogastric tube.

Monitor vital signs and WBC count with differential; each should normalize as the infection resolves. At 24 to 48 hours, aerobic bacterial culture results should be available. If a suspected pathogen is not susceptible to the antimicrobial agents being given, and the patient has not sufficiently improved, the regimen should be adjusted. If the isolated pathogen is susceptible to one antimicrobial and the patient is improving, therapy should be streamlined to a single agent.

With anaerobic culturing techniques and the slow growth of these organisms, anaerobes often are not identified until 4 to 7 days after culture, and sensitivity information is difficult to obtain. For this reason, anaerobic culture information generally is not helpful for selection of the antianaerobic component of the antimicrobial regimen.

Once the patient's temperature is normal for 48 to 72 hours, and the patient is eating, consider changing the IV antibiotic to an oral regimen for the duration of antibiotic treatment. Monitor the serum creatinine level to evaluate for renal complications as well as potential drug toxicity. Bowel sounds should return to normal. Evaluate the patient daily for development of rash or other drug-related adverse effects such as antibiotic-associated diarrhea.

For patients with primary peritonitis, if peritoneal dialysate cultures were positive initially, repeat cultures should be negative. For patients with secondary peritonitis, monitor the amount of fluid draining if a drain was placed. The volume of drainage should lessen as the infection resolves. Repeat abdominal radiographs should return to normal.

If symptoms do not improve, the patient should be evaluated for persistent infection. There are many reasons for poor patient outcome with IAI; improper antimicrobial selection is only one. The patient may be immunocompromised, which decreases the likelihood of successful outcome with any regimen. It is impossible for antimicrobials to completely compensate for a nonfunctioning immune system. There may be surgical reasons for poor patient outcome. Failure to identify all intra-abdominal foci of infection or leaks from a GI anastomosis may cause continued IAI. Even when IAI is controlled, accompanying organ system failure, most often renal or respiratory, may lead to patient demise.

KEY CONCEPT Healthcare–associated infections are becoming more commonly seen for IAIs with increasing prevalence of acute care hospital admissions or admissions from chronic care settings. The major pathogens include more resistant Gram-negative flora, *Candida* infections causing peritonitis, and *Enterococcus* species.[31]

The outcome from IAI is not determined solely by what transpires in the abdomen. Unsatisfactory outcomes in patients with IAIs may result from complications that arise in other organ systems. Infectious complications commonly associated with mortality after IAI are urinary tract infections and pneumonia.[19] Reasons for antimicrobial failure may not always be apparent. Even when antimicrobial susceptibility tests indicate that an organism is susceptible to the antimicrobial agent, therapeutic failures may occur. There may be poor penetration of the antimicrobial agent into the focus of infection, or bacterial resistance may develop after initiation of antimicrobial therapy. Superinfection—a secondary infection resulting from the preferential killing of the primary pathogen—can be caused by *Candida*; however, *Enterococci* or opportunistic Gram-negative bacilli such as *Pseudomonas* or ESBL-producing *Enterobacteriaceae* may also be involved.

Treatment regimens for IAI can be deemed successful if the patient recovers from the infection without recurrent peritonitis or intra-abdominal abscess and without the need for additional antimicrobials. A regimen can be considered unsuccessful if a patient

Patient Care Process

Collect Information:

- You should do a thorough patient medication history at the time of admission to document all recent medication use, including nonprescription medications and the use of complementary or alternative medicines. You should also document any drug allergies or intolerances for your patient. You should also search for all available patient information in the pertinent patient's medical record.

Assess the Information:

- Be cognizant for the initial antimicrobial regimen conforming to standard guidelines (unless an appropriate justification for an alternative regimen is evident).

Develop a Care Plan:

- You should review the dosages of all medications to be sure that they are appropriate for age, weight, and major organ function.
- You should also verify that the drugs selected are not contraindicated in the patient with allergies or drug–drug interactions.

Implement the Care Plan:

- You should select antimicrobials that are appropriate based on the susceptibility information, while reviewing the results of the cultures obtained both preoperatively or during the surgical procedure. Antimicrobials should be de-escalated when clinically appropriate. You should educate other practitioners on proper de-escalation technique.
- On the second or third day of antimicrobial treatment or when GI function returns, determine whether parenteral antimicrobial agents can be switched to oral agents to complete therapy. This again is part of a robust ASP best practice.
- Assess nutritional needs and recommend appropriate supplementation. When the patient is tolerating an oral diet, determine whether any parenteral medications can be switched to the oral route.

Follow-up: Monitor and Evaluate:

- You should monitor the patient for the development of potential complications of treatment such as delayed hypersensitivity reactions, antibiotic-induced diarrhea, pseudomembranous colitis, or fungal superinfections (eg, oral thrush).
- You should also educate the patient on the medications administered in the hospital as well as any new medications prescribed for use at home.
- You should also advise the patient to contact his or her doctor or pharmacist if he or she experiences any adverse effects from medications.

develops a tertiary peritonitis (ie, the need for reoperation or percutaneous drainage is necessary or if improvement is delayed beyond 1 or 2 weeks) or if a significant adverse drug reaction occurs.

Abbreviations Introduced in This Chapter

APD	Automated peritoneal dialysis
ASP	Antimicrobial stewardship program
CAPD	Continuous ambulatory peritoneal dialysis
CRE	Carbapenemase-resistant *Enterobacteriaceae*
DPL	Diagnostic peritoneal lavage
ESBL	Extended-spectrum producing β-lactamase *Enterobacteriaceae*
IAIs	Intra-abdominal infections
IP	Intraperitoneal
KPC	*Klebsiella* pneumonia carbapenemase
LD	Loading dose
MD	Maintenance dose
MDR	Multidrug-resistant
MRSA	Methicillin-resistant *S. aureus*
PD	Peritoneal dialysis

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82

Urinary Tract Infections and Prostatitis

Spencer H. Durham

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Determine the diagnostic criteria for significant bacteriuria, urinary tract infections (UTIs), and catheter-associated UTIs.
2. Recognize the signs and symptoms of UTIs, and differentiate asympotomatic bacteriuria from acute cystitis and pyelonephritis and acute prostatitis from chronic prostatitis.
3. Identify the pathogenic organisms most commonly implicated in different UTIs.
4. Assess the laboratory tests used in the diagnosis of UTIs.
5. Based on clinical signs, symptoms, and laboratory parameters, recommend appropriate empiric and targeted pharmacotherapy for the treatment of acute cystitis, pyelonephritis, and prostatitis, including drug, dose, and duration of therapy.
6. Formulate appropriate monitoring and education information for patients with UTIs.

INTRODUCTION

A urinary tract infection (UTI) is defined as the presence of pathogenic microorganisms in the genitourinary tract with associated signs and symptoms of infection. UTIs represent a diverse array of syndromes based on location within the urinary tract, including acute cystitis, pyelonephritis, and prostatitis.[1-3] UTIs are one of the most common reasons for the receipt of antimicrobial therapy.[4]

EPIDEMIOLOGY AND ETIOLOGY

The prevalence and type of UTIs generally vary according to age and gender.[5,6] In adults, bacteriuria is more common in young, nonpregnant women (range, 1%–3%) but uncommon in men (up to 0.1%).[7] Symptomatic UTIs occur most frequently in women of childbearing age. It is estimated that the lifetime risk of UTIs in women is as high as 60%, with 25% of those patients experiencing a recurrence within 1 year.[8] UTIs are much more common in women than men due to their inherently shorter urethra and proximity to the perineal area. However, older men may experience UTIs due to immunoscenesence and concomitant disease states, such as benign prostatic hypertrophy (BPH).

KEY CONCEPT UTIs are classified as either uncomplicated or complicated. Uncomplicated infections usually occur in women of childbearing age. Complicated UTIs usually occur in patients who have structural or functional abnormalities of the genitourinary tract and may involve the bladder or the kidneys.[2] UTIs in male patients and mostly older adults are considered complicated. Although complicated infections are usually treated similar to uncomplicated infections, a longer treatment duration is typically warranted in complicated infections. UTIs can also be classified as upper and lower depending on their anatomical location. Lower UTIs usually refer to acute cystitis, whereas upper UTIs refer to pyelonephritis. It is important to note that an upper UTI does not necessarily imply complicated UTI, nor does a lower UTI imply uncomplicated UTI.

The etiologic pathogens of most UTIs originate from the perirectal area. *Escherichia coli* is implicated in more than 80% of uncomplicated infections, with *Klebsiella pneumoniae* and *Proteus* species being less common.[9] Gram-positive organisms, such as *Staphylococcus saprophyticus* and *Enterococcus* species, are uncommon but potential causes.[10,11] Although *E. coli* is still implicated in complicated UTIs, it causes less than 50% of these infections. The bacteria responsible for complicated infections are generally more varied than with uncomplicated infections, and some complicated infections may be due to highly resistant organisms such as *Enterobacter* species and *Pseudomonas aeruginosa*.[12]

PATHOPHYSIOLOGY

There are three potential pathways for bacteria to enter the urinary tract and cause infection: the ascending, hematogenous, and lymphatic pathways. The most common route of infection is via the ascending pathway. **KEY CONCEPT** Due to the inherently short urethra and proximity to the perirectal area, bacteria often colonize the female urethra. The ascending pathway of infection involves ascension of colonized bacteria upward into the bladder, leading to acute cystitis[13] (Figure 82–1). Once in the bladder, bacteria may continue to ascend the urinary tract via the ureters and cause upper UTIs as well.

The hematogenous route involves the seeding of the urinary tract with pathogens carried through the blood from a distant site of infection. For example, *Staphylococcus aureus* bacteremia is known to cause UTIs and renal abscesses via the hematogenous route.[14] However, less than 5% of all UTIs are thought to be related to hematogenous spread. The lymphatic pathway is least understood because it is uncertain that bacterial transmission occurs in this manner.

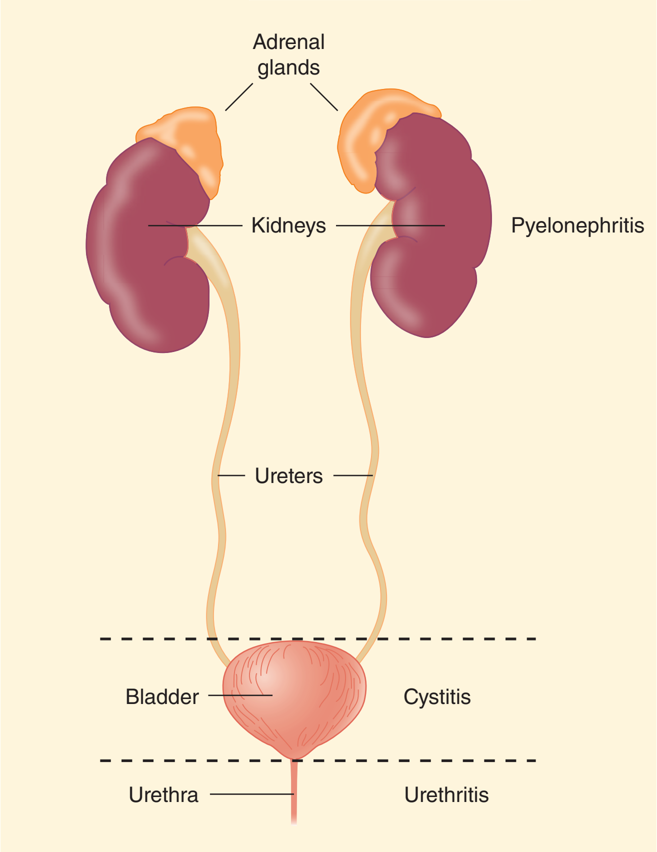

FIGURE 82–1. Anatomy and associated infection of the urinary tract. (From Sprandel KA, Lesch CA, Rodvold KA. Lower urinary tract infection. In: Schwinghammer TL, ed. 6th ed. New York, NY: McGraw-Hill; 2005:315; with permission.)

Host Defense Mechanisms and Risk Factors

Urine possesses numerous characteristics unsuitable for bacterial metabolism and growth, such as low pH, high urea concentration, and high osmolality. The presence of bacteria in the bladder stimulates an urge to urinate to void the bladder and release the bacteria. In addition, innate host response and adaptive immunity are defense mechanisms against bacterial infections, including UTIs.[15]

There are several risk factors for development of UTIs.[7] Common risk factors for uncomplicated infections in women include sexual intercourse, use of a cervical diaphragm or spermicidal jellies, diabetes, and pregnancy.[16-18] Risk factors in men include not being circumcised and, in older men, prostatic hyperplasia. In complicated infections, urinary tract obstruction is a common risk factor for both men and women. Vesicouretal reflux (VUR), which can result from obstruction or congenital abnormalities, results in urine being forced from the ureters into the kidneys, which can also predispose to infection.[19,20] Other risk factors common to both men and women include urologic instrumentation, urethral catheterization, renal transplantation, and neurogenic bladder.[21,22]

CLINICAL PRESENTATION AND DIAGNOSIS

Signs and symptoms of lower UTIs include increased urinary frequency, urgency, dysuria, nocturia, and suprapubic heaviness. Systemic signs and symptoms are uncommon with lower UTIs. By contrast, patients with pyelonephritis often present with systemic signs and symptoms, such as fever, chills, flank pain, nausea and vomiting, and elevated white blood cell count. Older adults often do not present with traditional signs and symptoms of a UTI due to the naturally impaired ability of their immune systems to mount a typical response to infections. Instead, they may experience altered mental status, poor appetite, and incontinence. While older adults often experience altered mental status, it is a nonspecific symptom, and other causes should also be considered when assessing for the presence of a UTI; altered mental status alone is not an indication for empiric treatment with antimicrobials.

The diagnosis of a UTI should generally be based on signs and symptoms in conjunction with laboratory tests to determine bacterial counts in the urine. Bacteriuria, defined as the presence of bacteria in the urine, does not always represent true infection. Asymptomatic bacteriuria (ASB) is the isolation of a quantitative amount of bacteria from an appropriately collected urine specimen in a patient without signs and symptoms of a UTI.[2] While a full discussion of ASB is beyond the scope of this chapter, it is important to note that it should only be treated with antimicrobial therapy in very selected circumstances (eg, pregnancy and endoscopic urological procedures associated with mucosal trauma) and not in premenopausal, nonpregnant women. To help diagnose true UTIs, quantitative diagnostic criteria have been developed based on the number of bacteria present in the urine combined with the presence or absence of infectious signs and symptoms (Table 82–1). A urinalysis is a microscopic examination of the urine and can be helpful to aid in diagnosis. Common abnormalities associated with UTIs seen on urinalysis can be seen in the clinical presentation and diagnosis of UTIs textbox. In particular, the presence of white blood cells (pyuria) and leukocyte esterase (by-products of white blood cells) will almost always be seen in patients with UTIs. In addition, the presence of nitrite-sis usually associated with infection. Nitrates are normally found in the urine, but some Gram-negative organisms, such as *E. coli*, *Klebsiella pnuemoniae*, and *Proteus mirabilis*, reduce nitrates into nitrites. A urine culture, which can identify the quantity of bacteria in the urine and the specific infecting organism, is considered the gold standard for confirmatory diagnosis of a UTI in symptomatic patients.

Table 82–1

Quantitative Diagnostic Criteria for UTIs

Condition	Quantitative Measure
Asymptomatic bacteriuria	• Two consecutive urine cultures with the same organism ≥ to 10^5 CFU/mL in asymptomatic patients
UTI	• ≥ 10^5 CFU/mL in a symptomatic woman[a] • ≥ 10^3 CFU/mL in a symptomatic man • Any growth of bacteria on suprapubic catheterization in a symptomatic patient
Catheter-associated UTI	• ≥ 10^3 CFU/mL of at least one pathogenic species in a symptomatic patient • ≥ 10^5 CFU/mL of at least one pathogenic species in any patient regardless of symptoms

[a] Some women may have signs and symptoms of a UTI but less organisms on culture results. Treatment is still indicated for these patients.

CFU, colony-forming unit; UTI, urinary tract infection.

Clinical Presentation and Diagnosis of UTIs

General

- Most otherwise healthy women present with local signs and symptoms, such as dysuria and increased urgency and frequency.
- Patients with lower UTIs rarely present with systemic signs and symptoms, whereas those with upper UTIs usually do.
- Older adults (≥ 65 years) are often asymptomatic or present with altered mental status.
- More than 95% of uncomplicated UTIs are caused by a single organism, most commonly *Escherichia coli*.

KEY CONCEPT Signs and Symptoms of Lower UTIs

- Dysuria, gross hematuria, suprapubic heaviness, nocturia, increased urinary frequency, and urgency

KEY CONCEPT Signs and Symptoms of Upper UTIs

- Fever, chills, nausea/vomiting, malaise, and flank pain

Laboratory Tests

Urinalysis abnormalities include:

- **Pyuria** typically greater than 10 white blood cells/mm^3 urine (10×10^6/L)
- Bacteriuria, usually greater than 10^5 CFU organisms/mL (10^8 CFU/L)
- Presence of nitrites
- Presence of leukocyte esterase
- Bacterial urine culture
- Gold standard for diagnosis in a symptomatic patient

Patient Encounter Part 1

JK is a 43-year-old woman who presents to her primary care physician complaining of a 3-day history of burning upon urination and having to urinate frequently throughout the day and during the night. She reports she "felt hot" at home but did not take her temperature, and she began experiencing mild flank pain today, which she reports as the reason for the physician visit. She denies vomiting and nausea. Her medical history is significant for depression, which is well-controlled with fluoxetine. The physician orders a urinalysis to be performed in the office.

What signs and symptoms are suggestive of a urinary tract infection (UTI)?

Would you classify this patient as uncomplicated or complicated UTI?

Would you classify this infection as a lower or upper UTI?

What additional patient information is required before creating an appropriate treatment plan for this patient?

TREATMENT

KEY CONCEPT The goals of treatment are to eradicate the causative pathogen, prevent or treat consequences of infection, administer appropriate empiric antimicrobial therapy or targeted therapy based on culture results, and prevent recurrence of infection.

Antimicrobial therapy is the cornerstone of treatment in symptomatic UTIs. Ideally, the selected antimicrobial should be well tolerated, be active against the most likely pathogenic organisms, require few total doses, achieve adequate concentrations in the urinary tract, possess few drug interactions, have a wide therapeutic index, and have good oral bioavailability. In addition, the empiric antimicrobial should be sufficiently narrow in antimicrobial spectrum to be unlikely to cause collateral damage (the ecological adverse effects of antimicrobial therapy).[1]

Nonpharmacologic Therapy

Several nonpharmacologic therapies have been proposed for prevention of UTIs with varying degrees of supportive evidence. Large volumes of cranberry juice have been associated with a decrease in the number of recurrent UTIs over a year period in small, randomized controlled trials, but efficacy is uncertain in the general population and with smaller intake volumes.[23-25] Probiotics such as *Lactobacillus* spp. lower urinary pH and may reduce the growth of pathogenic bacteria and show promise in preventing recurrent UTIs in women.[26] Although uncommonly used, topical estrogen replacement therapy has been shown to significantly decrease the incidence of UTIs in postmenopausal women as compared with placebo.[27] Methenamine hippurate and methenamine mandelate are hydrolyzed in acidic urine to the antimicrobial formaldehyde and effective in preventing UTIs in patients without renal tract abnormalities.[28] Although several of these therapies show promise in the treatment of UTIs, their roles in therapy are currently unclear due to overall limited evidence.

Pharmacologic Therapy

Table 82–2 reviews oral and intravenous (IV) antibiotics frequently used to treat UTIs with comments on their use, and Table 82–3 reviews frequency, duration, and doses of oral antibiotics used commonly for outpatient treatment of UTIs.

▶ *Uncomplicated UTIs*

Cystitis Because patients with uncomplicated acute cystitis rarely manifest systemic signs and symptoms of infection, treatment is generally provided in the outpatient setting.[1] Patients are subsequently monitored for resolution of signs and symptoms. **KEY CONCEPT** Uncomplicated UTIs are usually managed with a short-course antimicrobial therapy involving one-dose, 3-day, or 5-day regimens depending on the clinical factors involved. Because urine culture results take several days for complete results, empiric treatment in the outpatient setting will often be complete prior to obtaining final culture results. Therefore, urine cultures are rarely obtained.[1,29]

For acute uncomplicated UTIs, there are three primary oral empiric treatment options: one dose of fosfomycin, a 3-day course of trimethoprim–sulfamethoxazole (SXT), or a 5-day course of nitrofurantoin.[1] Due to increasing antimicrobial resistance to SXT, empiric therapy with this agent should only be considered if local resistance rate to *E. coli* is less than 20%.[1,9,30] A single dose of fosfomycin may be less effective compared to nitrofurantoin or SXT but is still recommended as a first-line therapy. Fluoroquinolone (as 3-day regimens) and oral β-lactam antimicrobials (3–7-day regimens) can also be used for empiric therapy but should be relegated for use only when one of the three primary treatment options cannot be utilized. Fluoroquinolones are broad-spectrum antimicrobials and have a high propensity to cause collateral damage. Some β-lactams are also broad-spectrum

Table 82–2

Commonly Used Antimicrobial Agents for the Treatment of UTIs

Agent	Comments
Oral Therapy	
Penicillins	
Amoxicillin	Amoxicillin is no longer recommended for empiric therapy due to increasing *Escherichia coli* resistance but can be considered for targeted therapy. Amoxicillin–clavulanic acid can be considered for empiric therapy if a β-lactam must be used.
Amoxicillin–clavulanic acid	
Pivmecillinam	Pivmecillinam is a prodrug of mecillinam and recommended for treatment of acute cystitis. It should be avoided in patients with suspected pyelonephritis. Neither pivmecillinam nor mecillinam is currently approved for use by the US FDA.
Cephalosporins	
Cephalaexin	Oral cephalosporins can be used as alternative therapies for the empiric treatments of UTIs, but they are less effective and have more adverse effects compared to nitrofurantoin and SXT. Concern also exists for use of these agents as a first-line option for uncomplicated cystitis therapy due to potential selection of cephalosporin-resistant organisms.
Cefaclor	
Cefadroxil	
Cefixime	
Cefpodoxime	
Cefuroxime	
Fluoroquinolones	
Ciprofloxacin	Fluoroquinolones are highly effective in the treatment of acute cystitis and pyelonephritis, but bacterial resistance is increasing. They should not be used empirically for acute cystitis due to the risk of collateral damage, unless a first-line agent cannot be used. They are first-line agents for pyelonephritis if *E. coli* resistance in the area is < 10%. Avoid in pregnancy and children. Moxifloxacin should not be used due to limited urinary excretion.
Levofloxacin	
Miscellaneous	
Trimethoprim–sulfamethoxazole	Considered a first-line option for acute cystitis if *E. coli* resistance in the area is < 20%. A 3-day treatment regimen is recommended. It can also be used as prophylaxis for recurrent infections. Generally well tolerated and low cost but increasing resistance rates above 20% in certain regions. Its use may be precluded in patients with sulfa allergies.
Nitrofurantoin	Broad-spectrum agent with a low-risk of collateral damage. Does not penetrate renal tissue well, so should not be used for pyelonephritis. It is considered a first-line agent for acute cystitis and a 5-day treatment is recommended. This agent is effective in treatment and prophylaxis in patients with uncomplicated or recurrent lower tract UTIs. Traditionally, the Beers criteria recommended to avoid use in CrCl < 60 mL/min due to limited urine concentrations, but recent evidence suggests it is effective even with a CrCl as low as 30 mL/min.
Fosfomycin	First-line, single-dose therapy for uncomplicated cystitis. Has been recommended for empiric therapy since resistance rates are low but may have inferior efficacy when compared with short courses of other oral antibiotic agents. Possesses a broad-spectrum of activity, so is sometimes used to treat multidrug-resistant organisms, including ESBL-producing organisms.
Parenteral Therapy	
Aminoglycosides	
Amikacin	Gentamicin and tobramycin given as a consolidated 24-hour dose are recommended as a one-time dose for the treatment of outpatient pyelonephritis, followed by oral antimicrobials, when resistance rates preclude the empiric use of other agents. They can also be used for empiric inpatient treatment of pyelonephritis. Amikacin generally is reserved for multidrug-resistant bacteria. Plazomicin was recently approved for the treatment of complicated UTIs
Gentamicin	
Tobramycin	
Plazomicin	
Penicillins	
Ampicillin	These agents can be used for the treatment of pyelonephritis in the inpatient setting.
Ampicillin–sulbactam	
Piperacillin–tazobactam	
Cephalosporins	
Ceftriaxone	Ceftriaxone is recommended as an initial dose for the treatment of outpatient pyelonephritis when resistance rates preclude the empiric use of other agents. Ceftriaxone and other extended-spectrum cephalosporins can be used in the empiric treatment of pyelonephritis in the inpatient setting. Several new cephalosporins are now approved for the treatment of complicated UTIs caused by multidrug-resistant organisms.
Ceftazidime	
Cefepime	
Ceftolozane/tazobactam	
Ceftazidime/avibactam	
Cefiderocol	
Carbapenems	
Doripenem	Broad-spectrum agents that can be used in the empiric treatment of pyelonephritis in the inpatient setting when multidrug resistance is suspected.
Ertapenem	
Imipenem–cilastatin	
Meropenem	
Meropenem/vaborbactam	
Fluoroquinolones	
Ciprofloxacin	IV dosage forms are considered first-line agents for pyelonephritis if *E. coli* resistance in the area is < 10%. These agents have broad-spectrum activity against both Gram-negative and Gram-positive bacteria. They provide high urine and tissue concentrations. Switch to oral therapy when possible due to excellent bioavailability. Resistance rates are increasing in the United States, so often cannot actually be used as a first-line therapy.
Levofloxacin	

CrCl, creatinine clearance; ESBL, extended-spectrum β-lactamase; FDA, Food and Drug Administration; IV, intravenous; SXT, trimethoprim–sulfamethoxazole; UTI, urinary tract infection.

Table 82–3

Overview of Outpatient, Oral Antimicrobial Therapy for Acute Cystitis, Pyelonephritis, and Prostatitis

Indications	Antibiotic	Adult Dose[a]	Frequency	Duration[b]
Acute Cystitis				
First-line options	Nitrofurantoin monohydrate/macrocrystals	100 mg	Every 12 hours	5 days
Alternative options:	Trimethoprim–sulfamethoxazole	One DS[c] tablet	Every 12 hours	3 days
	Fosfomycin	3000 mg	One-time dose	1 day
	Pivmecillinam[d]	400 mg	Every 12 hours	3–7 days
	Ciprofloxacin	250 mg	Every 12 hours	3 days
	Levofloxacin	250 mg	Every 24 hours	3 days
	Amoxicillin–clavulanic acid	500 mg	Every 8 hours	3–7 days
	Cefdinir	100 mg	Every 12 hours	3–7 days
	Cefaclor	250–500 mg	Every 8 hours	3–7 days
	Cefpodoxime-proxetil	100 mg	Every 12 hours	3–7 days
Recurrent infections—continuous prophylaxis	Trimethoprim–sulfamethoxazole	1/2 SS[e] tablet	Every 24 hours	6 months
	Trimethoprim	100 mg	Every 24 hours	6 months
	Ciprofloxacin	125 mg	Every 24 hours	6 months
	Nitrofurantoin	50 *or* 100 mg	Every 24 hours	6 months
	Cefaclor	250 mg	Every 24 hours	6 months
	Cephalexin	125 mg	Every 24 hours	6 months
Pyelonephritis				
Outpatient treatment	Ciprofloxacin	500 mg	Every 12 hours	7 days
	Ciprofloxacin (extended release)	1000 mg	Every 24 hours	7 days
	Levofloxacin	750 mg	Every 24 hours	5 days
Prostatitis	Trimethoprim–sulfamethoxazole	One DS[c] tablet	Every 12 hours	14 days
	Ciprofloxacin	500 mg	Every 12 hours	2–4 weeks[f]
	Levofloxacin	500 mg *or* 750 mg	Once daily	2–4 weeks[f]
	Trimethoprim–sulfamethoxazole	One DS[c] tablet	Every 12 hours	2–4 weeks[f]

[a] Majority of listed antimicrobial agents require dosage adjustment in patients with significant renal dysfunction.

[b] Duration of therapy may be longer if treating complicated infections.

[c] DS, double strength (160-mg trimethoprim/800 mg-sulfamethoxazole).

[d] Not approved for use by the US FDA.

[e] SS, single strength (80-mg trimethoprim/400-mg sulfamethoxazole).

[f] Treatment should be 6–12 weeks if treating chronic prostatitis.

but are also less efficacious and have a higher incidence of adverse effects compared to the three primary treatments. Ampicillin and amoxicillin should not be considered for empiric therapy due to low efficacy and high rates of resistance.[1]

▶ *Acute Pyelonephritis*

Patients experiencing acute pyelonephritis may be treated in either the outpatient or inpatient settings. Patients who may be dehydrated due to poor fluid intake or severe nausea and vomiting, or those with unstable vital signs should receive inpatient treatment.

Unlike patient with acute cystitis, urine culture and susceptibility testing should always be performed in patients experiencing pyelonephritis. For patients who can be treated as outpatients, oral fluoroquinolones as a 5- or 7-day regimen are the mainstay of therapy if local *E. coli* resistance is less than 10% (see Table 82–3 for specific regimens). A one-time initial dose of IV ciprofloxacin (400 mg) can also be considered. For patients who reside in areas where fluoroquinolone resistance is greater than 10%, oral fluoroquinolones can still be utilized, but an initial dose of IV ceftriaxone (1 g) or a consolidated 24-hour dose of an aminoglycoside should be given. The purpose of this initial IV dose is to provide long-acting empiric coverage while awaiting urine culture results. SXT can be used as a 14-day treatment, but only if susceptibility is confirmed. If SXT is utilized empirically, the initial IV dose of ceftriaxone or an aminoglycoside must be given. Another alternative regimen is an oral β-lactam for 10 to 14 days given with the initial IV dose of ceftriaxone or aminoglycoside. For patients who require empiric inpatient treatment, therapy with one of four general options is recommended: a fluoroquinolone alone; an aminoglycoside with or without ampicillin; an extended-spectrum penicillin or cephalosporin with or without an aminoglycoside; or a carbapenem. Local resistance patterns should be examined to determine appropriate empiric therapy in this case.[1,31,32]

Special Populations

▶ *Pregnant Women*

Pregnant women are predisposed to UTIs due to changes in the urinary tract, including alterations in amino acid and other nutrient concentrations in the urine and physiologic changes such as reduced bladder tone and dilation of the renal pelvis and ureters.[33,34]

UTIs during pregnancy can result in serious complications, such as fetal death, labor complications, mental retardation, and developmental delay.[35,36] Because of these risks, screening for UTIs during pregnancy is recommended, and patients should receive treatment regardless of symptoms.[2,16]. Although the best

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Depression (diagnosed 6 years ago)

FH: Mother living with hypertension and dyslipidemia; father deceased due to lung cancer

SH: Married for 14 years, sexually active; two daughters; occupation: social worker at a local hospital

Allergies: No known drug allergies

Meds: Norethindrone 0.5 mg/ethinyl estradiol daily; fluoxetine 20 mg daily

ROS: (+) dysuria, urinary frequency, flank pain; (–) nausea, vomiting

PE:

VS: BP = 126/78 mm Hg, P 72 = beats/min, RR = 18 breaths/min, T = 38.4°C

CV: RRR, normal S1, S2; normal findings

Abd: Soft, nontender, nondistended; (+) bowel sounds, no hepatosplenomegaly, heme (–) stool

Lab: WBC—13.6 cells/μL (84% neutrophils); all other labs within normal limits; (–) pregnancy test

Urinalysis: Greater than 200 white blood cells/mm^3 (200×10^6/L); urine nitrates positive; leukocyte esterase positive

Urine gram stain: Gram-negative rods, more than 10^5 CFU/mL (10^8 CFU/L)

Local resistance of *Escherichia coli* to SXT and ciprofloxacin is 24% and 20%, respectively

Given this additional information, what is your assessment of the patient's condition?

Identify your treatment goals for the patient.

What nonpharmacologic and pharmacologic alternatives are available for the patient?

length of therapy for pregnant women has not been elucidated, most women typically receive longer durations of therapy than nonpregnancy women. Fluoroquinolones should generally be avoided due to their ability to inhibit cartilage and bone development. SXT has the potential to cause congenital malformations and an increased risk of neonatal kernicterus and should therefore also not be prescribed. Nitrofurantoin can be safely used during pregnancy except in the last 30 days, where it should be avoided due to an increased risk of neonatal jaundice. Most β-lactams are safe in pregnancy and are historically considered first-line options for pregnant patients. Fosfomycin appears safe in pregnancy and can be considered, but less clinical experience exists.[37] In pregnant patients who do experience UTIs, follow-up usually consists of a urine culture 1 to 2 weeks after completion of therapy, then subsequent monthly urine cultures until birth.

Patient Encounter Part 3: Creating a Care Plan

Based on the information presented, create a care plan for this patient's UTI.

Your plan should include:

(a) A statement of the drug-related needs and/or problems,

(b) A patient-specific detailed therapeutic plan, and

(c) Monitoring parameters to assess efficacy and safety.

▸ *Catheterized Patients*

Catheter-associated UTIs (CA-UTIs) are common in patient with an indwelling urinary catheter.[21,38] Bacteria may be introduced into the bladder via the catheter by colonization and direct introduction during catheterization. UTIs as a result of an indwelling catheter are common and occur at a rate of 3% to 8% for each day the catheter is present.[38]

The primary treatment of CA-UTIs is removal and discontinuation of the catheter if possible. In patients without signs and symptoms of infection, removal of the catheter is likely sufficient, and antimicrobials may be withheld. In patients who are symptomatic, antimicrobials should be administered. In all patients, if the catheter cannot be permanently discontinued, a new catheter should be inserted if the previous catheter has been in place for longer than 2 weeks. Empiric antimicrobial regimens for the treatment of CA-UTIs have not been well defined, and treatment should be based on local susceptibility patterns. Results from urinalyses are often difficult to interpret in patients with indwelling catheters as the white blood cell count is usually elevated due to the presence of a foreign material. Urine cultures should always be obtained in CA-UTIs to guide ultimate selection of antimicrobials. In general, treatment for 7 days is sufficient if symptoms promptly resolve and 10 to 14 days if symptoms are slower to resolve.[38]

▸ *UTIs in Men*

KEY CONCEPT UTIs occurring in men are usually due to a structural or functional abnormality of the urinary tract and are therefore usually treated as a complicated infection.[39] For this reason, men should not generally be treated with a single dose or short course of therapy if diagnosed with a UTI. Antimicrobial therapy selection is similar to that used in otherwise healthy women, but men will usually receive 7 to 14 days of treatment.

▸ *Prostatitis*

KEY CONCEPT Prostatitis is an inflammation of the prostate gland due to infection, usually from bacterial causes. Prostatitis can be acute or chronic, with acute being the most common. It is uncommon in young men, but the incidence increases after the age of 30, and as many as half of all men will experience it at some point in their lifetimes. The pathogenesis of prostatitis is not completely understood but likely involves the reflux of infected urine directly into the prostate gland.[40]

Acute prostatitis differs from chronic in their respective signs and symptoms. **KEY CONCEPT** Patients with acute prostatitis present with fever, chills, localized rectal pain, dysuria, urinary straining, increased urinary frequency, and irritation. By contrast, patients with chronic prostatitis rarely present with these symptoms but instead have difficulty urinating, perineal pain, recurrent UTIs, epididymitis, urethritis, or low back pain.[40] The pathogenic organisms responsible for prostatitis are similar to those that cause UTIs, with *E. coli* accounting for 75% of cases. *K. pneumoniae* and *P. mirabilis* can also be implicated, with other Enterobacteriaceae, such as *Pseudomonas*, being infrequent causes. *Staphylococcus* is a rare but possible cause as well. Some men may also experience prostatitis following infection with the

Table 82–4

Monitoring Parameters for Select Antibiotics Used in the Treatment of UTIs

Drug Class or Drug	What to Monitor	Frequency	Endpoint
Aminoglycosides	SCr, urine output	Every 24 hours	Prevention of nephrotoxicity manifested by a rise in SCr
	Aminoglycoside serum concentrations	Depends on duration of therapy. At least once weekly; more frequently if evidence of changing renal function	Trough serum concentrations < 2 mg/L or < 8 mg/L for amikacin, to decrease risk of nephrotoxicity and ototoxicity. Peak goal 5–6 mg/L. If using extended-interval dosing, monitoring should be based on the specific nomogram chosen
Nitrofurantoin	SCr	Only if renal function changing or unstable	Nitrofurantoin metabolites may accumulate in renal insufficiency and lead to neuropathy; avoid if CrCl < 30 mL/min
	Liver profile	Periodic monitoring	Prevention of cholestasis
Nitrofurantoin Tetracyclines Sulfonamides	SCr	Only if renal function changing or unstable	Decreases in glomerular filtrate rate can significantly decrease the urine concentration of these agents

CrCl, creatinine clearance; SCr, serum creatinine.

sexually transmitted infections *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Chronic prostatitis usually occurs after a patient experiences acute prostatitis when the infecting organism is not completely removed from the prostate. Therefore, the same pathogens responsible for acute prostatitis also cause chronic.[41]

Acute prostatitis can be readily diagnosed based on symptoms and the presence of significant bacteriuria. The diagnosis of chronic prostatitis is more difficult due to the infrequent prostate symptoms. It is generally diagnosed when a male patient has a recurring UTI with the same organism each time.[40]

The pharmacologic treatment approach to the management of prostatitis is similar to that of UTIs. Antimicrobial penetration of the prostate must be taken under consideration as many antimicrobials do not penetrate well into prostatic tissue and fluids, although concentrations are improved through the inflammatory process in acute prostatitis. **KEY CONCEPT** Fluoroquinolones and SXT are considered the treatments of choice for prostatitis due to their activity against the most common organisms and their penetration into prostatic fluid. However, as discussed previously, bacterial resistance to these agents is increasing. Alternative agents to be considered include cephalosporins (such as cephalexin or cefuroxime) and penicillins (such as amoxicillin/clavulanate). Initial therapy with an IV agent may be necessary in some cases of acute prostatitis based on the clinical stability of the patient. Acute prostatitis should be treated for at least 2 weeks and can be extended to 4 weeks if patients are slow to improve. Chronic prostatitis is treated for a longer period of time, usually 6 weeks, but possibly up to 12 weeks.[40,42,43]

Outcome Evaluation for UTIs

- Monitor the patient for resolution of symptoms with the goal of 48 to 72 hours to resolution after start of antimicrobial therapy.
- Follow up with urine culture results to deescalate antimicrobial therapy if possible.
- Repeat urine culture is necessary only if symptoms do not acutely abate, reinfection, or recurrence occurs. Resistance rates to *E. coli* are increasing to antibiotics commonly prescribed for UTI, and certain isolates are multidrug resistant.[44]
- Depending on the chosen antibiotic therapy, evaluate the patient based on drug therapy–monitoring parameters including those presented in Table 82–4 to optimize therapy and decrease incidence of adverse events.

Patient Care Process

Collect Information:

- Based on physical examination, signs and symptoms, review of systems, and urinalysis, determine whether the patient is experiencing a UTI.
- Obtain the patient's medication history and risk factors for an antibiotic-resistant infection.
- Assess patient renal function and other laboratory tests for antibiotic dosing and systemic complications.
- Identify potential sources of infection, such as indwelling urinary catheters.

Assess the Information:

- Based on urinalysis and gram stain (if available), determine whether the empiric antibiotic selection is appropriate.
- Based on culture and susceptibility data (if available), determine whether any changes should be made from your initial empiric antimicrobial selection (ie, resistance to the regimen initially selected). Also, assess if the empiric antimicrobial selected can be deescalated to a lower-spectrum agent.

(Continued)

Patient Care Process (*Continued*)

- Evaluate the patient's symptoms to determine response to the antimicrobial regimen chosen.
- Evaluate the patient for the presence of adverse drug events, drug allergies, and potential drug interactions.

Develop a Care Plan:

- Determine the optimal antibiotic dose and duration of therapy based on the patient and infection type (complicated vs uncomplicated).
- Determine whether the patient may benefit from prophylactic therapy (ie, recurrent UTIs secondary to chronic urinary catheterization due to paraplegia).
- Identify lifestyle modifications as needed to minimize UTI recurrence.

Implement the Care Plan:

- Prescribe and dispense the optimal antibiotic at the correct dose and duration.
- Recommend lifestyle changes, if needed.

Follow-up: Monitor and Evaluate:

- Stress the importance of complying with the prescribed antimicrobial regimen and to follow up with the healthcare provider if signs and symptoms recur.

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Abbreviations Introduced in This Chapter

ASB	Asymptomatic bacteriuria
BPH	Benign prostatic hypertrophy
CA-UTI	Catheter-associated UTI
CFU	Colony-forming units
CrCl	Creatinine clearance
ESBL	Extended-spectrum β-lactamase
IV	Intravenous
SCr	Serum creatinine
SXT	Trimethoprim–sulfamethoxazole
UTI	Urinary tract infection
VUR	Vesicouretal reflux

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Sexually Transmitted Infections

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Assess the behavioral considerations and the importance of contraception with regard to the contributing factors of sexually transmitted infections (STIs).
2. Apply the "patient-delivered partner therapy" method when recommending treatment for STIs.
3. Describe the patient populations that are typically affected by specific STIs.
4. Identify causative organisms for STIs.
5. Devise a list of the clinical signs and symptoms corresponding to each type of STI and classify patients based on recommended criteria.
6. Select appropriate diagnostic procedures for STIs.
7. Recommend STI treatment regimens and recommend therapy, when appropriate.
8. Develop monitoring parameters based on recommended regimen.

INTRODUCTION

Though we have made significant progress in science and medicine, longstanding problems of infectious disease continue to plague us.[1] Even with the discovery of newly improved antibiotics, sexually transmitted infections (STIs) have not yet been eradicated. Several have reemerged secondary to modern social trends (eg, number of partners, sex workers, and swingers) of sexual activity, socioeconomic concerns, and the global lack of preventive education. **KEY CONCEPT** Since the correlation between risky sexual behavior and STIs is well documented,[2] many sexually active individuals may contract an infection at some point in their lives. Community approaches to reducing STIs (eg, access to quality health care, promotion of personal health, and advancement of community wellness) have been proven effective.[3] Though inconsistent and incorrect condom use increases the probability of new STIs, counseling patients on the consistent use of condoms, spermicides, or diaphragms is also important component in reducing overall incidence. Additionally, healthcare providers who manage persons at risk for STIs should counsel women concerning the option for emergency contraception, when indicated. Mifepristone, levonorgestrel, ulipristal, ethinyl estradiol, and copper T intrauterine devices have been employed in the United States for the prevention of unintended pregnancy.[4]

Optimal detection and treatment of sexually transmitted diseases depend on counseling by a patient-friendly and knowledgeable clinician who can effectively establish open communication. Acknowledging the hierarchy of human needs is the cornerstone to establishing open communication. When these needs are met in a safe and collaborative environment, it increases patients' confidence and gives them a sense of trust, which encourages interpersonal and open communication. Open communication with patients may also be encouraged by (a) incorporating training on effective communication within the organization's mandatory training program, (b) making communication a part of the organization's culture, (c) implementing patient satisfaction surveys, (d) utilizing technology when appropriate, and (e) ensuring that continuous quality improvement is incorporated. Additionally, clinicians, healthcare workers, and healthcare facilities should strive to incorporate strategies regarding communication improvement, especially when suggested by patients.

In addition to an increasing number of adolescents and young adults engaging in unsafe sexual practices, there is a high incidence of men who have sex with men (MSM) and women who have sex with women (WSW). In fact, MSM is documented as the risk group most severely affected by HIV in the United States. Changes in sexual behaviors and STI diagnosis was noted in patients who used pre-exposure prophylaxis (PrEP). PrEP is discussed in detail in Chapter 87 (HIV). Among MSM using PrEP, STIs were highly concentrated among a subset, and receipt of PrEP was associated with an increased incidence of STIs.[5] These findings highlight the importance of frequent STI testing among gay and bisexual men using PrEP. Although limited data are available with regard to STIs in WSW, transmission generally occurs through fisting, fingering, oral sex, menstrual blood, or the use of sexual toys. Additionally, if bisexual, transmission may also occur when WSW are involved with male partners. The chances of transmission are higher if a WSW has gingivitis and performs unprotected oral sex, and if the same occurs during the menstrual cycle of the receiver.[6] Sharing penetrative items or employing practices involving digital vaginal or digital anal contact most likely represent the most common modes of transmission. This possibility is supported by reports of metronidazole-resistant trichomoniasis and genotype-specific HIV transmitted sexually between women who reported such behaviors and an increased prevalence of bacterial vaginosis (BV) among monogamous WSW. Additionally, when screening for STIs, special populations must be considered, which include pregnant women, transgender men and women, and women in correctional facilities. Data suggests that clinicians should assess, respectively, STI-related risks for the special populations based on sexual identity, practices, and risk behaviors.

Sexual abuse in adolescents and children is becoming more ubiquitous in the United States. STIs are rare in sexually abused children and adolescents. However, when present, they can be crucial to making the diagnosis of sexual abuse and protecting children.[7] Children or adolescents with an STI should be evaluated for sexual abuse. The identification of an STI in a child can have serious medical and legal implications and is used to support the presence or allegation of abuse. In cases of abusive contact, commonly found infections include *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. Abusive cases should be reported to Child Protective Services.

Defined as a person who engages in the exchange of spouses for sexual activities, the emergence of "swingers" as a new category of at-risk patients has been seen in STI clinics throughout the world. In a study conducted by Spauwen et al., the authors concluded that approximately half of STI clinic–attending swingers whose sexual behavior agrees with the definition of swinging do not identify themselves as such. As many STI clinics internationally do not specifically ask clients about their swinging behavior, swingers may be a missed target population in care.[8] Most swingers are likely to be diagnosed with HIV, herpes, chlamydia, or gonorrhea. To this end, although little data exists, swingers now represent a group with risky behaviors that must be identified and treated, when necessary.

KEY CONCEPT Optimally, both sex partners should be treated simultaneously for an STI. Clinics and health departments often proactively attempt dual treatment by providing a prescription for the partner to the index patient (the patient who is evaluated by a clinician), a practice commonly known as patient-delivered partner therapy. Medications or prescriptions should be accompanied by treatment instructions and appropriate warnings. Counseling regarding the appropriate use of condoms, cervical diaphragms, spermicides, and emergency contraception is also important to mitigate the occurrence of reinfection.

Accurate reporting of STIs is imperative to the evaluation of trends in sexual behaviors; reporting may be provider- or laboratory-based. State and local health departments may assist with the mechanism by which STI cases are reported in accordance with statutory requirements. Confidentiality should always be exercised in such cases.[9,10]

GONORRHEA

INTRODUCTION

A curable STI caused by the Gram-negative diplococcus *N. gonorrhoeae*, gonorrhea is the second most commonly reported bacterial STI. Proper therapeutic management with antimicrobial agents is essential to eradicate this infection and prevent the development of associated sequelae, such as urethritis, cervicitis, or dysuria. There are currently no vaccines available for gonorrhea.

EPIDEMIOLOGY AND ETIOLOGY

In the United States, diagnosis of gonorrhea increased by 5% in the past 5 years. The highest rate of gonococcal infection is seen within the 15- to 24-year-old age groups for both sexes, although more cases are reported in men.[9,10] Factors associated with an increased risk of infection include ethnicity (ie, African Americans aged 15–24), low socioeconomic status, illicit drug use, and age (ie, < 25 years of age and older women at increased risk of infection [ie, new sex partner, more than one sex partner, or a partner who has a STI]). Strategic screening of young women, less than 25 years of age, who are at an increased risk has been correlated to gonorrhea control in the United States.[9] In fact, the risk of a cervical infection after a single episode of vaginal intercourse is approximately 50% and increases with multiple exposure. Furthermore, rates of reinfection are significantly higher among ethnic minorities. Additionally, routine screening should be considered for sexually active MSM and WSM, bisexual men and women, pregnant women, swingers, and transgender men and women. Targeted screening of high-risk populations may reduce the number of new infections and associated sequalae.

PATHOPHYSIOLOGY

Attachment to mucosal epithelium, mediated in part by pili and opa (outer membrane opacity proteins), is followed by penetration of *N. gonorrhoeae* through epithelial cells into the submucosal tissue within 24 to 48 hours. A vigorous response by neutrophils begins with sloughing of the epithelium, development of submucosal microabscesses, and exudation of pus. Stained smears usually reveal large numbers of gonococci within a few neutrophils, whereas most cells contain no organisms.[11]

CLINICAL PRESENTATION AND DIAGNOSIS

Several laboratory tests are available to aid in the diagnosis of gonorrhea and include Gram-stained smears, endocervical or vaginal specimens, culture, or the DNA hybridization probe.

Clinical Presentation and Diagnosis of Gonorrhea[9-11]

General

- Purulent discharge
- Greater urinary frequency
- Persistent sore throat

Signs

- Painful or swollen testicles
- Tubal scarring

Symptoms

Men:

- May be asymptomatic, though acute urethritis is the predominant manifestation
- Urethral discharge and dysuria, usually without urinary frequency or urgency
- When compared with nongonococcal urethritis, the discharge in gonococcal urethritis is generally more profuse and purulent
- Pain during urination

Women:

- May be asymptomatic
- Cervicitis, urethritis, increased vaginal discharge, dysuria, and intermenstrual bleeding
- Pain during urination
- Abdominal pain

A Gram stain of a male urethral specimen that demonstrates polymorphonuclear leukocytes with intracellular Gram-negative diplococci may be considered diagnostic in symptomatic men. A Gram-negative stain is insufficient for ruling out infection in asymptomatic men.[9] Additionally, Gram stain of endocervical, pharyngeal, or rectal specimens are also insufficient to detect infections. All patients who test positive for gonorrhea should be tested for other STIs, including chlamydia, syphilis, and HIV. The recommended method for gonorrhea testing, however, is the nucleic acid amplification test (NAAT), which detects the genetic material for *N. gonorrhoeae*. Specimen may be collected from the urine, vagina, rectum, conjunctiva, nasopharynx, and conjunctiva.

TREATMENT

The desired outcome is complete eradication of *N. gonorrhoeae* and avoidance of sequelae.

Pharmacologic Therapy[4,9,10,13,14]

KEY CONCEPT Patients infected with gonorrhea are often coinfected with *C. trachomatis* and should receive concurrent therapy to eradicate both organisms. Treatment is now complicated by the development of resistance to *N. gonorrhoeae*. To mitigate the probability of resistance, the most recent guidelines recommend the combination of cephalosporins and azithromycin or doxycycline (ie, uncomplicated gonococcal infections).[9,10] The treatment algorithm for gonorrhea may be found in Table 83–1.

▶ Side Effects and Contraindications

- *Cephalosporins:* Side effects include black tarry stools, diarrhea (pseudomembranous colitis) chills, cough, fever, and swollen glands. Contraindications include hypersensitivity to ceftriaxone or cephalosporins.
- *Azithromycin:* Side effects include diarrhea, nausea, abdominal pain, and palpitations. Contraindications include hypersensitivity to azithromycin, erythromycin, other macrolide antibiotics (eg, azalide or ketolide) antibiotics or any component of the formulation.
- *Doxycycline:* Side effects include increase in blood pressure, diarrhea, abdominal distention, increased serum aspartate aminotransferase, nasopharyngitis, sinus headache, and fungal infection. Contraindications include hypersensitivity to doxycycline, tetracyclines, or any component of the formulation.
- *Aminoglycosides:* Side effects include renal toxicity, ototoxicity, dizziness, increased or decreased frequency of urination, increased thirst, loss of appetite, vomiting, burning of face and mouth (streptinomycin only), and numbness. Contraindications include hypersensitivity to aminoglycosides or any component of the formulation.
- *Spectinomycin:* Side effects nausea, dizziness, soreness at injection site, hives, insomnia, chills, and fever. Contraindications include in patients who have hypersensitivity to it.
- *Erythromycin:* Nausea, diarrhea, stomach pain, and dark urine. Contraindications include hypersensitivity to this antibiotic. Additionally, erythromycin is contraindicated in patients taking terfenadine, astemizole, pimozide, or cisapride.

▶ Recommendations During Pregnancy

- Pregnant women should be treated with a recommended or alternative cephalosporin. Ceftriaxone 250-mg IM plus azithromycin 1 g PO may be employed.
- For women who cannot tolerate a cephalosporin, azithromycin 2 g PO may be prescribed. When allergies or other issues preclude treatment, consultation with an infectious disease specialist is recommended.

▶ Allergy, Tolerance, or Adverse Reactions

- When cephalosporin allergy is a consideration, single doses of gemifloxacin 320 mg PO *plus* azithromycin 2 g or dual treatment with single doses of IM gentamicin 240 mg *plus* azithromycin 2 g may be used.
- Spectinomycin for treatment of urogenital and anorectal gonorrhea can be considered when available.
- Doxycycline and fluoroquinolones are contraindicated.

▶ Expedited Partner Treatment for Uncomplicated Urogenital, Rectal, or Pharyngeal Gonococcal Infection[10]

- The partner may be treated with a single 800-mg oral dose of cefixime, if chlamydial infection has been excluded.
- If chlamydial infection is confirmed, the partner may be treated with a single oral 800-mg cefixime dose plus oral doxycycline 100 mg twice daily for 7 days.

▶ Cephalosporin Treatment Failure[10]

- Suspect treatment failure in (a) persons whose symptoms do not resolve in 3 to 5 days after treatment and report no sexual contact during post-treatment follow-up, (b) persons with a positive test-of-cure (ie, positive culture ≥ 72 hours or positive NAAT ≥ 7 days after receiving recommended treatment) when no sexual contact is reported during the post-treatment follow-up period, and (c) persons who have a positive culture on test-of-cure if there is no evidence of decreased susceptibility to cephalosporins on antimicrobial susceptibility testing.
- Obtain relevant clinical specimen for culture and antimicrobial susceptibility testing.
- Consult an infectious disease specialist or STI expert for guidance in management.
- Report the case to the Center of Disease Control (CDC) within 24 hours.
- Prioritize notification and culture evaluation for the patient's partner(s) from the requisite 60 days for those with suspected cephalosporin treatment failure or persons whose gonococcal isolates show mitigated susceptibility to cephalosporins.

OUTCOME EVALUATION

- Order diagnostic test for gonorrhea. If positive, recommend antibiotics that cover gonorrhea and chlamydia.
- Provide treatment for partner to mitigate the probability of reinfection.
- Counsel patient on the significance of refraining from sex for 7 days after treatment.
- Subsequent to treatment, expect the eradication of organisms responsible for gonorrhea and chlamydia.
- Order a test-of-cure 14 days after treatment for patients with pharyngeal gonorrhea who were treated with an alternative regimen.
- Retest after 3 months for men or women who have been treated for gonorrhea, irrespective of whether sex partners

Table 83–1

Treatment Recommendations for Gonorrhea

Indications	Drugs	Dose	Route	Duration	Alternative	Allergies
Uncomplicated Gonococcal Infection of the Urogenital, Rectum, or Pharynx and Rectum MSM or Heterosexuals with a History of Recent Travel[a]	Ceftriaxone ***Dose by Weight***				Cefixime 800 mg PO as a single dose if ceftriaxone is unavailable	Cephalosporin: Gentamicin 240 mg IM PO *plus* azithromycin 2 g dual treatment
	(< 150 kg)	500 mg	IM	One-time dose		
	(≥ 150 kg)	1 g	IM	One-time dose		
	and					
	Doxycycline *(if chlamydia is not excluded)*	100 mg	PO	Twice daily For 7 days		
Gonococcal Arthritis[a]	Ceftriaxone	1 g	IM or IV	Every 24 hours for 7 days		Cephalosporin: Gemifloxacin 320 mg PO plus azithromycin 2 g or dual treatment with single doses of IM gentamicin 240 mg *plus* azithromycin 2 g
	and					
	Azithromycin	1 g	PO	For 7 days		
Pregnancy and Gonococcal Infection[a]	Ceftriaxone	250 mg	IM		Azithromycin 2 g PO as a one-time dose	Cephalosporin: Gemifloxacin 320 mg PO plus azithromycin 2 g or dual treatment with single doses of IM gentamicin 240 mg *plus* azithromycin 2 g
	and					
	Azithromycin	1 g	PO			
Disseminated Gonococcal Infection[a]	Ceftriaxone	1 g	IM or IV every 24 hours	For 24-48 hours after improvement is noted	Cefotaxime 1 g IV every 8 hours or ceftizoxime 1 g IV every 8 hours plus azithromycin 1 g PO as a single dose	
	and					
	Azithromycin	1 g	PO			
Gonococcal Conjunctivitis[a]	Ceftriaxone	1 g	IM	One-time dose	One-time lavage of the eye(s) once with saline (consult with infectious disease specialist)	
	and					
	Azithromycin	1 g	PO	One-time dose		
Uncomplicated Infections of the Cervix, Urethra, and Rectum in Children Less Than 45 kg	Ceftriaxone	250 mg	IM	One-time dose		
	or					
	Spectinomycin	40 mg/kg	IM	One-time dose (not to exceed 2 g)		
Gonococcal Scalp Access in Newborns	Ceftriaxone	25–50 mg/kg/day	IM or IV	7 days		
	or					
	Cefotaxime	25 mg/kg every 12 hours	IM or IV	7 days Both medications may be used for 10–14 days if meningitis is documented.		
Gonococcal Meningitis[a]	Ceftriaxone	1–2 g	IV	Every 12–24 hours for 10–14 days		
	and					
	Azithromycin	1 g	PO	One-time dose		
Gonococcal Endocarditis[a]	Ceftriaxone	1–2 g	IV	For at least 4 weeks		
	and					
	Azithromycin	1 g	PO	One-time dose		

(Continued)

Table 83–1

Treatment Recommendations for Gonorrhea (*Continued*)

Indications	Drugs	Dose	Route	Duration	Alternative	Allergies
Ophthalmia Neonatorum Prophylaxis	Erythromycin	0.5%	Into the affected eye(s)	One-time dose		
Gonococcal Ophthalmia	Ceftriaxone	25–50 mg/kg	IM or IV	One-time dose (not to exceed 125 mg)		
Neonates Born to Mothers Who Have Gonococcal Infection	Ceftriaxone	25–50 mg/kg	IM or IV	One-time dose (not to exceed 125 mg)		
Infants and Children Who Weigh ≤ 45 kg and Who Have Uncomplicated Gonococcal Vulvovaginitis, Cervicitis, Urethritis, Pharyngitis or Proctitis	Ceftriaxone	25–50 mg/kg	IM or IV	One-time dose (not to exceed 125 mg)		
Infants and Children Who Weigh > 45 kg and Who Have Uncomplicated Gonococcal Vulvovaginitis, Cervicitis, Urethritis, Pharyngitis, or Proctitis (Adult Dose Recommended)[a]	Ceftriaxone ***Dose by Weight*** (< 150 kg) (≥ 150 kg) and Doxycycline *(if chlamydia is not excluded)*	 500 mg 1 g 100 mg	 IM IM PO	 One-time dose One-time dose Twice daily For 7 days		
Recommended Regimen for Children Who Weigh ≤ 45 kg and Who Have Bacteremia or Arthritis	Ceftriaxone	50 mg/kg	IM or IV	As a single dose daily for 7 days		
Recommended Regimen for Children Who Weigh > 45 kg and Who Have Bacteremia or Arthritis	Ceftriaxone	1 g	IM or IV	As a single dose daily for 7 days		

[a]Treatment for both *Neisseria gonorrhoeae* and *Chlamydia trachomatis* may be indicated based on infection type and host.

Data from Refs. [9,10,12,15,16,17].

were treated. If retesting is impossible at 3 months, retest at the next medical visit within 12 months following treatment.

- Symptoms that persist after treatment should be evaluated by culture for *N. gonorrhoeae* and any gonococci isolated should be tested for antimicrobial susceptibility.

CHLAMYDIA

INTRODUCTION

Chlamydia is a STI caused by the bacteria *C. trachomatis*. Individuals infected with chlamydia are usually asymptomatic and the infection is easily treated with antibiotics. No vaccine exists for this infection.

EPIDEMIOLOGY AND ETIOLOGY

Infection with *C. trachomatis* has increased dramatically in recent years. In 2018, 1,758,668 cases of chlamydia were reported to the CDC, corresponding to a rate of 539.9 cases per 100,000 population. Chlamydia is most common among young people. Almost two-thirds of new chlamydia infections occur among youth aged 15 to 24 years.[9-11] Substantial racial disparities in chlamydia infection exist,

Patient Encounter 1

TS is a 20-year-old Mexican woman that works as a cross fit trainer at the local gym. Although TS generally understands English, she does not speak it fluently. She is currently enrolled in night courses to improve English comprehension.

Upon her last gynecology visit, a test for STIs was initiated due to a prescription she found at one of her boyfriend's home for erythromycin 500 mg that was prescribed four times daily for 7 days. Although asymptomatic, the results of TS's diagnostic test reveal her culture is positive for chlamydia.

PMH: Asthma; no prior history of STIs

Meds: Advair HFA 250/50 twice daily, CBD oil for anxiety

What information is suggestive of chlamydia?

What risk factors does she have for chlamydia?

Should any cultural competence concerns be considered?

Clinical Presentation of Chlamydia[9,10,11,14]

General

- Asymptomatic

Signs

- Beefy red cervix that bleeds easily (women)

Symptoms

- When present, the urethral discharge is watery and slightly purulent. Complications resulting from lack of treatment or inadequate treatment include epididymitis (in men), and pelvic inflammatory disease (PID) including associated complications in women.

Other Diagnostic Tests

- Culture can be positive for both chlamydia and gonorrhea.
- Gonorrhea and chlamydia should be treated concomitantly.

with a prevalence among non-Hispanic Black patients 5.6 times the prevalence among non-Hispanic White patients. Chlamydia is also common among MSM. Among MSM screened for rectal chlamydia infection, 0.5% to 2.3% were positive. Many cases remain unreported because most people are asymptomatic and do not seek testing. This bacterium is the most common cause of nongonococcal urethritis, accounting for as many as 40% of cases.

PATHOPHYSIOLOGY

C. trachomatis possesses characteristics resembling both bacteria and viruses. Its major membrane is comparable to that of Gram-negative bacteria, although it lacks a peptidoglycan cell wall and requires cellular components from the host for replication. Chlamydia transmission risk is thought to be less than that of gonorrhea.

CLINICAL PRESENTATION AND DIAGNOSIS

Common tests used to diagnose *C. trachomatis* include the NAAT, culture, enzyme immunoassay, DNA hybridization probe, or the direct fluorescent monoclonal antibody test. The NAAT is the most sensitive exam and the one which is commonly seen in practice.

Diagnosis has been confirmed in women through first-catch urine or swab specimens collected from the endocervix and in men using a urethral swab or first-catch urine specimens. Most women are asymptomatic; therefore, an annual screening or physical is necessary, as early detection may reduce rates of transmission.

Screening young sexually active men is recommended in clinical settings with a high prevalence of chlamydia (eg, correctional facilities, adolescent clinics) or areas with high infection rates. The primary focus for women should be to detect chlamydia, present complications, and to test and treat their partners. In some cases, frequent screening for certain women (eg, adolescents) and men (eg, MSM) is suggested.

TREATMENT[9,19]

The desired outcome is complete eradication of *C. Trachomatis* and avoidance of sequelae.

Pharmacologic Therapy[4,9,13,14]

Pharmacologic therapy for the treatment of chlamydia may be found in Table 83–2.

▶ *Recommendations During Pregnancy*

The recommended regimen for pregnant patients is azithromycin 1 g PO as a single dose *or* amoxicillin 500 mg three times daily for 7 days *or* erythromycin 500 mg four times daily for 7 days *or* 250 mg four times daily for 14 days.

Azithromycin 1 g orally as a single dose *or* amoxicillin 500 mg orally three times daily for 7 days *or* erythromycin base 500 mg orally four times daily for 7 days *or* erythromycin 250 mg orally four times daily for 14 days *or* erythromycin ethylsuccinate 800 mg orally four times daily for 7 days *or* erythromycin ethylsuccinate 400 mg orally four times daily for 14 days is recommended.

▶ *C. trachomatis Infection in Infants*

Treatment of ophthalmia neonatorum or infant pneumonia should be with erythromycin base or ethylsuccinate 50 mg/kg/day PO divided into four doses daily for 14 days. An association between oral erythromycin and infantile hypertrophic pyloric stenosis (IHPS) has been reported in infants aged less than 6 weeks, who were treated with this drug. Infants treated with erythromycin should be monitored for signs and symptoms of IHPS.

OUTCOME EVALUATION

- Order diagnostic test for chlamydia. If positive, recommend antibiotics that cover gonorrhea and chlamydia.
- Provide treatment for partner to mitigate the probability of reinfection.
- Counsel patient on the significance of refraining from sex for 7 days after treatment.
- Test of cure to detect therapeutic failure (ie, repeat testing 3–4 weeks after completing therapy) is not advised for individuals treated with the recommended or alternative regimens, unless therapeutic adherence is questionable, symptoms persist, or reinfection is suspected.
- Retest for chlamydia approximately 3 months after treatment, irrespective of whether sex partner was treated.

SYPHILIS

Attributed to the spirochete *Treponema pallidum*, syphilis can have numerous and complex manifestations. Clinician familiarity, stage-specific diagnosis, and effective treatment are vital. Missed or inappropriately treated syphilis may result in cardiovascular complications, neurologic disease, or congenital syphilis. No vaccine exists for syphilis.

EPIDEMIOLOGY AND ETIOLOGY

The incidence of syphilis declined drastically following the introduction of penicillin; however, prevalence rose when HIV arrived from obscurity in the 1980s. In 2018, there were more than 115,000 cases reported. Rates of primary and secondary syphilis increased 14% to more than 35,000 cases, the highest number reported since 1991.[20] Additionally, a dangerous trend of congenital syphilis has emerged: a 40% increase in cases was noted, and five states—Texas, California, Florida, Arizona, and Louisiana—accounted for 70% of cases. Data suggests

Table 83–2

Treatment Recommendations for Chlamydia

Indications	Drugs	Dose	Route	Duration	Alternative	Allergies
Uncomplicated Genital	Azithromycin Doxycycline	1 g 100 mg	PO PO	One-time dose (drug of choice) Twice daily for 7 days	Erythromycin 500 mg PO four times daily for 7 days OR erythromycin ethylsuccinate 800 mg four times daily OR levofloxacin 500 mg PO once daily for 7 days OR ofloxacin 300 mg twice daily (or 600 mg once daily) for 7 days	
Anorectal Infection	Azithromycin Doxycycline	1 g 100 mg	PO PO	One-time dose Twice daily for 7 days		
Chronic Reactive Arthritis	Doxycycline Rifampin	100 mg 300 mg	PO PO	Twice daily for 7 days Once daily for 6 months		
Uncomplicated Urethral, Endocervical or Rectal Infections in Adults	Azithromycin Doxycycline	1 g 100 mg	PO PO	One-time dose Twice daily for 7 days	Erythromycin 500 mg PO four times daily for 7 days OR erythromycin ethylsuccinate 800 mg four times daily OR levofloxacin 500 mg PO once daily for 7 days OR ofloxacin 300 mg twice daily (or 600 mg once daily) for 7 days ***Pregnancy*** Azithromycin 1 g PO as a single dose OR Amoxicillin 500 mg three times daily for 7 days OR Erythromycin base 500 mg four times daily for 7 days OR Erythromycin 250 mg four times daily for 14 days OR Erythromycin ethylsuccinate 800 mg four times daily for 7 days OR Erythromycin ethylsuccinate PO four times daily for 14 days	Erythromycin base 500 mg PO four times daily for 7 days OR Erythromycin base 250 mg PO four times daily for 14 days OR Erythromycin ethylsuccinate 800 mg PO four times daily for 7 days OR Erythromycin ethylsuccinate 400 mg PO four times daily for 14 days
Infection in Infants[a]	Azithromycin	1 g	PO	For 24–48 hours after improvement is noted; Ceftriaxone 1 g IV/IM indicated for concurrent *Neisseria gonorrhoeae* treatment	Cefotaxime 1 g IV every 8 hours or ceftizoxime 1 g IV every 8 hours plus azithromycin 1 g PO for 24–48 hours after improvement is noted	

[a] Treatment for both *Neisseria gonorrhoeae* and *Chlamydia trachomatis* may be indicated based on infection type and host.

Data from Refs. [9,10,14-18].

that several factors account for the elevation of cases reported, including gaps in testing, lack of treatment during prenatal care, drug use, poverty, decreased condom use, and cuts to STI programs at the state and local level.[9] Currently, no vaccine exists for this infection.

PATHOPHYSIOLOGY

T. pallidum rapidly penetrates intact mucous membranes or microscopic dermal abrasions, and within a few hours, the organism enters the lymphatics and blood to produce systemic illness. During the secondary stage, examinations commonly demonstrate abnormal findings in the cerebrospinal fluid (CSF). As the infection progresses, the parenchyma of the brain and spinal cord may subsequently be damaged.

DIAGNOSIS AND CLINICAL PRESENTATION

Stages of Syphilis

▶ *Primary Syphilis*

Usually manifests as a solitary, painless chancre. Primary syphilis develops at the site of infection approximately 3 weeks after exposure to *T. pallidum*; the chancre is highly infectious. The ulcer is typically indurated without exudate. There may be regional lymphadenopathy.[9,21]

▶ *Secondary Syphilis*

Without appropriate treatment, primary syphilis will advance to secondary syphilis—a stage usually apparent from its clinical symptomatology. Symptoms include fatigue, diffuse maculopapular rash involving the trunk, sore throat, myalgias, malaise, fever, lymphadenopathy, and genital or perineal condyloma latum. Hepatitis, patch alopecia, and renal insufficiency may also be seen. Ocular manifestations may include retinitis, optic neuritis, and uveitis.

▶ *Latent Syphilis*

Early Latent Individuals who have latent syphilis and who acquired syphilis during the preceding year are classified as early latent. Although, in this stage, the absence of signs and symptoms may be noted, serologic tests are positive. Usually occurs during the first year after infection and may be established in patients who have seroconverted, had symptoms of primary or secondary syphilis, or had sex with a partner with primary, secondary, or latent syphilis.

Late Latent Patients should be considered to have late latent syphilis, if the aforementioned criteria (early latent) are not met. In both stages, patients are usually asymptomatic, and the lesions noted in the primary and secondary phase usually resolve; however, individuals are still seropositive for *T. pallidum*.

Tertiary Syphilis Develops years (one or more decades) after the initial infection and may involve any organ in the body. Progressive dementing illness and tabes dorsalis are considered classic late neurological manifestations. Aortitis, cardiovascular disease (ie, aortic aneurysm, aortic valve insufficiency, and coronary stenosis), and nodular lesions in skin and bones may also be seen.

Congenital Syphilis

Congenital syphilis is a condition in which the fetus is infected with *T. pallidum* as a result of the hematogenous spread from an infected mother, although transmission may also occur from direct contact with the infectious genitalia of the mother. Since the primary stage of syphilis is characterized by spirochetemia, infectious rates of the fetus are nearly 100% if the mother has untreated primary syphilis, resulting in a 40% fetal death rate in infected infants.[21,22]

Diagnostic Procedures

There are three basic tests used in screening for syphilis. Diagnostic procedures include dark-field microscopy, nontreponemal exams (ie, the Venereal Disease Laboratory [VDRL] and the rapid plasma reagin [RPR] test), and treponemal exams (ie, enzyme immunoassay, the *T. pallidum* hemagglutination test, the fluorescent treponemal antibody test, and the enzyme-linked immunosorbent assay [ELISA]).[9,21] The paradigm recently shifted in many health centers to screen first with a treponemal antibody test and order a nontreponemal test only if the treponemal test is positive.

In a healthy patient, tests should be negative. This means that no antibodies to *T. pallidum* should be present. However, even if one of the aforesaid tests is positive, it would be inappropriate to provide an opinion about the infective status of the patient. Therefore, a good history should be taken and additional tests performed to exclude other diseases and scenarios, which may yield a false-positive result. Serologic exams generally provide indirect evidence of syphilis and may be reactive in the absence of clinical or historical evidence. Reactivity, in such cases, is usually in low dilutions (< 1:8); however, false reactivity in high titers has been seen. As such, quantitative titers cannot be used distinguish between a false-positive reaction and syphilis. To this end, careful and deliberate clinical evaluation of lab values and other evidence is requisite for proper diagnosis.

SCREENING

Recommendations for asymptomatic screening by population include:

▶ *MSM*

- At least annually if sexually active
- More frequently (eg, every 3 months) for persons with ongoing risk of infection or reinfection since last screened

▶ *Patients Taking PrEP for HIV Infection*

- At PrEP initiation
- Every 6 months for all patients on PrEP; every 3 months for MSM at high risk

▶ *Transgender Women and Men*

- Make an individualized assessment of STI/HIV-related risk and offer screening as appropriate for asymptomatic infections

▶ *Nonpregnant Women and Non-MSM Men*

- No national recommendations for routine screening in the general population
- Screening annually is recommended in sexually active persons who are at increased risk for infection

▶ *WSM*

- No national recommendations for routine screening in the general population

▶ *Pregnant Women*

- At first prenatal medical encounter
- At delivery (including live births, still births, or termination)
- At the time of fetal death, if applicable (after 20 weeks gestation)
- High-risk patients should be rescreened early in the third trimester (at approximately 28 weeks' gestation) and at delivery
- Assessment of sexual risk for syphilis at each prenatal visit
- Serologic rescreening if patient reports
    - New partner
    - Recent bacterial STI
    - Sex with MSM or transgender woman

TREATMENT

After confirming the diagnosis of syphilis, the desired outcome is a fourfold decrease in quantitative nontreponemal titers over a 6-month period and within 12 to 24 months after treatment of latent or late syphilis. An algorithm for the treatment of syphilis is shown in Figure 83–1.

With regard to neurosyphilis, a reduction in neurologic manifestations is desired, which may include seizures, paresis, meningitis, stroke, hyperreflexia, visual disturbances, hearing loss, neuropathy, or loss of bowel and bladder function. In late neurosyphilis, vascular lesions (meningovascular neurosyphilis) may also be observed; thus, a reduction in the number of observed lesions is warranted. A diminution in CSF white blood cell (WBC) (< 10 × 103/mm^3 [10 × 109/L]) or protein levels (0.05 g/dL [0.5 g/L]) is also preferred.

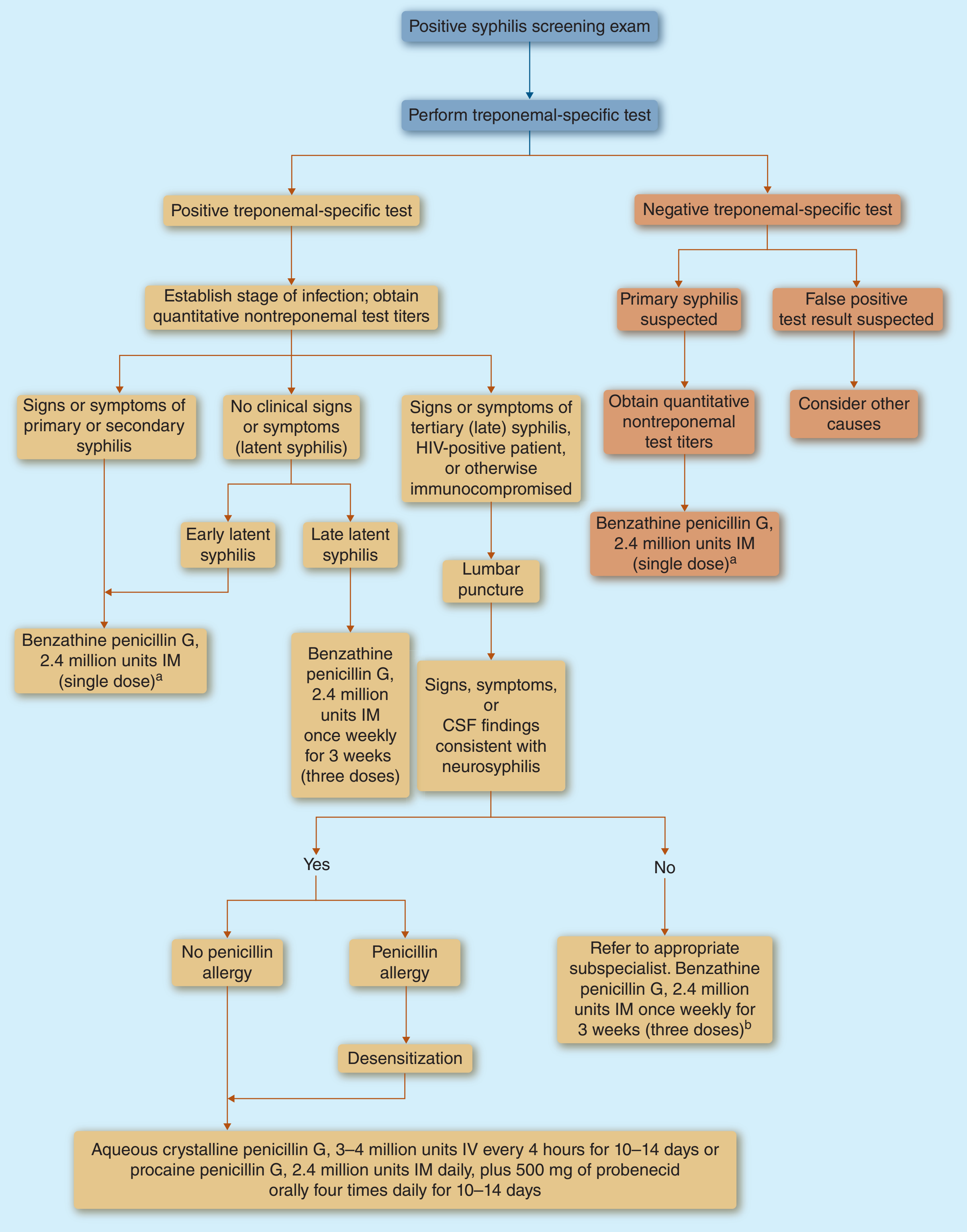
Positive syphilis screening exam
Perform treponemal-specific test
Positive treponemal-specific test
Negative treponemal-specific test
Establish stage of infection; obtain quantitative nontreponemal test titers
Primary syphilis suspected
False positive test result suspected
Signs or symptoms of primary or secondary syphilis
No clinical signs or symptoms (latent syphilis)
Signs or symptoms of tertiary (late) syphilis, HIV-positive patient, or otherwise immunocompromised
Obtain quantitative nontreponemal test titers
Consider other causes
Early latent syphilis
Late latent syphilis
Benzathine penicillin G, 2.4 million units IM (single dose)a
Lumbar puncture
Benzathine penicillin G, 2.4 million units IM (single dose)a
Benzathine penicillin G, 2.4 million units IM once weekly for 3 weeks (three doses)
Signs, symptoms, or CSF findings consistent with neurosyphilis
Yes
No
No penicillin allergy
Penicillin allergy
Refer to appropriate subspecialist. Benzathine penicillin G, 2.4 million units IM once weekly for 3 weeks (three doses)b
Desensitization
Aqueous crystalline penicillin G, 3–4 million units IV every 4 hours for 10–14 days or procaine penicillin G, 2.4 million units IM daily, plus 500 mg of probenecid orally four times daily for 10–14 days

FIGURE 83–1. Treatment of syphilis. [a]Alternative treatments for nonpregnant penicillin-allergic patients: doxycycline 100 mg PO twice daily for 2 weeks, or tetracycline 500 mg four times daily for 2 weeks; limited data support ceftriaxone 1 g once daily IM or IV for 8 to 10 days; or azithromycin, 2 g PO (single dose). [b]Alternative treatments for nonpregnant penicillin-allergic patients: doxycycline, 100 mg PO twice daily for 4 weeks, or tetracycline 500 mg PO four times daily for 4 weeks. (CSF, cerebrospinal fluid; IM, intramuscularly.) (Reprinted with permission from Diagnosis and Management of Syphilis, July 15, 2003, Vol. 68, No. 2, American Family Physician Copyright © 2003 American Academy of Family Physicians, All Rights Reserved.)

Table 83–3

Benzathine and Procaine Penicillin G Informational Chart

Categories	Benzathine Penicillin G	Procaine Penicillin G
Potential adverse reactions	CNS: convulsions, confusion, drowsiness, myoclonus, fever Dermatologic: rash Metabolic: electrolyte imbalance; Hematologic: positive Coombs test, hemolytic anemia Local: pain, thrombophlebitis Renal: acute interstitial nephritis Miscellaneous: anaphylaxis, hypersensitivity, Jarisch-Herxheimer reaction	CNS: seizures, confusion, drowsiness, myoclonus, CNS stimulation Cardiovascular: myocardial depression, vasodilation, conduction disturbances Hematologic: positive Coombs test, hemolytic anemia, neutropenia Local: thrombophlebitis, sterile abscess at injection site Renal: interstitial nephritis Miscellaneous: pseudoanaphylactic reactions, hypersensitivity, Jarisch–Herxheimer reaction, serum sickness
Monitoring parameters	Observe for anaphylaxis during first dose	Periodic renal and hematologic function tests with prolonged therapy; fever, mental status, WBC
Pregnancy category	B	B
Lactation	Enters breast milk	Enters breast milk
Availability	Bicillin L-A: 600,000 units/mL (1, 2, and 4 mL) Permapen Isoject: 600,000 units/mL (2 mL)	Injection, suspension: 600,000 units/mL (1, 2 mL)
Combination	Bicillin C-R: (1, 2, 4 mL) Bicillin C-R: 900/300: (2 mL)	Same

CNS, central nervous system; IM, intramuscular.

Data from Lacy C, Armstrong L, Goldman M, Lance L. Lexi-Comp's Drug Information Handbook, 17th ed. Hudson, OH: Lexi-Comp; 2019:1128–1132.

Pharmacologic Therapy

KEY CONCEPT Parenterally administered penicillin is recommended for all stages of syphilis (Table 83–3).[9] Although penicillin is the drug of choice, combinations of benzathine penicillin with procaine penicillin or oral penicillin preparations are not considered appropriate treatment regimens. Several reports demonstrated the misuse of the benzathine–procaine combination (Bicillin C-R) instead of the standard benzathine penicillin (Bicillin L-A) for treatment of syphilis.[23] Clinicians and purchasing agents should be aware of the similarities in product names to avoid errors in the prescribing and administration of these agents. Pertinent information germane to penicillin G is found in Table 83–4.

Alternative agents may be used in allergic individuals and include doxycycline, minocycline, tetracycline, or erythromycin base or stearate. Some patients (such as young children or pregnant women) may not respond favorably to alternative modalities or should not receive tetracyclines.

Persons with a history of severe non-IgE-mediated reactions are not candidates for skin testing or challenge and should avoid penicillins indefinitely.[9] After employing a full battery of tests, persons who report an allergy and who are skin-test negative may receive penicillin. However, in those with a positive skin test, desensitization should be performed before beginning treatment. Desensitization refers to a process of giving a medication in a controlled and gradual manner, which allows the patient to tolerate a drug temporarily without an allergic reaction.

Patients may experience fever, chills, tachycardia, and tachypnea, a condition commonly known as the Jarisch–Herxheimer reaction, an acute febrile reaction accompanied by headache, myalgia, fever, and other symptoms within the first 24 hours after the initiation of therapy. This reaction is postulated to occur secondary to spirochete lysis and proinflammatory cytokine cascades. Treatment is supportive and may include antipyretic and anti-inflammatory agents, as well as fluid resuscitation and bed rest. Additionally, in most cases, treatment for the Jarisch–Herxheimer reaction does not require halting penicillin or pursuing alternate therapy.

OUTCOME EVALUATION

The CDC has provided patient care monitoring guidelines for syphilis (Figure 83–2).[9,12,20,23]

Primary and Secondary Syphilis

- After 6, 12, and 24 months of treatment, reexamine the patient and recommend a follow-up quantitative nontreponemal titer. More frequent assessment might be sensible if follow-up is uncertain. If the patient is asymptomatic and a fourfold increase in nontreponemal titer or persistent or recurrent symptoms are observed, order an HIV test and a lumbar puncture; if the patient is HIV-positive, suggest an infectious disease consult.
- In patients who are both negative for HIV and the lumbar puncture, administer benzathine penicillin G 2.4 million units IM once weekly for 3 additional weeks. Perform a patient follow-up in 6 months including a clinical examination and another nontreponemal titer. In HIV-negative patients with lumbar puncture findings compatible with neurosyphilis, treat the patient accordingly for neurosyphilis.
- Six months after the original diagnosis, institute a standard clinical follow-up examination in patients who show no symptomatology and a fourfold decrease in nontreponemal titers. By testing and observing the patient for signs of remission, you may be able to initiate proper treatment or recommend a consult in a timely fashion, thereby decreasing the propensity of the patient's condition to advance to a higher stage.
- If serologic titers do not decline despite a negative CSF examination and a repeated course of therapy, it is unclear whether additional therapy or CSF examinations are needed; additional testing or repeated therapy is not generally recommended.

Early and Late Latent Syphilis

- Order nontreponemal titers 6, 12, and 24 months after instituting treatment for early or late latent syphilis.

Table 83–4

Treatment Recommendations for Syphilis

Indications	Drugs	Dose	Route	Duration	Alternative	Allergies
Primary Syphilis ***Adults*** ***Children***	Benzathine penicillin Benzathine penicillin	2.4 Million units 50,000 Units/kg, up to adult dose of 2.4 million units	IM IM	Single dose Single dose	Two injections of 1.2 million units as single doses Procaine penicillin 1.2 million units IM for 10–14 days Doxycycline 100 mg PO twice daily for 2 weeks Ceftriaxone 1 g IM daily for 10–14 days	Doxycycline 100 mg PO twice daily for 2 weeks
Secondary and Early Latent Syphilis (< 1-year duration) ***Adults*** ***Children***	Benzathine penicillin Benzathine penicillin	2.4 Million units 50,000 Units/kg, up to adult dose of 2.4 million units	IM IM	Single dose Single dose	Two injections of 1.2 million units as single doses Procaine penicillin 1.2 million units IM for 10–14 days Doxycycline 100 mg PO twice daily for 2 weeks Ceftriaxone 1 g IM daily for 10–14 days	Doxycycline 100 mg PO twice daily for 2 weeks
Late Latent Syphilis ***Adults*** ***Children***	Benzathine penicillin Benzathine penicillin	2.4 Million units 50,000 Units/kg, up to adult dose of 2.4 million units	IM IM	Once weekly for 3 weeks (total dose is 7.2 million units) Once weekly for 3 weeks (total dose 150,000 units/kg up to the adult dose of 7.2 million units)		
Tertiary Syphilis	Benzathine penicillin	2.4 Million units	IM	Once weekly for 3 weeks (total dose is 7.2 million units)	Doxycycline 100 mg PO twice daily for 4 weeks in nonpregnant patients Erythromycin 500 mg PO four times daily for 4 weeks may be used with caution in pregnant patients[23,24]	
Gummatous and Cardiovascular Syphilis	Benzathine penicillin (may be used as long as no evidence exists of CNS involvement)	2.4 Million units	IM	Once weekly for 3 weeks (total dose is 7.2 million units)	Doxycycline 100 mg PO twice daily for 4 weeks in nonpregnant patients Erythromycin 500 mg PO four times daily for 4 weeks may be used with caution in pregnant patients[23,24]	
Neurosyphilis	Penicillin G	3–4 Million units	IV	Every 4 hours for 10–14 days (may also be continuously infused) Benzathine penicillin 2.4 million units IM once weekly for up to 3 weeks may be used after intravenous therapy	Procaine penicillin 2.4 million units IM once daily, plus probenecid 500 mg four times daily, both for 10–14 days	
Congenital Syphilis	Benzathine penicillin	2.4 Million units	IM	Once weekly for 3 weeks (total dose is 7.2 million units)	Procaine penicillin 0.6–0.9 million units IM for 10–14 days Ceftriaxone 1 g IM or IV daily for 8–10 days	Asymptomatic neonates: 50,000 units/kg as a single IM dose Symptomatic neonates: 50,000 units/kg of aqueous crystalline every 12 hours IM for the first 7 days of life, then every 8 hours for 3 days or procaine penicillin G 50,000 IU/kg IM daily for 1015 days

Data from Refs. [9,24,25].

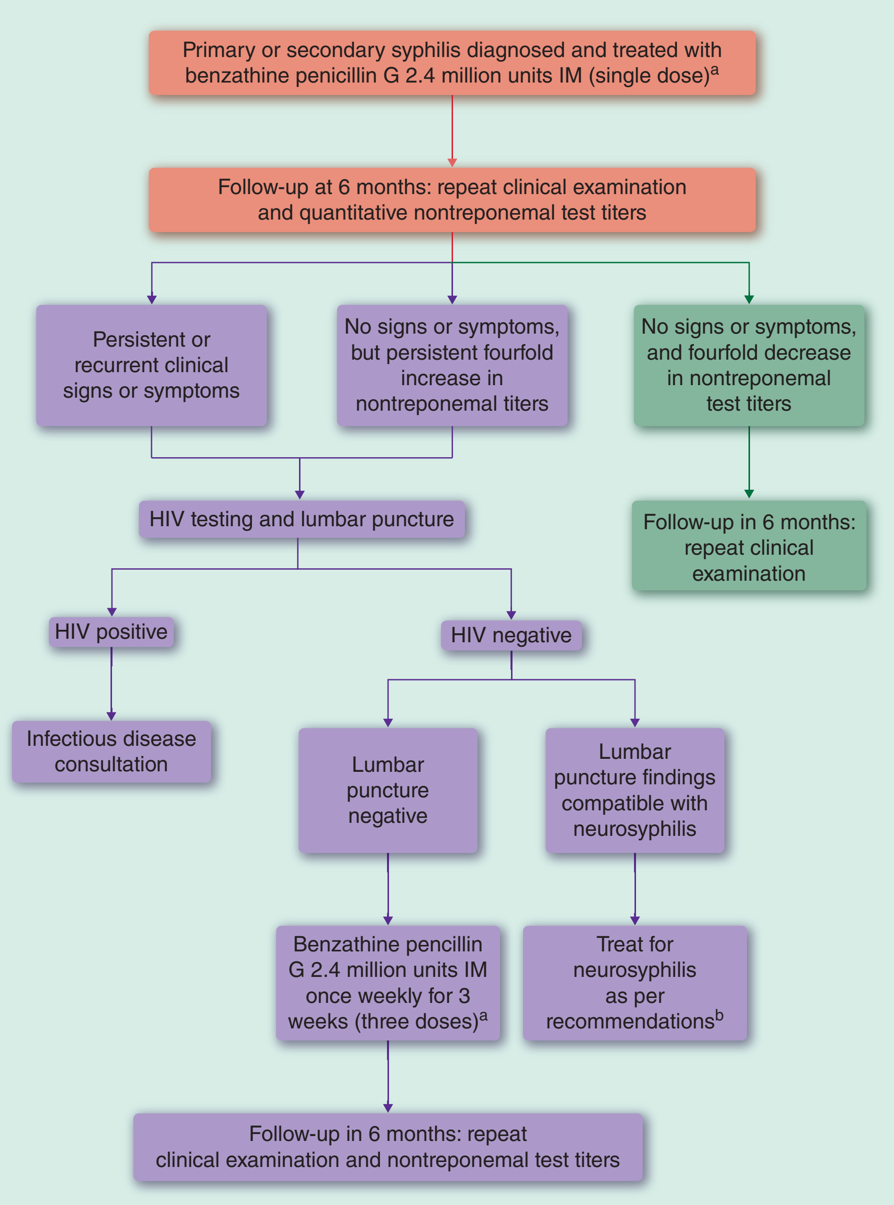
Primary or secondary syphilis diagnosed and treated with benzathine penicillin G 2.4 million units IM (single dose)a
Follow-up at 6 months: repeat clinical examination and quantitative nontreponemal test titers
Persistent or recurrent clinical signs or symptoms
No signs or symptoms, but persistent fourfold increase in nontreponemal titers
No signs or symptoms, and fourfold decrease in nontreponemal test titers
HIV testing and lumbar puncture
Follow-up in 6 months: repeat clinical examination
HIV positive
HIV negative
Infectious disease consultation
Lumbar puncture negative
Lumbar puncture findings compatible with neurosyphilis
Benzathine pencillin G 2.4 million units IM once weekly for 3 weeks (three doses)a
Treat for neurosyphilis as per recommendationsb
Follow-up in 6 months: repeat clinical examination and nontreponemal test titers

FIGURE 83–2. Patient care monitoring for syphilis. [a]See text for alternative treatment recommendations for nonpregnant penicillin-allergic patients. [b]See text for treatment recommendations for neurosyphilis. (Reprinted with permission from Diagnosis and Management of Syphilis, July 15, 2003, Vol. 68, No. 2, American Family Physician Copyright © 2003 American Academy of Family Physicians, All Rights Reserved.)

Neurosyphilis should be strongly considered in patients who show a fourfold increase in titers, patients who have an initially high titer (1:32 or greater) that fails to decline at least fourfold within 12 to 24 months of therapy, HIV-infected patients, and patients who develop signs or symptoms associated with neurosyphilis.[9,22,25]

Neurosyphilis

- Follow-up is dependent on the CSF findings. If pleocytosis is present, reexamine the CSF every 6 months until the WBC count normalizes. Consider recommending a second course of treatment if the CSF white count does not decline after 6 months or completely normalize after 2 years.[4,9,21] Failure to normalize may require retreatment; most treatment failures occur in immunocompromised patients.

Congenital Syphilis

- Observe the patient for changes in clinical features; hepatomegaly, jaundice, and bone changes will usually resolve in 3 months.[26]
- Monitor elevated serologic markers (nontreponemal tests) for reduction in titer levels. Given effective treatment, clinical features will usually disappear after 6 months. On this basis, evaluate seropositive infants periodically for at least 6 months.

TRICHOMONIASIS

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis* and is far more prevalent than *C. trachomatis* or *N. gonorrhoeae*. In the United States, approximately 5 million new cases appear annually, compared with 3 million chlamydial and 650,000 gonococcal cases annually.[27] No vaccine exists for trichomoniasis.

Patient Encounter 2

WC, a 31-year-old Caucasian woman, walks into the clinic today complaining of a yellowish-green discharge along with a vaginal odor for the past several days. WC is a herbalist and vegetarian. WC does not believe in relational attachments and admits to having multiple sexual partners. Safe sex is always performed with new partners for the first 3 months states WC. She drinks a glass of red wine daily along with smoking medical marijuana for PTSD and indulges in other recreational drugs for entertainment.

What characteristics are indicative of trichomoniasis?

What would be the consequences of her daily alcohol consumption while taking metronidazole?

PATHOPHYSIOLOGY

T. vaginalis, a protozoa, may be isolated from the vagina, urethra, and Bartholin or Skene glands. After attachment to the host cells, it ignites an inflammatory response exhibited as a discharge containing elevated levels of polymorphonuclear leukocytes. The pathogen causes direct damage to the epithelium, leading to microulcerations.

CLINICAL PRESENTATION AND DIAGNOSIS

Diagnosis is usually performed with a wet mount or Papanicolaou smear. In women, symptoms are characterized by diffuse, malodorous, yellow-green vaginal discharge with vulvar irritation. Some women may be asymptomatic.

TREATMENT

The desired outcome is the complete eradication of *T. vaginalis* in both partners and elimination of the signs and symptoms observed.

Clinical Presentation of Trichomoniasis[9,27]

General

- Asymptomatic

Signs

- Strawberry cervix (women)
- Colpitis macularis (women)
- Prostatitis or epididymitis (men)

Symptoms

- Vaginal/vulvar erythema
- Excessive yellow-green discharge
- Vulvar itching
- Vaginal odor
- Urethral discharge or irritation
- Dysuria
- Vaginal pH greater than 4.5

Table 83–5

Treatment Recommendations for Trichomoniasis

Indications	Drugs	Dose	Route	Duration
Trichomoniasis	Metronidazole	2 g	PO	Single dose
	Tinidazole	500 mg	PO	Twice daily for 7 days
	Effective for metronidazole-resistant trichomoniasis	2 g	PO	Single dose

Data from Refs. [9,27,28].

Pharmacologic Therapy

KEY CONCEPT The 5-nitroimidazoles (metronidazole and tinidazole) have been the standard therapy for trichomoniasis for over 45 years. When using these agents, advise patients to avoid the consumption of alcohol. Pharmacologic treatment for trichomoniasis may be found in Table 83–5.[9,27,28]

▶ *Side Effects and Contraindications*

Metronidazole

Common side effects, which are gastrointestinal disturbances, are typically mild. Occasional adverse effects have also been reported, which include an unpleasant metallic taste, reversible neutropenia, urticaria, rash, flushing, dry mouth, darkened urine, and a disulfiram-like reaction.

Tinidazole

Tinidazole is associated with fewer side effects that metronidazole. Possible side effects include an unpleasant metallic taste, dizziness, loss of coordination, seizures, severe diarrhea, darkened urine, nausea, vomiting, and a swollen or discolored tongue.

Contraindications

Contraindications include hypersensitivity to nitroimidazole derivatives or any components of the formulation and use of disulfiram (past 2 weeks) or alcohol (within 3 days of therapy).

▶ *Allergies*

Patients who allergic to metronidazole should not be prescribed tinidazole.

▶ *Pregnancy*

Recommend a single 2-g dose of metronidazole, if treatment is deemed necessary. Retreatment of trichomoniasis during pregnancy may relieve symptoms of vaginal discharge or prevent the rare complication of neonatal respiratory infection with trichomoniasis. In breastfeeding women, the CDC recommends stopping breastfeeding during the course of metronidazole treatment and for 12 to 24 hours after the last day. For treatment with tinidazole, the CDC recommends stopping breastfeeding for the course of treatment and for 3 days after the last dose.

OUTCOME EVALUATION

- Order diagnostic test for trichomoniasis. If positive, recommend antibiotics that cover *T. vaginalis*.
- Subsequent to treatment, expect the eradication of the protozoa.

- Provide treatment for partner(s) to mitigate the probability of reinfection.
- Counsel patient on the significance of refraining from sex for 7 days after treatment.
- Rescreen patients 3 months after treatment, if there is a high probability of reinfection.

GENITAL WARTS

Genital warts, caused by the human papillomavirus (HPV), usually appear in the genital area (penis, vulva, vagina, cervix, perineum, and perianal area) as very contagious, small bumps. Responsible for various visible, keratotic, and nonkeratotic manifestations, HPV has more than 150 noted strains, some of which have been linked to squamous cell carcinoma.[29] More than 60 strains have been linked to the genital area.[30] Two general categories of genital HPV exist as low-risk benign HPV lesions and high-risk neoplastic HPV lesions. The low-risk strains are responsible for genital warts and low-grade cervical lesions.[31]

EPIDEMIOLOGY AND ETIOLOGY

Genital warts are caused by several strains of HPV and spread by skin-to-skin contact (ie, vaginal, anal, or oral) during sexual activity with an infected person.[31,32] HPV can be passed when an infected person has no signs or symptoms. Affecting over 79 million Americans, HPV is the most common, newly diagnosed STI in the United States, with prevalence of approximately 52%. Almost 14 million new HPV infections occur every year in the United States.[29] Nearly half of new infections occur among persons aged 15 to 24 years. Condoms offer incomplete (grade B, level II [fair research-based evidence to support the recommendation]) protection against HPV because HPV can infect areas not covered by a condom.[31,32]

The greatest incidence of HPV was noticed in men with three or more sex partners and women whose most recent regular sexual partner had two or more lifetime partners. Smoking, an uncircumcised male, being immunocompromised, oral contraceptives, and early coital age are also risk factors for acquiring genital warts. Most people with HPV do not develop symptoms. At least half of sexually active persons will become infected at least once in their lifetime. In 90% of the cases, the body immune system clears HPV naturally within 2 years. Routine testing of HPV DNA infection is not recommended because test results would not alter clinical management of the condition. **KEY CONCEPT** HPV types 16 and 18 cause 99.7% of all cervical cancer while HPV types 6 and 11 are responsible for about 90% of genital and perianal warts.[31,33]

PATHOPHYSIOLOGY

HPV invades cells of the basal layer of the epidermis, penetrating skin, and mucosal microabrasions in the genital area. A latency period of 3 weeks to 9 months may ensue. Following that period, viral DNA, capsids, and particles are produced. Host cells become infected and develop the morphologic atypical koilocytosis of genital warts.[31,34] Genital warts are the clinical manifestation of active viral replication and virion production at the infection site.

CLINICAL PRESENTATION AND DIAGNOSIS

- A definitive diagnosis of HPV is based on DNA, RNA, or capsid protein detection.
- Diagnosis is generally made from the clinical presentation or by visual inspection. It may be classified into several categories: classic condyloma acuminata, which are pointed or cauliform; keratotic warts with a thick, horny surface resembling common skin warts and flat warts, which are frequently observed on the surface.
- Tissue biopsy or viral typing is only indicated if the diagnosis is uncertain and is not recommended for patients with routine or typical lesions.
- Since HPV is highly associated with cervical cancer and has more than 20 different cancer-associated HPV types, patients who are diagnosed with HPV should be tested for cervical cancer.

Clinical Presentation of Genital Warts[9,34]

General

- Appear as rough, thick, cauliflower-like lesions

Signs

- Black dots within warts
- Disrupted surface

Symptoms

- Anogenital pruritus
- Burning
- Vaginal discharge or bleeding
- Although rare, dyspareunia may occur with vulvovaginal condyloma

TREATMENT

The most reliable method to avoid genital warts is to abstain from sexual activity.[9] Genital warts are usually asymptomatic but can be painful or pruritic. Approximately 40% to 60% of untreated warts will spontaneously resolve in 9 to 12 months if left untreated.[31] Treatment of benign, symptomatic genital warts is aimed at alleviation of physical symptoms and cosmetic improvement. Removal of visible warts and reduction of infectivity are the goals of treatment. Many cases of genital warts fail to respond to treatment or recur after adequate response.[31]

A comparison of adverse effects related to treatment options may be found in Table 83–6.

Patient-Applied Treatment

▶ *Podofilox*

- 0.5% gel or solution
- Podofilox inhibits the formation of the mitotic spindle and prevents cell division
- Surface area treated must not exceed 10 cm^2
- Apply solution (using a cotton swab) or gel (using a finger) twice daily for 3 consecutive days, followed by 4 consecutive days without treatment. This cycle may be repeated until there are no visible warts for a maximum of 4 weeks.

▶ *Imiquimod*

- 3.75% or 5% topical cream in single-dose application packets
- Imiquimod is a cell-mediated immune-response modifier

Table 83–6

Comparison of Adverse Effects Seen With Treatments for Genital Warts

Treatment	Adverse Effects
Podofilox	Burning at site of application, pain, inflammation
Imiquimod	Erythema, irritation, ulceration, pain, burning, edema, pigmentary changes
Sinecatechins	Burning at site of application, erythema, pruritus, edema
Podophyllin resin	Local irritation, erythema, burning, soreness at application site; possibly oncogenic
Bichloroacetic and trichloroacetic acid	Local irritation and pain, minimal systemic effects
Cryotherapy	Pain or blisters at application site
Surgical excision	Pain, bleeding, scarring; possible burning or allergic reaction to local anesthetic
Vaporization	Pain, bleeding, scarring; risk of HPV spreading via smoke plumes
Intralesional interferon	Burning, itching, irritation at injection site, systemic myalgia, headache, fever, chills, leukopenia, elevated liver enzymes, and thrombocytopenia

HPV, human papillomavirus.

Data from Refs. [9,31,35].

- There are two recommended dosage regimens:
  a. Apply 5% cream at bedtime, three times a week for up to 16 weeks or every other day for three applications.
  b. Apply 3.75% cream applied once at bedtime.

The treatment area should be washed with soap and water 6 to 10 hours after application. Mild-to-moderate erythema has been noted with imiquimod use; however, this generally suggests that the drug is reaching a therapeutic range and clearing the lesion.[9]

▶ *Sinecatechins*

- A total 15% of the ointment is green tea extract with an active product catechins
- Apply a thin layer (0.5 cm) using a finger to each wart three times a day until complete clearance of warts.
- Do not wash off after use, and all sexual contact should be avoided while ointment is on the skin
- This product should not be continued for longer than 16 weeks.[9]
- The safety of sinecatechins during pregnancy is unknown.

Physician-Applied Treatments

▶ *Podophyllin Resin*

- A 10% to 25% solution of podophyllin resin in a compound tincture of benzoin has been the standard in-office treatment for genital warts.
- Because podophyllin is neurotoxic and systemically absorbed, only a small amount (no > 0.5 mL) should be applied.
- Application should be limited to less than 0.5 mL of podophyllin on an area of less than 10 cm^2 of warts per session and no open lesions or wounds should exist in the area to which treatment is administered.[9,31]
- Topical podophyllin is applied once weekly and the area should be allowed to dry. Immediately following treatment, the dried drug should be removed using alcohol or soap and water.
- Topical podophyllin is contraindicated in pregnant patients.

▶ *Bichloroacetic (BCA) and Trichloroacetic (TCA) Acids*

- They are in 80% to 90% concentrations and are not systemically absorbed
- These caustic agents destroy warts by chemical coagulation of proteins
- The products are effective when used to treat a few small, moist lesions
- Apply once a week until the wart is resolved
- May be used in pregnancy

To avoid these adverse effects, place petroleum jelly around the external lesion, including unaffected skin, and carefully apply the agent with a small applicator.

▶ *Other Treatments*

Other treatments may include fluorouracil/epinephrine/bovine collagen gel, an intralesional injection that has been proven effective in clinical trials for refractory patients or an intralesional injection of interferon.[34,35]

Ablative Therapy

Several ablative options have been employed in the treatment of genital warts and include cryotherapy with liquid nitrogen or cryoprobe, surgical removal by excision, and vaporization. Cryotherapy destroys warts by thermal-induced cytolysis. Use an open spray or cotton-tipped applicator for 10 to 15 seconds and repeat, as needed. Wart clearance occurs about 75% of the time. Pain during and after application of the liquid nitrogen, followed by necrosis and sometimes blistering is common.[9]

Special Therapeutic Issues[9,31]

▶ *Large Warts*

Treat warts greater than 10 mm in diameter with surgical excision, carbon dioxide (CO_2) laser, or by curettage.[30] Use imiquimod for three to four treatment cycles to reduce the number of warts and improve surgical outcomes. Fifty percent reduction in wart size after four treatment cycles warrants continued use of imiquimod until warts clear or eight cycles have been completed; less than 50% reduction warrants surgical excision or other ablative therapy.

▶ *Subclinical Warts*

Subclinical warts may be identified through colonoscopy, biopsy, acetic acid application, or laboratory serology. However, early treatment has not been linked to a favorable effect during the course of therapy in the index patient or the partner with regard to reduction of the transmission rate.

▶ *Pregnancy*

Agents contraindicated in pregnancy include podofilox, sinecatechins, fluorouracil, and podophyllin. Imiquimod is not approved for use in pregnancy, although it has been considered after signed consent has been obtained. Bichloroacetic and trichloroacetic acids have been used without problems. Ablative therapy is also a viable option.

OUTCOME EVALUATION

- Monitor the patient for any visible warts and relief of symptoms.
- Apply powder with talc, baking soda, or liquid soap to remove unreacted trichloracetic or bichloroacetic acid.
- Dry area before contact with normal mucosa after application of podophyllin.
- Repeat TCA, BCA, podophyllin treatment weekly if necessary.
- Administer a different agent if warts persist after one type of therapy.
- Refer all recalcitrant patients to local STI clinics, gynecologists, dermatologists, or urologists.

VACCINES AND TOXOIDS

Thirteen HPV types (33, 35, 39, 40, 43, 45, 51–56, 58) have moderate risk for neoplastic conversion.[31] Several HPV genotypes have been linked to the development of cervical cancer. Gardasil, a quadrivalent vaccine (4vHPV) developed to protect against HPV genotypes 6, 11, 16, and 18, was the first vaccine employed to prevent cervical cancer, precancerous genital lesions, and genital warts due to HPV. Cervarix, a bivalent vaccine (2vHPV), prevents cervical cancer and precancers caused by HPV types 16 and 18. Both Gardasil (4vHPV) and Cervarix (2vHPV) were discontinued in the United States in October 2016. Gardasil 9, a 9-valent vaccine, protects against infection with HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

The CDC recommends the HPV vaccine for all 11- and 12-year-old girls and boys (may start at age 9). Vaccination is also recommended for females aged 13 through 26 years and males 13 to 21 years old who have not been previously vaccinated or who have not completed the full series of shots.[29,33] In the past, inactivated vaccines were given in a series of three IM injections over a 6-month period. Second and third doses were given at 2 and 6 months, respectively, after the first dose. However, the CDC guidelines now recommend that 11- to 12-year-olds receive two doses of the HPV vaccine, rather than the previously mentioned three doses. The second dose should be given 6 to 12 months after the first. HPV vaccine may be given at the same time as other vaccines.

In June 2019, the Advisory Committee on Immunization Practices (ACIP) recommended shared clinical decision-making for HPV vaccination of adults aged 27 to 45 years.

HPV vaccines are very safe and efficacious in preventing genital warts; however, they will not clear those that are already present. Either vaccine is recommended for girls/women, whereas only one vaccine (Gardasil) is recommended for boys/men.[29] In adults up to 45 years old with HPV, Gardasil was 88% effective in preventing genital warts and precancerous lesions.[31,35,36]

HPV vaccine is not recommended for use during pregnancy.[29]

GENITAL HERPES

Genital herpes (GH) is caused by herpes simplex virus (HSV) types 1 and 2. HSV is a chronic, ubiquitous, lifelong viral infection, for which there is no cure. Once latency is established, neither competent host immunity nor therapeutic agents can eradicate the virus.[9] Currently, there is no vaccine available for HSV, and it seems that the development of one is unlikely in the near future. HSV-1 is mainly transmitted by oral-to-oral contact to cause oral herpes (cold sores) but can also cause GH through oral sex. HSV-2 is an STI that causes GH.[37]

Clinical Presentation of Genital Herpes[9,37,38]

General

- Asymptomatic

Classic Sign

- A cluster of painful vesicles on an erythematous base

Symptoms

- Itching
- Burning
- Tingling
- Groin lump
- Dysuria
- Dyspareunia
- Increased urinary frequency

Other Symptoms

- Ulcerative lesions, fissures, cervicitis

EPIDEMIOLOGY AND ETIOLOGY

Approximately 50 million Americans have GH. HSV-2 is the most common cause of recurrent GH. Roughly one in six people in the United States (16.2%) aged 14 to 49 is infected with HSV-2, with over 500,000 new cases of HSV-2 occurring annually.[9] Most HSV-1 infections are acquired during childhood. Many persons infected with HSV-2 have not been diagnosed; therefore, most GH infections are transmitted by persons unaware of their status.[37]

PATHOPHYSIOLOGY

HSV can cause primary or reactivation (recurrent) infections. Since HSV is only found in humans, infection may only be transmitted from infectious secretions onto mucosal surfaces (ie, cervix or urethra) or direct contact with an active lesion (abraded skin). The virus may survive for a limited amount of time on environmental surfaces. **KEY CONCEPT** Nearly all HSV-2 infections are sexually acquired. Most sexual transmission occurs while the source case is asymptomatic. Most patients with unrecognized genital HSV infections will still shed virus intermittently in the genital tract. Patients will have small, painful blisters that are filled with fluid. The first outbreak takes 2 to 4 weeks to heal. Because there is no cure for this illness, treatment will only help reduce the signs, symptoms, and number of attacks.[9] Persons with GH should be tested for HIV infection because of their epidemiological synergy.[37] The severity and frequency of the disease and the recurrence rate depends on numerous factors including viral type, gender, and immune status of host. Recurrent infections are typically milder and shorter.[37,38]

CLINICAL PRESENTATION AND DIAGNOSIS

There are several methods by which a definitive diagnosis of HSV may be acquired, including virologic typing, serologic diagnosis, rapid point-of-care antigen detection, ELISA, immunoblot, and DNA polymerase chain reaction.[38] Glycoprotein G-based assays may also be used to aid in the diagnosis of HSV. Ulcerative or multiple vesicular lesions are absent in many infected persons.

Laboratory confirmation is vital to effective treatment, especially in individuals in whom a clinical diagnosis cannot be obtained.

TREATMENT

The virus is very evasive and can lay dormant for many years before infecting a person. Management of genital HSV should address the chronic nature of the disease rather than focusing solely on treatment of acute episodes of genital lesions. The desired outcome is to curtail the number of episodic prodromes and to minimize any side effects experienced due to the antivirals. Counseling of infected persons and their partners is vital to the management of HSV.

First Episode

The first episode is a systemic illness associated with the vesicular lesions, may last up to 21 days, usually has an uncomplicated course of infection and, in severe cases, may require hospitalization. This initial presentation occurs 4 to 7 days after sexual exposure. Several agents are effective during this period (Table 83–7).[37,38]

At the cited dosages, these agents produce excellent outcomes with regard to lesion healing time, viral shedding, and reduction in pain. Common adverse effects are nausea, headache, and diarrhea. It is important to note that the first episode does not necessarily indicate recent infection and the genital symptoms may develop several years after the infection was acquired. Condom use in new or uninfected partners, particularly in the 12 months after the first attack, is recommended.

Episodic Therapy

In a patient with a previous diagnosis of GH, the appearance of new vesicular lesions is synonymous with HSV reactivation. For most patients, GH recurrence is self-limiting and short-lived, lasting approximately 6 to 7 days.

Suppressive Therapy

Suppressive therapy is effective for controlling all symptoms related to the disease and may impact troublesome complications of infection. Before beginning suppressive therapy, discuss

Table 83–7

Comparison of Antiviral Agents Used for Herpes Simplex Infection

Agent	Dose	Side Effects
First Episode		
Acyclovir	*200 mg PO five times a day × 7–10 days* ***or*** 400 mg PO three times daily × 7–10 days	Headache, confusion, nausea, vomiting, thrombocytopenia, renal insufficiency, rash, pruritus, fever, arthralgias, myalgia, thrombotic thrombocytopenic purpura, hallucinations, somnolence, depression
Valacyclovir	*1 g PO two times daily × 7–10 days*	Refer to acyclovir
Famciclovir	250 mg PO three times daily × 7–10 days	Refer to acyclovir
Episodic		
Acyclovir	*200 mg PO five times daily × 5 days* ***or*** 400 mg PO every 8 hours × 5 days ***or*** 800 mg PO two times daily × 5 days ***or*** 800 mg PO three times daily × 2 days	Refer to acyclovir (WHO)
Valacyclovir	*500 mg PO two times daily × 3 days* ***or*** 1 g PO once daily × 5 days	Refer to acyclovir
Famciclovir	125 mg PO two times daily × 5 days ***or*** 1000 mg PO twice daily × 1 day	Refer to acyclovir
Suppressive		
Acyclovir	400 mg PO two times daily continuously ***or***	Refer to acyclovir
Valacyclovir	500 mg PO once daily continuously ***or***	Less effective if > 10 episodes per year
Valacyclovir	1000 mg PO once daily continuously ***or***	Refer to acyclovir
Famciclovir	250 mg PO two times daily continuously	Refer to acyclovir
Reserved Agents		
Foscarnet	40 mg/kg IV every 8 hours until clinical resolution is attained	Renal insufficiency, metabolic disturbances, hypophosphatemia
Cidofovir	1% topical agent (gel) used daily on a compassionate basis for acyclovir-resistant herpes lesions for 5 days	Application site reactions, lesion recrudescence
Imiquimod	Topical alternative used daily on a compassionate basis for acyclovir-resistant herpes lesions for 5 days	Application site reactions, lesion recrudescence

Italicized data indicate preferred dosages.

Data from Refs. [9,37].

patient expectations. Encourage patients to record any breakthrough episodes, as this may require treatment reevaluation and adjustment.

Preventive Therapy

Valacyclovir 500 mg PO once daily has been used to prevent the sexual transmission of HSV to an uninfected partner. In addition to pharmacologic therapy, counsel patients regarding safe sex practices.

Drug Resistance

All acyclovir-resistant strains are resistant to valacyclovir and the majority are resistant to famciclovir. Foscarnet, cidofovir, and trifluridine have been administered in acyclovir-resistant patients.[36] These agents are usually reserved for use after other medications have failed because of their associated toxicities.

Pregnancy

Women who are pregnant may transmit the virus to the neonate during delivery. There are two management strategies: caesarean section and antiviral therapy. Acyclovir 200 to 400 mg every 8 hours has been administered from 38 weeks' gestation until delivery. Acyclovir, famciclovir, and valacyclovir are all classified as category B (no evidence of risk in humans) for use during pregnancy. Suppressive treatment includes the use of acyclovir or valacyclovir from week 36 until delivery. The goal of therapy is to reduce the number of lesions and asymptomatic shedding at delivery.

Neonates

The risk for transmission from an infected mother to a neonate is highest among women who acquired GH near time of delivery.[39,40] Women who have GH prior to pregnancy are at very low risk of transmitting HSV to their infants. HSV infections should be considered in all neonates who present with nonspecific symptoms such as fever, poor feeding, lethargy, or seizures in the first month of life. Infants suspected to have or who are diagnosed with an HSV infection should be treated parenterally. Acyclovir 20 mg/kg/day in three divided doses IV for 21 days for disseminated and CNS disease *or* 14 days for disease limited to skin, eyes, and mucous membranes.

HIV Infection

Lesions caused by HSV are common among persons with HIV infection due to increased shedding. Affected individuals may have prolonged episodes of GH. Oral antiviral agents are effective in decreasing the clinical manifestations of HSV among those infected with HIV.[9,39]

OUTCOME EVALUATION

- Monitor for systemic symptom improvement and a decrease in viral shedding when initiating HSV treatment.
- Take lukewarm baths three to four times a day to ease itching and pain. Pat dry affected areas.
- Wear loose-fitting underwear to help the sore dry.
- Avoid sexual contact until treatment is finished.
- Consider stopping suppressive therapy after 1 year to assess recurrence rate.
- Compound topical 1% cidofovir gel in acyclovir-resistant strains where IV foscarnet is not preferred.

PELVIC INFLAMMATORY DISEASE

Pelvic inflammatory disease (PID) usually affects young, menstruating, sexually active women. PID includes a spectrum of inflammatory disorders of the upper female genital tract. In the majority of cases, the pathogens responsible are *C. trachomatis* and *N. gonorrhoeae*; although anaerobes, enteric Gram-negative rods and cytomegalovirus have also been implicated in the pathogenesis.[41] PID has been correlated with ectopic pregnancy, infertility, tubo-ovarian abscess, and chronic pelvic pain.[42] Currently, no vaccine exist for the treatment of PID despite ongoing efforts.

EPIDEMIOLOGY AND ETIOLOGY

PID is most common in minority women younger than 25 years of age, who have more than one sex partner and does not use contraception. PID leads to approximately 2.5 million office visits each year in the United States that cause 125,000 to 150,000 hospitalizations. The highest rates of PID occur in teenagers and first-time mothers. Up to 10% to 20% of untreated chlamydia or gonorrhea infections progress to PID and affected women may become infertile as a result.[9] Since many cases of PID are asymptomatic or inadequately treated, the potential for damage to reproductive health is increased. Additionally, there is an elevated risk for women with past STIs and for those who have more than one partner. However, over the past decade, evidence suggests a decline in PID diagnoses in the United States.[42]

PATHOPHYSIOLOGY

PID is an infection that occurs when bacteria traverses from a woman's vagina to her reproductive organs, including the uterus, fallopian tubes, and adjacent pelvic structures. Normally, the cervix prevents bacteria from spreading to the reproductive organs. However, when the cervix is exposed to STIs due to unprotected sex, bacteria may be disseminated into female internal organs. Less commonly, bacteria can enter the reproductive tract during menstruation, after childbirth, or abortion. Chlamydia, the primary organism associated with PID in the United States, may produce a heat-shock protein that causes tissue damage through a delayed hypersensitivity reaction. *C. trachomatis* may also possess DNA evidence of toxin-like genes that code for high-molecular-weight proteins with structures similar to *Clostridium difficile* cytotoxins, enabling inhibition of immune activation. This may explain the observation of a chronic chlamydia infection in subclinical PID.[43]

Patient Encounter 3

TS decided against medical treatment and utilized a herbalist to treat her chlamydia. The alternate treatment did not work, and intercourse became painful. TS was evaluated today by her primary physician due to a fever of 101°F and lower abdominal pain.

Given this additional information, what is suggestive of PID?

Identify treatment goals for this patient

Identify monitoring parameters of the antibiotics doxycycline and metronidazole used in her treatment.

Clinical Presentation of Pelvic Inflammatory Disease[9,41]

General

- Signs and symptoms may vary from mild to severe.

Signs

- Vague

Symptoms

- Lower abdominal or pelvic pain
- Malodorous vaginal discharge
- Abnormal uterine bleeding
- Dyspareunia
- Dysuria
- Nausea and/or vomiting
- Fever

CLINICAL PRESENTATION AND DIAGNOSIS[41,42]

Because many women with PID have subtle symptoms, delays in diagnosis and treatment may lead to inflammatory sequelae in the upper reproductive tract. Women who receive a diagnosis of acute PID should be tested for HIV, gonorrhea, and chlamydia. Because of the lack of severity in the symptoms for PID, protection of female fertility takes precedence in the diagnosis. Patients with uterine or cervical motion tenderness, painful urination, lower abdominal pain, painful intercourse, abnormal uterine bleeding (especially during or after intercourse), and adnexal tenderness with no other cause of these signs warrant treatment. Additional criteria include:

- Oral temperature greater than 38.3°C (101°F)
- Abnormal cervical or vaginal discharge which has an unusual color (green or yellow)
- WBC presence on saline microscopy of vaginal secretions
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein
- Laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*

TREATMENT

Presumptive treatment of PID should be initiated in young, sexually active women if they are experiencing pelvic or lower abdominal pain with one or more of the minimum clinical criteria present on the pelvic examination. KEY CONCEPT The removal of causative bacteria and reduction of any related sequelae are the desired goals of treatment. Bacteria that travel into the fallopian tubes can lead to inflammation, which causes scar tissue to form. This scar tissue can create blockages in the tubes and make it harder for sperm to fertilize an egg. Resolution of infection (ie, *N. gonorrhoeae, C. trachomatis*, *Streptococcus* spp., and Gram-negative facultative bacteria) and mitigation of sequelae should be the main goal of pharmacologic therapy. Treatment regimens for PID must provide empiric, broad-spectrum coverage of likely pathogens. Parenteral and oral regimens appear to have similar efficacy in women with PID of mild or moderate clinical severity. CDC-approved treatment regimens are shown in Table 83–8.[9,41]

Table 83–8

Treatment Regimens for Pelvic Inflammatory Disease

Parenteral Option A

Cefotetan 2 g IV every 12 hours (active against both aerobic and anaerobic Gram-positive and Gram-negative microorganisms) plus doxycycline 100 mg PO or IV every 12 hours (treatment of Gram ± bacteria, aerobes, and anaerobes)

or

Cefoxitin 2 g IV every 6 hours (active against Gram-negative bacteria and anaerobes) plus doxycycline 100 mg PO or IV every 12 hours

Parenteral Option B

Clindamycin 900 mg IV every 8 hours (treatment of anaerobic bacteria, Gram + cocci, and Gram ± bacilli) plus gentamicin, loading dose IV or IM (2 mg/kg) followed by maintenance dose (1.5 mg/kg) every 8 hours. A single daily dose of gentamicin (3–5 mg/kg) may be used (treatment of Gram ± bacteria, aerobes, and anaerobes)

Alternative Parenteral Treatment

Ampicillin–sulbactam 3 g IV every 6 hours (treatment of Gram + organisms) plus doxycycline 100 mg PO or IV every 12 hours

Oral

Ceftriaxone 250 mg intramuscular single dose (broader and stronger Gram-negative coverage and multiresistant enterobacteriaceae) plus doxycycline 100 mg PO twice daily for 14 days with or without metronidazole 500 mg PO twice daily for 14 days (treatment of various anaerobic organisms and trichomoniasis)

or

Cefoxitin 2 g intramuscular single dose and probenecid 1 g single dose, plus doxycycline 100 mg PO twice daily for 14 days with or without metronidazole 500 mg PO twice daily for 14 days

or

Third-generation cephalosporin (ceftizoxime or cefotaxime) (treatment of aerobic and anaerobic Gram ± organisms) plus doxycycline 100 mg PO twice daily for 14 days with or without metronidazole 500 mg PO twice daily for 14 days

Data from Refs. [9,41,42].

Though outpatient management remains contentious, many feel that outpatient management should be limited to individuals who remain afebrile, tolerate oral nourishment, or have a WBC counts less than 11 × 103/mm^3 (11 × 109/L), minimal evidence of peritonitis, or active bowel sounds. Nonetheless, outpatient therapy with a parenteral cephalosporin followed by doxycycline and metronidazole is recommended.

OUTCOME EVALUATION

- Reevaluate any patient who does not respond significantly within 72 hours of parenteral/oral treatment.
- Initiate parenteral therapy (inpatient or outpatient) for patients who do not respond to oral treatment.
- Continue parenteral therapy for 14 days; however, it may be discontinued 24 hours after clinical improvement. Doxycycline should be prescribed to complete 14 days of therapy.
- Hospitalization and reassessment of the antimicrobial regimen and diagnostics are recommended in women without clinical improvement.
- Repeat testing of all women who have been diagnosed with chlamydia or gonorrhea is recommended 3 to 6 months

after treatment, regardless of whether their sex partners were treated.

- Inform the patient that an alteration in sexual behavior should be the first concern, as high-risk sexual activity augments the probability of infection.

Abstinence is the best course of action, especially in patients with herpes during lesional episodes. However, compliance in some may be minimal, in which case, appropriate condom use should always be recommended. To alleviate any possible misconceptions about condom application, either demonstrate how to apply a condom or ask the patient to demonstrate. During the demonstration, explicitly educate the patient with regard to application, storage, and the use of lubricants.[43,44] Additionally, a woman's sexual partner(s) should be treated to decrease the risk of reinfection, even if the partner(s) has no symptoms.

Abbreviations Introduced in This Chapter

CSF	Cerebrospinal fluid
ELISA	Enzyme-linked immunosorbent assay
GH	Genital herpes
HPV	Human papillomavirus
HSV	Herpes simplex virus
L-A	Long acting
MSM	Men who have sex with men
PID	Pelvic inflammatory disease
RPR	Rapid plasma reagent
STI	Sexually transmitted infection
WSW	Women who have sex with women

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84

Sepsis and Septic Shock

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Compare and contrast the definitions of syndromes related to sepsis.
2. Identify the pathogens associated with sepsis.
3. Discuss the pathophysiology of sepsis as it relates to systemic inflammation, coagulation, and tissue hypoperfusion.
4. Identify patient symptoms as early or late sepsis and evaluate diagnostic and laboratory tests for patient treatment and monitoring.
5. Assess complications of sepsis syndromes and discuss their impact on patient outcomes.
6. Design desired treatment outcomes for septic patients.
7. Formulate a treatment and monitoring plan (pharmacologic and nonpharmacologic) for septic patients.
8. Evaluate patient response and devise alternative treatment regimens for nonresponding septic patients.

INTRODUCTION

KEY CONCEPT Sepsis occurs across a continuum of physiologic stages in response to infection, which manifests as systemic inflammation, coagulation, and tissue hypoperfusion, potentially leading to organ dysfunction.[1] The Third International Consensus Definitions for Sepsis and Septic Shock define sepsis as a life-threatening organ dysfunction caused by a dysregulated host response represented by an increase of at least 2 points in the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score (Table 84–1). Septic shock is defined as a subset of patients with further increases in mortality resulting from underlying circulatory, cellular, and/or metabolic abnormalities. These patients require the use of vasopressor support in addition to adequate volume resuscitation to maintain a mean arterial pressure (MAP) of at least 65 mm Hg and have an elevated serum lactate level greater than 2 mmol/L. Adult patients with suspected sepsis may be screened using a bedside clinical scoring system known as the quickSOFA (qSOFA) to rapidly identify patients who may need further diagnostic workup and intervention (Table 84–2).[2,3]

EPIDEMIOLOGY AND ETIOLOGY

Sepsis is the leading cause of morbidity and mortality for critically ill patients and the 10th leading cause of death overall.[4,5] Mortality rates remain high for patients with sepsis and septic shock, with septic shock and multiorgan failure as the most common causes of death.[1] Annually, there are approximately 1.7 million adults who develop sepsis in the United States with nearly 270,000 deaths.[6]

Risk factors for developing sepsis include increased age, cancer, immunodeficiency, chronic organ failure, genetic factors (male gender and non-White ethnic origin in North America), and the presence of bacteremia.[5,7-10] Pulmonary infections cause approximately half of all sepsis cases within the United States, followed by intra-abdominal and genitourinary infections.[2] In approximately one-third of sepsis cases, a pathogen is not identified making deescalation from broad spectrum to a more narrowed antimicrobial regimen difficult.[2] A recent study demonstrated that diarrheal illness is the most common etiology of sepsis globally, with patterns of sepsis incidence varying significantly by geographical location, highlighting the need for knowledge of local patterns to determine the overall risk by an organism.[11]

KEY CONCEPT Gram-positive and Gram-negative bacteria, fungal species, and viruses may cause sepsis (Table 84–3). Gram-positive infections account for 30% to 50% of sepsis and septic shock cases.[5,7,8] The percentages of Gram-negative, polymicrobial, and viral sepsis cases are 25%, 25%, and 4%, respectively.[5,7,8,12] A multinational study of 14,000 critically ill patients showed an increase in Gram-negative bacterial causes of infection compared to Gram-positive bacterial and fungal causes.[2] Multidrug-resistant (MDR) bacteria are responsible for approximately 25% of sepsis cases, are difficult to treat due to fewer antimicrobial options, and increase mortality.[7,8] The rate of fungal infections has significantly increased with *Candida albicans* as the most common fungal species identified; however, nonalbicans species (*Candida glabrata, Candida krusei,* and *Candida tropicalis*) have increased from 24% to 46%.[5,13,14] Other fungi identified as causes of sepsis include species of *Cryptococcus, Coccidioides, Fusarium*, and *Aspergillus*.

PATHOPHYSIOLOGY

The development of sepsis is complex and multifactorial. The normal host response to infection is designed to localize and control microbial invasion and initiate repair of injured tissue through phagocytic cells and inflammatory mediators.[4] KEY CONCEPT Sepsis results when the interplay between the host's immune, inflammatory, and coagulant responses becomes exaggerated, extending to normal tissue distant from the initial tissue site.

Table 84–1

The SOFA Score

SOFA Score	1	2	3	4
Respiration PaO$_2$/FiO$_2$, mm Hg	< 400	< 300	< 200 ___with respiratory support___	< 100
Coagulation Platelets × 10^3/mm^3	< 150	< 100	< 50	< 20
Liver Bilirubin, mg/dL (µmol/L)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	≥ 12.0 (> 204)
Cardiovascular Hypotension	MAP[a] < 70 mm Hg	Dopamine ≤ 5 or dobutamine (any dose)[b]	Dopamine > 5–15, epinephrine ≤ 0.1, or norepinephrine ≤ 0.1	Dopamine > 15, epinephrine > 0.1, or norepinephrine > 0.1
Central nervous system Glasgow Coma Score	13–14	10–12	6–9	< 6
Renal Creatinine, mg/dL (µmol/L) or urine output	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–400) or < 500 mL/day	≥ 5.0 (> 440) or < 200 mL/day

[a] MAP (mean arterial pressure) = 1/3 (SBP – DBP) + DBP.

[b] Adrenergic agents administered for at least 1 hour (doses given are in mcg/kg/min).

Reproduced, with permission, from Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707–710.

Pro- and Anti-inflammatory Mediators

The key factor in the development of sepsis is inflammation, which is intended to be a local and contained response to infection or injury. Infection or injury is controlled through proinflammatory and anti-inflammatory mediators. Proinflammatory mediators facilitate clearance of the injuring stimulus, promote resolution of injury, and are involved in processing of damaged tissue.[4,14-17] To control the intensity and duration of the inflammatory response, anti-inflammatory mediators are released that act to regulate proinflammatory mediators.[16,17] The balance between pro- and anti-inflammatory mediators localizes infection/injury of host tissue.[14-17] However, systemic responses ensue when equilibrium in the inflammatory process is lost.

The inflammatory process in sepsis is linked to the coagulation system. Proinflammatory mediators may have procoagulant and antifibrinolytic effects, whereas anti-inflammatory mediators may have fibrinolytic effects. A key factor in the inflammation of sepsis is activated protein C that enhances fibrinolysis and inhibits inflammation. Protein C levels are decreased in many septic patients.

The initial immune response to a severe infectious syndrome like sepsis is associated with increased neutrophil production and the release of both immature (eg, bands) and mature forms of neutrophils into the bloodstream. This increased immature neutrophil presence is associated with more severe disease and is more likely to result in the formation of neutrophil extracellular traps leading to decreased functional capacity. Ultimately, this increased number of band neutrophils over time can lead to endothelial tissue damage and hypercoagulation.[18]

Table 84–2

Quick SOFA (qSOFA) Criteria

- Respiratory rate ≥ 22 breaths/min
- Altered mentation
- Systolic blood pressure ≤ 100 mm Hg
- Positive qSOFA score indicated by meeting ≥ 2 criteria

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of sepsis varies, and the rate of development of clinical manifestations may differ from patient to patient.

A physical examination should be performed rapidly and efficiently when sepsis is suspected, with efforts directed toward uncovering the most likely cause of sepsis. The patient may not provide any medical history; therefore, historical data may be obtained from medical records and/or family. The patient's medical condition, recent illnesses, infections, or activities may provide valuable information about the cause of sepsis.

Table 84–3

Pathogens in Sepsis

Organism	Frequency (%)
Gram-positive bacteria	50–55
Gram-negative bacteria	35–40
Fungi	5
Polymicrobial	5
Anaerobes (alone)	1
Parasites	Variable
Viruses	Variable

Data from Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003;348(16):1546–1554.

Possible Physical Examination Results in Sepsis

HEENT: Scleral icterus, dry mucous membranes, pinpoint pupils, dilated and fixed pupils, nystagmus

Neck: Jugular venous distention, carotid bruits

Lungs: Crackles (rales), consolidation, egophony, absent breath sounds

CV: Irregular rhythm, S_3 gallop, murmurs

Abd: Tense, distended, tender, rebound, guarding, hepatosplenomegaly

Rectal: Decreased tone

Exts: Swollen calf, disparity of blood pressure between upper extremities

Neurologic: Agitation, confusion, delirium, obtundation, coma

Skin: Cold, clammy, or warm; hyperemic skin; rashes

Diagnostic and Laboratory Tests

Microbiologic cultures should be obtained before antimicrobial therapy is initiated as long as this does not significantly delay the start of therapy. However, cultures take 6 to 72 hours for results to be completed and often are negative (no growth of bacterial organisms). Negative cultures do not rule out the presence of infection. Administering antimicrobials before obtaining cultures may lead to a false-negative culture. Rapid diagnostics of blood cultures allows for identification of specific pathogens within as little as 20 minutes to 3 hours after initial growth is identified. However, not all healthcare systems have this technology available. Additionally, if these technologies are used, they must be in conjunction with antimicrobial stewardship personnel to be cost-effective.[19]

At least two sets of blood cultures should be obtained to rule out contamination, with at least one set drawn percutaneously and one set drawn through each vascular access device present for greater than 48 hours.

Cultures of urine (with urinalysis), respiratory secretions, cerebrospinal fluid, and wounds should be obtained if the clinical presentation suggests infection of these specific fluids, tissues, or organs. Laboratory tests should be performed to evaluate infection or complications of sepsis, including complete blood count (CBC) with differential, coagulation parameters, comprehensive metabolic panel (CMP), serum lactate concentration, arterial blood gas (ABG), and appropriate diagnostic radiographic imaging studies.

The use of biomarkers of sepsis, such as endotoxin and procalcitonin, has been controversial. Measurement of endotoxin, procalcitonin, or other markers in blood or serum is not routinely recommended. Concentrations of procalcitonin in serum are usually increased in sepsis but fail to differentiate between infection and inflammation. However, procalcitonin has a high negative predictive value and may allow for the discontinuation of antibiotics. It is important to note that the measurement of any biomarker, including procalcitonin, should be used in conjunction with the patient's overall clinical assessment and never be used as the sole indicator for altering microbial therapy.

Complications of Sepsis

KEY CONCEPT Recognition and treatment of sepsis complications, particularly organ failure, is essential to improve outcomes. The cumulative burden of sepsis complications is the leading factor of mortality. The risk of death increases 20% with the failure of each

Clinical Presentation and Diagnosis of Sepsis

The signs and symptoms of septic patients are referred to as early and late sepsis.

Signs and Symptoms

The initial clinical signs and symptoms represent early sepsis, and they include fever, chills, and change in mental status. Other signs and symptoms include the following:

- **Tachycardia**
- **Tachypnea**
- Nausea and vomiting
- Hyperglycemia
- Myalgias
- Lethargy and malaise
- **Proteinuria**
- Leukocytosis
- Hypoxia
- Hyperbilirubinemia

Septic patients may have an elevated, low, or normal temperature. The absence of fever is common in neonates and elderly patients. Hypothermia is associated with a poor prognosis. Hyperventilation may occur before fever and chills and may lead to respiratory alkalosis. Disorientation and confusion may develop early in septic patients, particularly in the elderly and patients with preexisting neurologic impairment. Disorientation and confusion may be related to the infection or due to sepsis signs and symptoms (eg, hypoxia).

Late sepsis represents a slow process that develops over several hours of hypoperfusion. Signs and symptoms of late sepsis include the following:

- Lactic acidosis
- **Oliguria**
- **Leukopenia**
- Thrombocytopenia
- Myocardial depression
- Pulmonary edema
- Hypotension
- Hypoglycemia
- Gastrointestinal hemorrhage

Oliguria often follows hypotension because of decreased renal perfusion. Metabolic acidosis ensues because of diminished clearance of lactate by the kidneys and liver.

Patient Encounter Part 1

A 58-year-old man with a history of hypertension, obesity, and COPD presents to the emergency department with complaints of fever, cough, and increased sputum production for the last 2 days. The patient is becoming increasingly short of breath and confused.

What information is suggestive of infection and/or sepsis?

What information do we need in order to confirm or diagnose sepsis in this patient?

additional organ. The most common complications are respiratory and cardiovascular compromise, usually seen as acute respiratory distress syndrome (ARDS), hemodynamic compromise, and elevated serum lactate levels. Other complications include altered mentation, acute kidney injury (AKI) that may require renal replacement therapy, paralytic ileus, disseminated intravascular coagulation (DIC), and adrenal insufficiency.[2]

TREATMENT AND OUTCOME EVALUATION

Desired Outcomes

KEY CONCEPT The primary treatment goal of sepsis is to prevent morbidity and mortality through rapid recognition and intervention. Treatment is aimed at early implementation of therapies, such as fluid resuscitation and antimicrobials, reducing or eliminating organ dysfunction, eliminating the source of infection, avoiding adverse reactions of treatment, and providing cost-effective therapy.[20-26]

General Approach to Treatment

Once a diagnosis of sepsis has been made, rapid intervention with appropriate therapies is crucial to decrease morbidity and mortality.[20,22]

In addition to appropriately timed diagnostic tests, pertinent approaches in the management of septic patients are as follows (Figure 84–1)[26]:

1. Prompt recognition of the septic patient and early implementation of therapies.
2. Fluid therapy, using crystalloids primarily, to restore intravascular volume depletion.
3. Early administration of broad-spectrum antimicrobial therapy.
4. Vasopressor therapy, using norepinephrine initially, to maintain hemodynamic stability (on average an MAP of 65 mm Hg [8.6 kPa]) in patients with septic shock refractory to fluid resuscitation.
5. Intravenous (IV) hydrocortisone may be considered for patients who remain hemodynamically unstable despite adequate fluid resuscitation and vasopressor support.
6. Glycemic control via infusion of regular insulin to maintain glucose levels between 140 and 180 mg/dL (7.8 and 10.0 mmol/L).
7. Adjunctive therapies: blood product administration, analgesia, sedation, neuromuscular blockade, renal replacement therapy, sodium bicarbonate therapy, venous thromboembolism (VTE) prophylaxis, stress ulcer prophylaxis, and nutrition.

Treatment for sepsis focuses on infection, inflammation, hypoperfusion, and widespread tissue injury. Septic patients may require multiple simultaneous treatment regimens to achieve desired outcomes of decreased morbidity and mortality.

Initial Resuscitation

A landmark study of early goal–directed therapy (EGDT) using a standardized protocol that required the use of a special catheter for central venous oxygen saturation monitoring decreased 28-day mortality in septic patients by approximately 16%.[25] Three subsequent randomized controlled studies comparing EGDT to groups of patients receiving contemporary care (with or without the use of protocols) found no differences in mortality.[27] These results demonstrate that continued focus on early recognition and treatment of these patients may play a more important role than protocol-based therapy; however, the use of EGDT was not associated with harm.

Upon recognition of sepsis, resuscitation should begin immediately. Within the first 3 hours, at least 30 mL/kg of crystalloid fluid should be administered intravenously. Subsequent fluid administration should be guided by frequent reassessment of hemodynamic status and dynamic variables to predict fluid responsiveness and prevent volume overload. The use of static variables, such as central venous pressure (CVP), to assess the need for additional fluid administration should not be used alone. Rather, these variables in conjunction with dynamic measures, such as the passive leg raise technique, fluid challenges, and stroke volume or pulse pressure variation, may be better predictors of fluid responsiveness.[22,25,26,28]

Emerging noninvasive techniques, such as the use of cardiac ultrasound, have recently shown reliability in assessing intravascular volume status through measuring inferior vena cava diameter changes and collapsibility.[29,30] Resuscitation should also target the normalization of blood lactate levels in patients with an initially elevated blood lactate as a marker of improved tissue perfusion.[22]

Fluid Therapy

Crystalloid fluids (such as 0.9% sodium chloride or lactated Ringer solutions) or colloids (albumin products) are used for resuscitation, and clinical studies comparing these two fluids types have found them to be equivalent.[28,31,32] Crystalloids require more fluid volume, which may lead to more edema (utilize caution in patients at risk of fluid overload, eg, congestive heart failure, renal failure, and ARDS); however, albumin is significantly more expensive. Hydroxyethyl starch (HES), another type of colloid, should not be used due to studies demonstrating increased morbidity and mortality.[33,34] For these reasons, crystalloids are preferred versus colloids for initial resuscitation, except in cases where large amounts of crystalloids are needed, and hypervolemia may be harmful to the patient.[22]

After initial fluid administration, there remains clinical controversy surrounding the appropriate type of fluid for continued resuscitation. There are data that suggest potential benefit of using balanced crystalloid solutions or a chloride-restrictive strategy. Large (n > 29,000), prospective, multiple-crossover trials suggest the administration of large volumes of isotonic saline may be associated with increased incidences of AKI and renal replacement therapy secondary to hyperchloremic metabolic acidosis.[35,36]

Anti-infective Therapy

KEY CONCEPT Appropriate empiric antimicrobial therapy decreases 28-day mortality compared with inappropriate

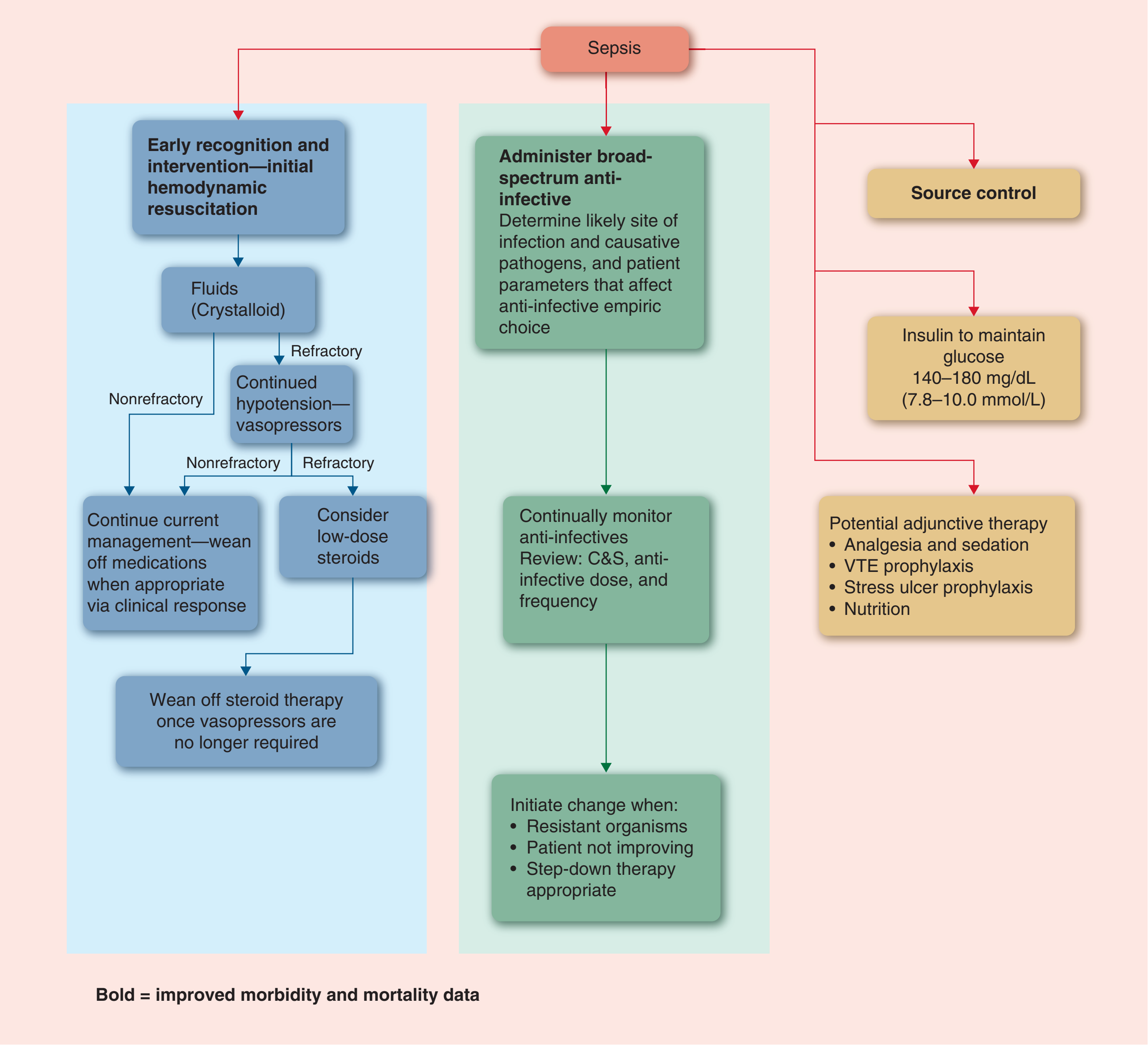
Sepsis
Early recognition and intervention—initial hemodynamic resuscitation
Fluids (Crystalloid)
Refractory
Nonrefractory
Continued hypotension—vasopressors
Nonrefractory
Refractory
Continue current management—wean off medications when appropriate via clinical response
Consider low-dose steroids
Wean off steroid therapy once vasopressors are no longer required
Administer broad-spectrum anti-infective
Determine likely site of infection and causative pathogens, and patient parameters that affect anti-infective empiric choice
Continually monitor anti-infectives
Review: C&S, anti-infective dose, and frequency
Initiate change when:
• Resistant organisms
• Patient not improving
• Step-down therapy appropriate
Source control
Insulin to maintain glucose 140–180 mg/dL (7.8–10.0 mmol/L)
Potential adjunctive therapy
• Analgesia and sedation
• VTE prophylaxis
• Stress ulcer prophylaxis
• Nutrition
Bold = improved morbidity and mortality data

FIGURE 84–1. Therapeutic approach to sepsis. (C&S, cultures and susceptibilities.)

empiric therapy (24% vs 39%).[20,21,37] Additionally, appropriate therapy administered within 1 hour of sepsis recognition also decreases complications and mortality.[20,21,37] Empiric antimicrobial therapy should include multiple agents for most cases, depending on the likely site of infection and causative pathogens. Anti-infective clinical trials in sepsis and septic shock patients are scarce and have not demonstrated differences among agents; therefore, factors that determine selection are as follows:

- Site/source of infection.
- Causative pathogens.
- Community- or nosocomial-acquired infection.
- Immune status of patient.
- Antibiotic susceptibility and resistance profile for the institution and local community. Clinicians should be cognizant of growing prevalence of bacterial resistance in community and healthcare settings.
- Patient history (underlying disease, previous cultures or infections, including any recent antibiotic therapy, and drug allergy/intolerance).
- Adverse reactions.
- Cost.

Anti-infective regimens should be broad spectrum since delays in the appropriate therapy result in increased mortality. In the subset of patients with septic shock, empiric therapy should include combination regimens with multiple antibiotics from different mechanistic classes (eg, two antipseudomonal antimicrobials in patients with known risk factors to ensure appropriate coverage of MDR organisms). Please reference Chapter 69 for more antimicrobial information and other chapters based on specific disease state leading to sepsis.

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Hypertension, obesity, COPD

FH: Father has a history of hypertension, hyperlipidemia, and chronic kidney disease; mother had a history of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, died from myocardial infarction at age 68

SH: High school teacher; previous smoker (one pack per day, quit 1 year ago); rare alcohol intake

Allergies: NKDA

Meds: Lisinopril 20 mg by mouth once daily; hydrochlorothiazide 25 mg by mouth once daily; tiotropium respimat two inhalations once daily; albuterol inhaler two puffs every 6 hours as needed; multivitamin one tablet by mouth once daily, aspirin 81 mg by mouth once daily

ROS: Unable to obtain; patient has become more confused

PE:

Within normal limits except as noted below

VS: BP 86/48 mm Hg, P 132 beats/min, RR 34 breaths/min, T 39.2°C (102.6°F)

Neurologic: Obtunded, oriented to person only

Skin: Cool, clammy

Labs: Serum creatinine 2.2 mg/dL (194.5 μmol/L); glucose 201 mg/dL (11.2 mmol/L); white blood cells: leukocytosis (18,300/mm^3 [18.3×10^9/L]) with left shift; lactic acid 4.2 mEq/L (4.2 mmol/L)

Cultures: Blood and sputum cultures pending

Radiology: Chest X-ray consistent with left lower lobe infiltrate

According to the patient's parameters, what is his most likely diagnosis (ie, systemic inflammatory response syndrome, sepsis, or septic shock)?

What are the goals of treatment?

Formulate an initial plan for therapy.

Monitoring and Treatment Strategies to Maximize Efficacy and Minimize Toxicity for Antimicrobials

- Administer broad-spectrum antimicrobials for initial therapy as early as possible and within the first hour of recognition of sepsis.
- Appropriate cultures should be obtained before initiating antibiotic therapy but should not prevent prompt administration.
- Administer antibiotics that concentrate at the site of infection.
- Evaluate and integrate rapid diagnostic findings if available to ensure optimal therapy.
- Monitor patient parameters to ensure adequate dosing.
- Abnormal renal and hepatic function will increase drug concentration and predispose the patient to toxicity.
- Ensure antibiotic dosing is changed to normal doses once renal dysfunction has resolved to limit the development of treatment failure, antimicrobial resistance, or both.
- Septic patients may have increased volume of distribution due to initial large-volume resuscitation.
- Reevaluate the initial dosing regimen daily to optimize activity, prevent the development of resistance, reduce toxicity, and decrease costs.
- Initiate step-down therapy based on microbiologic cultures to prevent resistance, reduce toxicity, including *Clostridioides difficile* infection, and minimize cost.
- Monotherapy is equivalent to combination therapy once a causative pathogen has been identified in the vast majority of cases.

Patient Encounter Part 3: Treatment and Outcome Evaluation

The patient has been intubated for acute hypoxic respiratory failure secondary to pneumonia. He remains hypotensive despite previous interventions. His serum creatinine remains elevated at 3.1 mg/dL (274.1 μmol/L), and he has no urinary output.

What additional therapies will you consider adding to this patient?

Duration of Anti-infective Therapy

Average duration of antimicrobial therapy for septic patients is 7 to 10 days. However, durations vary depending on the site of infection and response to therapy. Step-down therapy from IV to oral antimicrobials is recommended in certain targeted patients who are hemodynamically stable, afebrile for 48 to 72 hours, have a normalized WBC, have an organism susceptible to oral therapies, and are able to take oral medications. Antimicrobials should be discontinued if it is determined the cause of shock was not infectious.

Source Control

Evaluate septic patients for the presence of a localized infection amenable to source control measures. Common source control measures include drainage and debridement, device removal, and amputation.[22,23] Implementation of source control methods should be instituted as soon as possible following initial fluid resuscitation. The selection of optimal source control methods must weigh benefits and risks of the intervention. Source control measures may cause complications (bleeding, fistulas, and organ injury); therefore, the method with the least risk should be employed.[22]

HEMODYNAMIC SUPPORT

Vasopressors and Inotropic Therapy

KEY CONCEPT When fluid resuscitation does not provide adequate arterial pressure and organ perfusion, vasopressors and/or inotropic agents should be initiated. Vasopressors are recommended in patients with a systolic blood pressure less than 90 mm Hg or MAP lower than 60 to 65 mm Hg (8.0–8.6 kPa), after failed treatment with crystalloids.[22,25,26] Vasopressors and inotropes are effective in treating life-threatening hypotension and improving cardiac index, but complications such as tachycardia and myocardial ischemia require slow titration of the adrenergic agents to restore MAP without impairing stroke volume. Vasopressor therapy may also be required transiently to sustain life and maintain perfusion in the face of life-threatening hypotension, even when fluid resuscitation is in progress and hypovolemia has not yet been corrected. Agents commonly considered for vasopressor or inotropic support include norepinephrine, epinephrine, dopamine, phenylephrine, vasopressin, and dobutamine. Norepinephrine is the first-line vasopressor to correct hypotension in septic shock.[22]

Norepinephrine is a potent α-adrenergic agent with less pronounced β-adrenergic activity. Doses of 0.01 to 3 mcg/kg/min can reliably increase blood pressure through vasoconstriction with small changes in heart rate or cardiac index. Norepinephrine is a more potent agent than dopamine in refractory septic shock.[22,25,26] Norepinephrine induces less arrhythmias compared with dopamine.[38]

Dopamine is an α- and β-adrenergic agent with dopaminergic activity. Low doses of dopamine (1–5 mcg/kg/min) maintain renal perfusion; higher doses (> 5 mcg/kg/min) exhibit α- and β-adrenergic activity and are frequently utilized to support blood pressure and improve cardiac function, mainly through increasing stroke volume and heart rate. Because of the effects on heart rate, dopamine causes more tachycardia and thus increases potential for arrhythmias versus norepinephrine. Based on these data, dopamine should not be used routinely in the management of septic shock.[22,38] Low doses of dopamine should not be used for renal protection as part of the treatment of sepsis.[22,25,26]

Epinephrine is a nonspecific α- and β-adrenergic agonist that can increase cardiac index and produce significant peripheral vasoconstriction. Some human and animal studies suggest it can also increase lactate levels and impair blood flow to the splanchnic system; however, studies comparing norepinephrine to epinephrine show no difference in mortality rates. Epinephrine may be added to norepinephrine in patients with persistent hypotension.[22,25,26]

Phenylephrine is a fast-acting, short-acting pure α_1-agonist. Phenylephrine is the least likely vasopressor to cause tachycardia but may decrease stroke volume. Phenylephrine should be reserved for use in patients with high cardiac output in whom tachycardia or ischemia limits the use of other vasopressors or as salvage therapy.[22,25,26]

Vasopressin levels are increased during hypotension to maintain blood pressure by vasoconstriction. However, there is a vasopressin deficiency in septic shock. Low, fixed doses of exogenous vasopressin increase MAP, leading to the discontinuation of catecholamines. However, routine use of vasopressin with norepinephrine is not recommended because of no difference in mortality compared with norepinephrine monotherapy.[39] Vasopressin is a direct vasoconstrictor without inotropic or chronotropic effects and may result in decreased cardiac output and hepatosplanchnic flow. The addition of vasopressin to norepinephrine may be considered in patients with refractory shock despite adequate fluid resuscitation and high-dose catecholamines.[22,25,26]

Dobutamine is recommended as the first-line inotropic agent. Dobutamine is a β-adrenergic inotropic agent that can be utilized for the improvement of cardiac output and oxygen delivery. Doses of 2 to 20 mcg/kg/min increase cardiac index; however, heart rate increases significantly. Dobutamine should be considered in septic patients with adequate filling pressure and blood pressure, but low cardiac index. If used in hypotensive patients, dobutamine should be combined with vasopressor therapy.[22,25,26]

Patient Encounter Part 4

Three days later, the patient's blood pressure begins to respond to therapy with an MAP remaining greater than 65 mm Hg (8.6 kPa) on minimal vasopressor support.

What changes to the patient's medication regimen do you recommend?

Angiotensin II is the newest drug approved for the treatment of hypotension in adults with septic or other distributive shock states. A naturally occurring hormone of the renin–angiotensin–aldosterone system, angiotensin causes vasoconstriction and increases the release of aldosterone, which increases blood pressure. A recent study evaluated the use of angiotensin II in patients with vasodilatory shock states, like septic shock, who were requiring high-dose vasopressors and found that administration of angiotensin II was associated with a significant increase in the number of patients who reached goal MAP at 3 hours and allowed for decreased catecholamine doses of other vasopressors.[40] The exact place in therapy for angiotensin II has not been established, but multimodal utilization of different vasoactive medications may allow for decreased individual vasopressor doses, potentially decreasing side effects.

Corticosteroids

Stress-induced adrenal insufficiency complicates 9% to 24% of septic patients and is associated with increased mortality. The role of steroid use in septic shock remains unclear. Previous studies have demonstrated a mortality benefit or quicker reversal of shock in patients with sepsis-induced adrenal insufficiency treated with hydrocortisone.[41] However, a large, multicenter, randomized controlled trial (CORTICUS) showed no difference in mortality rates in septic shock patients treated with hydrocortisone.[42] KEY CONCEPT For these reasons, the use of IV hydrocortisone at a dose of 200 mg/day should be reserved for patients who remain hemodynamically unstable despite fluid and vasopressor therapy.[22] Patients should be tapered from steroid therapy when vasopressors are no longer required. The decision of whether to taper and how to taper hydrocortisone doses is dependent on individual patient characteristics or provider preference. There is no standard recommendation; however, an example of a steroid tapering regimen may be seen in the CORTICUS trial.[42]

Glucose Control

The optimal blood glucose range in septic patients is unknown. Tight glycemic control (80–110 mg/dL [4.4–6.1 mmol/L]) improved survival in postoperative surgical patients but did not show a benefit in medical critically ill patients.[43,44] Subsequent studies, such as the large NICE-SUGAR trial, do not demonstrate a mortality benefit in favor of tight glycemic control, but actually a higher incidence of severe hypoglycemia and increased mortality rates.[45] KEY CONCEPT Following initial stabilization of septic patients, current guidelines recommend initiating IV insulin therapy when two consecutive blood glucose measurements are greater than 180 mg/dL (10.0 mmol/L) and then maintaining a blood glucose of less than or equal to 180 mg/dL (10.0 mmol/L). Blood glucose levels should be monitored frequently, every 1 to 2 hours, until glucose values and insulin infusion rates are stable, every 4 hours thereafter.[22]

Adjunctive Therapies

▶ *Blood Product Administration*

There are no trials showing the optimal hemoglobin concentration in patients with sepsis. However, based on other studies that included subgroups of septic patients, with the exception of myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic coronary artery disease, it is recommended to target a hemoglobin concentration of 7 to 9 g/dL (70–90 g/L; 4.34–5.59 mmol/L), and red blood cell transfusion should occur when the hemoglobin concentration is less than 7 g/dL (70 g/L; 4.34 mmol/L).[22,46] Erythropoietin-stimulating agents, fresh frozen plasma, and antithrombin should not be administered, unless other compelling indications exist, to treat sepsis-induced abnormalities.[22]

▶ *Sedation, Analgesia, and Neuromuscular Blockade*

It is common for sepsis patients to require mechanical ventilation during their course of therapy. These patients may require analgesic or sedative agents to facilitate mechanical ventilation. Historically, concerns for patient safety and posttraumatic stress disorder emphasized the need for sedation in these patients. However, there continues to be ample data indicating that, while sedation may be necessary, limiting exposure to certain sedative medications, specifically benzodiazepines, may improve morbidity and mortality rates. When sedation is needed, a standardized protocol targeting specific endpoints should be utilized.[22,47]

Neuromuscular blockade usually is reserved for patients in whom sedation alone does not improve the effectiveness of mechanical ventilation. Neuromuscular blockers may lead to prolonged skeletal muscle weakness and should be avoided if possible, especially if receiving concomitant corticosteroid therapy, which can increase the risk of critical illness polyneuropathy. Patients requiring neuromuscular blockade should be monitored, and intermittent bolus doses or continuous infusion should be utilized. Monitor depth of neuromuscular blockade with either train-of-four stimulation or other forms of clinical assessment when using continuous infusion. Patients with early, sepsis-induced ARDS with a partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) less than 150 mm Hg (20.0 kPa) may benefit from a short course of a neuromuscular blocking agent not to exceed 48 hours.[22]

▶ *Renal Replacement Therapy*

Patients who develop AKI as a manifestation of sepsis may require some type of renal replacement therapy. There are no data currently that suggest superiority for either continuous or intermittent modalities of hemodialysis as both have demonstrated similar mortality rates. In patients who are hemodynamically unstable, continuous renal replacement therapy may be more beneficial due to less overall hypotension during therapy.

▶ *Sodium Bicarbonate Therapy*

It has been theorized that vasopressors that act on catecholamines to increase blood pressure (eg, norepinephrine, epinephrine, phenylephrine, dopamine) may become less responsive at pH values less than 7.15. However, there are no robust data that have demonstrated improved hemodynamics, decreased vasopressor requirements, or improved clinical outcomes when sodium bicarbonate is administered at lower pH values. Conversely, bicarbonate administration has been associated with sodium and fluid overload although direct causality has not been established. For these reasons, sodium bicarbonate therapy should only be considered in patients with pH less than 7.15 who are not responsive to vasopressors or have increasing vasopressor requirements to maintain an MAP of at least 65 mm Hg.[22]

▶ *Metabolic Resuscitation*

There has been growing interest in vitamin deficiencies in patients with sepsis, specifically vitamin C and thiamine (vitamin B1). Several studies have evaluated the administration of high-dose vitamin C, thiamine, or the combination of vitamin C, thiamine, and hydrocortisone (commonly referred to as metabolic resuscitation) on vasopressor requirements and patient outcomes.[48,49] There are no robust data to support the use of these medications in patients with septic shock. Ongoing studies will help elucidate if there is clinical value in the future use of these interventions.

▶ *Venous Thromboembolism Prophylaxis*

Combination of pharmacologic and mechanical prophylaxis against VTE is recommended for septic patients when possible. Low-dose unfractionated heparin, low-molecular-weight heparin (eg, enoxaparin or dalteparin), or pentasaccharide therapy (eg, fondaparinux) may be utilized. Graduated compression stocking or an intermittent compression device is recommended for patients with a contraindication to heparin products (thrombocytopenia, severe coagulopathy, active bleeding, or recent intracerebral hemorrhage).[22]

▶ *Stress Ulcer Prophylaxis*

Patients with severe sepsis are at increased risk of developing a stress ulcer bleeding event. Stress ulcer prophylaxis using either a histamine-receptor antagonist (H2 blocker) or proton pump inhibitor (PPI) is recommended in septic patients. Patients at the greatest risk of stress ulcers include those who are coagulopathic, mechanically ventilated (> 48 hours), or hypotensive. Histamine 2–receptor antagonists (eg, ranitidine) are more efficacious than sucralfate. There is an ongoing debate to determine if PPIs (eg, omeprazole) are more efficacious than H2 blockers with low-quality data showing conflicting outcomes.[22,50] Both, however, demonstrate equivalence in the ability to increase gastric pH.[22] The benefit of prophylaxis must be weighed against the potential effect of increased stomach pH and development of infectious complications, such as hospital-acquired pneumonia and/or *C. difficile* infection. When patients no longer have an indication for stress ulcer prophylaxis or at major transitions of care (eg, transition out of the ICU), it is imperative that the stress ulcer prophylactic medication is discontinued to avoid patients being discharged home on unnecessary medications.

▶ *Nutrition*

Meeting the nutritional needs of septic patients can be challenging, especially in patients who are hemodynamically unstable. When possible, early initiation of enteral nutrition should be considered to maintain gut mucosa and potentially decrease the risk of bacterial translocation leading to infection. Patients who are hemodynamically unstable may not tolerate enteral nutrition and are at risk of gut ischemia. Parenteral nutrition alone or in conjunction with enteral nutrition should not be initiated in the first 7 days as this has not been shown to improve outcomes.[22]

Prognosis

There are various factors that influence an outcome. Gram-negative bacteria are more likely to produce septic shock than Gram-positive bacteria (50% vs 25%) and have a higher mortality rate than other pathogens. This may be related to the severity of the underlying condition. Patients with rapidly fatal conditions, such as leukemia, aplastic anemia, and burns, have a worse prognosis than patients with nonfatal underlying conditions, such as diabetes mellitus or chronic renal insufficiency. Other factors that worsen the prognosis of septic patients include advanced age, malnutrition, resistant bacteria, utilization of medical devices, and immunosuppression. Data for long-term mortality are lacking (it is estimated that the mortality for sepsis survivors within the first year is 20%).[51] Patients may have prolonged physical disability related to muscle weakness and posttraumatic stress.

SEPSIS AND SEPTIC SHOCK: CORONAVIRUS DISEASE 2019 (COVID-19)

While most patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) will experience mild–moderate COVID-19 infection, a significant percentage (~5%) will require intensive care unit management due to mechanical ventilation and/or septic shock. In these patients, viral replication rapidly increases, highlighting the profound inflammatory response (ie, cytokine storm) leading to diffuse alveolar wall thickening and macrophage distribution into airspaces with subsequent pulmonary edema and formation of ground-glass infiltrates. These pathophysiologic features can lead ultimately to ARDS and profound respiratory failure.[52] In addition, SARS-CoV-2 infection is associated with significant arterial and venous complications, occurring in as much as 35% of hospitalized critically ill patients. Prothrombotic divergence is characterized by decreased concentrations of protein C, protein S, and antithrombin coupled with elevated D-dimer, fibrinogen, and factor VIII concentrations. This coagulation imbalance leads to microthrombi findings upon autopsy in multiple organ systems.[53] These findings are primarily responsible for the significant morbidity and mortality in COVID-19 patients complicated by sepsis syndromes.

Treatment is divided primarily into nonpharmacologic and pharmacologic therapies for severe COVID-19. Nonpharmacologic therapy is similar to ARDS with a specific emphasis on proning, which is recommended for patients with persistent hypoxemia despite increasing supplemental oxygen requirements who otherwise are not indicated for intubation. Pharmacologic treatment for septic shock is similar to other etiologies (including VTE prophylaxis/anticoagulation when indicated). A number of treatments aimed at critically ill patients with severe COVID-19 have been attempted, including convalescent plasma, remdesivir, and dexamethasone. While data are mixed with regard to clinical outcomes of convalescent plasma and remdesivir, dexamethasone is currently recommended for all hospitalized patients requiring supplemental oxygen, with the greatest benefit of decreased mortality demonstrated in those patients receiving mechanical ventilation.[54]

Patient Care Process

Collect Information:

- Retrieve available diagnostic and laboratory data, especially CBC with differential, CMP, ABG, and lactic acid.
- Measure vital signs, including temperature, heart rate, respiratory rate, and blood pressure.
- Speak with patient/family and review records to identify previous antimicrobial history, microbiologic cultures, and medication allergies.

Assess the Information:

- Based on physical examination and review of systems, determine whether the patient meets criteria for sepsis.
- Assess for a potential source of infection.
- Identify comorbidities, concomitant medications, and/or laboratory findings that may impact antimicrobial choices.
- Understand which parameters indicate effective/ineffective resuscitation. Plan for additional resuscitation therapy if the patient remains hypotensive.

Develop a Care Plan:

- Formulate an appropriate plan for antimicrobial therapy, which should include starting broad-spectrum agents that cover the most likely pathogens within 1 hour of suspecting sepsis.
- Make recommendations to control the source of infection.
- Develop a strategy to optimize hemodynamics. Crystalloid fluids should be used first, followed by vasopressors and/or inotropes. Corticosteroids may be utilized in patients who remain hemodynamically unstable.
- Formulate appropriate dosing regimens for medications involved in therapy and revise as needed.
- Consider the need for adjunctive therapies such as analgesics, sedatives, insulin, neuromuscular blockers, blood product administration, renal replacement therapy, sodium bicarbonate, venous thromboembolism prophylaxis, stress ulcer prophylaxis, and nutrition.

Implement the Care Plan:

- Patient parameters may change frequently, thus requiring modifications of therapy. Reassess vital signs and laboratory values often and adjust medications and dosing regimens as needed.
- Involve the patient and family members in each step of the care plan.

Follow-up: Monitor and Evaluate:

- Continually monitor patient parameters to ensure optimal therapy to minimize morbidity and mortality.
- Continue antimicrobial therapy on average for a total of 7 to 10 days, depending on the site of infection and response to therapy. Monitor for ongoing signs and symptoms of infection, including leukocytosis, fever, hypotension, and tachycardia.
- Step-down therapy from IV to oral antimicrobials when the patient is hemodynamically stable, afebrile, has a normalized WBC, has a pathogen susceptible to oral therapy, and is able to take oral medications.
- Escalate or deescalate antimicrobial therapy based on culture and susceptibility results, which should be assessed daily.

Abbreviations Introduced in This Chapter

ABG	Arterial blood gas
AKI	Acute kidney injury
ARDS	Acute respiratory distress syndrome
CBC	Complete blood count
CMP	Comprehensive metabolic panel
CVP	Central venous pressure
DIC	Disseminated intravascular coagulation
EGDT	Early goal–directed therapy
Fio$_2$	Fraction of inspired oxygen
HES	Hydroxyethyl starch
IV	Intravenous
MAP	Mean arterial pressure
MDR	Multidrug-resistant
Pao$_2$	Partial pressure of oxygen
PPI	Proton pump inhibitor
SOFA	Sequential (Sepsis-related) Organ Failure Assessment
VTE	Venous thromboembolism

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Superficial Fungal Infections

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the underlying pathophysiology of vulvovaginal candidiasis (VVC), oropharyngeal candidiasis (OPC), esophageal candidiasis, and fungal skin infections.
2. Identify symptoms of VVC, OPC, esophageal candidiasis, and fungal skin infections.
3. Identify the desired therapeutic outcomes and monitoring parameters for resolution and safety for patients with uncomplicated and complicated VVC, OPC, esophageal candidiasis, and fungal skin infections.
4. Recommend appropriate lifestyle modifications and pharmacotherapy interventions for patients with VVC, OPC, esophageal candidiasis, and fungal skin infections.
5. Recognize when long-term suppressive therapy is indicated for a patient with VVC.
6. Identify when topical versus oral treatment is indicated for a patient with OPC, esophageal candidiasis, VVC, and fungal skin infections.
7. Educate patients regarding their disease state, appropriate lifestyle modifications, and medication therapy required for effective treatment of VVC, OPC, esophageal candidiasis, and fungal skin infections.

INTRODUCTION

Superficial fungal infections, also referred to as mycoses, are common and treatable conditions seen in everyday practice. Treatment largely focuses on the use of azole and allylamine antifungal agents, either topically or orally, depending on the site, severity, and immune status of the patient.

VULVOVAGINAL CANDIDIASIS

Vulvovaginal candidiasis (VVC), whether symptomatic or asymptomatic, refers to an infection in women whose vaginal cultures are positive for *Candida* species.

EPIDEMIOLOGY AND ETIOLOGY

VVC, also known as moniliasis, is a common form of vaginitis, accounting for 20% to 25% of vaginitis cases. Although VVC is uncommon prior to menarche, an estimated 75% of women will have at least one occurrence of VVC.[1]

According to the treatment guidelines of the Centers for Disease Control and Prevention (CDC),[1] VVC can be classified as uncomplicated or complicated. Uncomplicated infections occur sporadically, cause mild-to-moderate symptoms, and occur in nonimmunocompromised women. Uncomplicated infections, most often caused by *Candida albicans*, have no identifiable precipitating cause. Complicated infections, including recurrent, severe infections, and those in women with uncontrolled diabetes, debilitation, or immunosuppression, may be caused by nonalbicans or azole-resistant fungal organisms. Recurrent VVC, defined as four or more infections per year, occurs in less than 5% of women and is distinguishable from a persistent infection by the presence of a symptom-free interval between infections.[1]

C. albicans is the primary pathogen responsible for VVC, accounting for 66% of cases. Other nonalbicans implicated pathogens include *Candida glabrata*, *Candida tropicalis*, *Candida krusei*, and *Candida parapsilosis.*[2]

PATHOPHYSIOLOGY

The normal vaginal environment protects women against vaginal infections. Under the influence of estrogen, vaginal epithelium cornifies to reduce the risk of infection. Vaginal discharge, composed of exfoliated cells, cervical mucus, and colonized bacteria, cleans the vagina. The normal pH of vaginal secretions, near 4.0, is toxic to many pathogens and is maintained by *Lactobacillus acidophilus*, diphtheroids, and *Staphylococcus epidermidis*. Alterations in the vaginal environment, including pH changes, allow for overgrowth of organisms that are normally suppressed, increasing the risk of vulvovaginitis.

RISK FACTORS

A variety of factors may increase the risk of developing symptomatic VVC in certain women (Table 85–1).

TREATMENT

The goals of treatment of VVC are as follows:

- Relief of symptoms
- Eradication of infection
- Reestablishment of normal vaginal flora
- Prevention of recurrent infections

Table 85–1

Possible Risk Factors Associated with VVC

Risk Factor	Proposed Mechanism
Broad-spectrum antibiotic use	Altered vaginal flora allowing overgrowth of *Candida* organisms; risk increases with duration of antibiotic use
Systemic corticosteroid or immunosuppressant use	Reduced vaginal protection by immunoglobulins
Sexual activity	VVC is often associated with the onset of sexual activity; partners may have penile or oral colonization; the use of vaginal irritants or devices, including diaphragms and intrauterine systems, can irritate vaginal mucosa
Tight-fitting and nonabsorbent clothing	Promotes warm, moist environment for fungus growth
Elevated estrogen levels, hormonal contraceptives, and pregnancy	Estrogen enhances *Candida* adherence to vaginal epithelial cells and yeast-mycelial transformation; this is supported by the fact that infection rates are lower before menarche and after menopause (except in women taking hormone replacement therapy), whereas rates are higher during pregnancy
Vaginal pH	Changes in glycogen and lactic acid levels
Gastrointestinal reservoir of *Candida* organisms	Transfer of organism from rectum to vagina; irritation of the vulvovaginal area during sexual intercourse may enhance invasion of organisms
Diabetes	Enhanced binding of *Candida* to epithelial cells due to hyperglycemia; asymptomatic colonization is more common in patients with diabetes; elevated sugar levels may cause conversion to symptomatic infection

VVC, vulvovaginal candidiasis.

Nonpharmacologic Treatments

Basic nonpharmacologic approaches to treatment and prevention of VVC should be recommended by the practioner in combination with pharmacologic treatment.

- Keep the genital area clean and dry
- Avoid prolonged use of hot tubs
- Avoid constrictive clothing
- Avoid vaginal douching
- Wear underwear made of breathable materials, such as cotton
- Avoid soaps and perfumes in the genital area
- Although study results are conflicting, possibly due to the strain or concentration studied, the daily consumption of active *Lactobacillus* may reduce recurrence. Newer studies have found that ingestion of *Lactobacillus rhamnosus* and *Lactobacillus reuteri* suppressed metabolic activity and killed *C. albicans*,[3] whereas older studies found no difference in infection rates in women who ingested yogurt.[4]

Pharmacologic Treatment of Uncomplicated VVC

For most cases of uncomplicated VVC, the CDC guidelines recommend a short course of therapy (1–3 days) with an oral or vaginal antifungal agent, either nonprescription or prescription.[1]

Clinical Presentation and Diagnosis of VVC

Patients with VVC may present with vulvar and/or vaginal symptoms. Symptoms often develop the week before menses and resolve with the onset of menses.

Symptoms

- Vaginal itching
- Vaginal soreness
- Vaginal burning
- Irritation
- Dysuria
- **Dyspareunia**

Signs

- Nonodorous vaginal discharge (may vary from watery to curd-like)
- Yellow or yellowish green discharge
- Erythema and edema of the labia and vulva
- Fissures
- Pustulopapular lesions
- Normal cervix

Diagnostic Testing

- Microscopic investigation for the presence of **blastospores** or **pseudohyphae**; saline wet mount has a sensitivity of 40% to 50%, whereas a potassium hydroxide (KOH) preparation has a sensitivity of 50% to 70%.[7] Asymptomatic vaginal colonization of *C. albicans* is not diagnostic of VVC since 10% to 20% of women are asymptomatic carriers of *Candida* species. Asymptomatic vaginal colonization does not require treatment; therefore, the presence alone of *Candida* should not determine care.
- Vaginal pH less than or equal to 4.5; pH should remain normal in cases of fungal infection, whereas an elevated pH suggests bacterial infection.
- *Candida* cultures should be obtained only if signs and microscopy are inconclusive or in cases of recurrent VVC.

Patient Encounter 1

A 19-year-old woman presents to your clinic complaining of itching in her vaginal area and a white discharge. After questioning the woman, you determine that she has vaginal burning, soreness, and itching, accompanied by a curd-like discharge. Although she has had vaginal infections before, she admits to recently becoming sexually active and is very concerned that she may have contracted a sexually transmitted disease. On examination, she has erythema of the labia and a nonodorous discharge.

What information is suggestive of VVC?

What additional information do you need to know before creating a treatment plan for this patient?

Nonprescription azole antifungal products are available as one-, three-, and seven-night regimens in a variety of formulations, including cream, suppository, and vaginal tablets (Table 85–2). Oral fluconazole offers the option of treatment with one dose administered without regard to time of day. Due to the risk of severe hepatotoxicity, the use of oral ketoconazole should be reserved for severe fungal infections resistant to other antifungal options.

Inability to resolve an infection may indicate a mixed infection, infection owing to a nonalbicans strain, an infection that is not fungal, or indicative of serious underlying conditions, such as diabetes or human immunodeficiency virus (HIV) infection. For these reasons, if infection does not resolve with a single antifungal course or if symptoms return within 2 months, practitioners should check cultures and further evaluate the patient's health status.

Due to the numerous treatment options available, a variety of factors can influence product selection, with patient preference playing a significant role. To improve adherence with therapy, the practitioner should discuss with the patient what options are available and what her preferences are.

Adherence rates are greater with oral treatment than with vaginal therapy, possibly due to ease of administration, short duration, and administration flexibility. Vaginal creams provide rapid relief of itching and burning, while symptom resolution may take 1 to 2 days with oral treatment. The practitioner may wish to recommend applying a vaginal cream externally to reduce itching and burning when using an oral agent, although this increases the cost of therapy. Most over-the-counter (OTC) products cost $10 to $20 per course of therapy. The cost of prescription products can vary based on insurance coverage. If the patient does not have prescription coverage, nonprescription products may prove less expensive than even one or two fluconazole tablets.

Table 85–2

Treatment Options for Uncomplicated VVC

1-Day Therapies

Butoconazole 2% sustained-release cream, 5 g intravaginally as a single application
Fluconazole 150 mg, one tablet orally as a single dose
Tioconazole 6.5% ointment, 5 g intravaginally as a single application

3-Day Therapies

Butoconazole 2% cream, 5 g intravaginally for three nights
Clotrimazole 100-mg vaginal tablet, two tablets for three nights
Miconazole 200-mg vaginal suppository, one suppository for three nights
Terconazole 0.8% cream, 5 g intravaginally for three nights
Terconazole 80-mg vaginal suppository, one suppository for three nights

7–14-Day Therapies

Boric acid 600-mg vaginal suppository, one suppository intravaginally twice daily for 14 days
Clotrimazole 1% cream, 5 g intravaginally for 7–14 nights
Clotrimazole 100-mg vaginal tablet, one tablet for seven nights
Miconazole 2% cream, 5 g intravaginally for seven nights
Miconazole 100-mg vaginal suppository, one suppository for seven nights
Nystatin 100,000-unit vaginal tablet, one tablet for 14 nights
Terconazole 0.4% cream, 5 g intravaginally for seven nights

VVC, vulvovaginal candidiasis.

▶ *Risk of Adverse Effects and Interactions*

Systemic adverse effects associated with vaginally administered azoles are less frequent than with oral products. With topical products, local discomfort such as burning, itching, stinging, and redness may occur, particularly with the first application. In contrast, common adverse effects associated with fluconazole include headache, diarrhea, nausea, dizziness, abdominal pain, and taste alterations. Around 15% of patients experience gastrointestinal side effects with orally administered fluconazole.[5]

Oral azoles are associated with significant drug interactions, particularly due to potent inhibition of cytochrome P-450 (CYP) 2C9 and moderate inhibition of CYP 3A4. For patients receiving only one dose of oral fluconazole, these interactions may not pose a significant risk but can with long-term suppressive therapy for recurrent infections.

TREATMENT OF RECURRENT VVC

The goal of treating recurrent VVC is control of the infection, rather than cure. First, any acute episodes are treated, followed by maintenance therapy. Although acute episodes of recurrent VVC will respond to azole therapy, some patients may require prolonged therapy to achieve remission. To achieve remission, 14 days of topical azole therapy or a second dose of oral fluconazole 150 mg repeated 3 days after the first dose can be used. The practitioner should consider that nonalbicans infections are more common in recurrent VVC; therefore, fluconazole and itraconazole resistance may make these agents less effective.

After achieving remission, recurrent VVC requires long-term suppressive therapy for 6 months (Table 85–3). Per CDC

Table 85–3

Treatment Options for Maintenance Therapy

Daily

Boric acid 600 mg in gelatin capsule vaginally daily during menses (5 days)
Itraconazole 100 mg orally once daily
Ketoconazole 100 mg orally once daily

Weekly

Clotrimazole 500 mg vaginal suppository once weekly
Fluconazole 100 or 150 mg orally once weekly
Terconazole 0.8% cream 5 g vaginally once weekly

Monthly

Fluconazole 150 mg orally once monthly
Itraconazole 400 mg orally once monthly

guidelines, oral fluconazole 100-, 150-, or 200-mg weekly for 6 months is first-line treatment.[1] Cessation of suppressive therapy is associated with resurgence of symptomatic infection in 30% to 50% of women.[1]

TREATMENT OF NONALBICANS INFECTIONS

Treatment response rates are lower for nonalbicans infections (eg, *C. glabrata* and *C. krusei*). Although an optimal regimen is unknown, use of nonfluconazole azole therapy for 7 to 14 days is recommended.[1] For second-line therapy, boric acid 600 mg in a gelatin capsule administered vaginally daily for 2 weeks is recommended.[1] This regimen provides mycologic cure rates of 40% to 100%,[6] although local irritation often limits its use. Oral itraconazole 200 mg twice daily 1 day per month for 6 months is also effective.[7] Other topical options include nystatin intravaginal suppositories, 100,000 U/day for 2 weeks. Topical 4% flucytosine is also effective, but use should be limited due to the potential for resistance.

VVC DURING PREGNANCY

During pregnancy, VVC may prove difficult to treat due to elevated estrogen levels, lower response rates, and frequent recurrences, accompanied by concern for the fetus. Vaginal antifungals remain the preferred treatment during pregnancy, although therapy should continue for 1 to 2 weeks to ensure effectiveness.[8] Most topical antifungals are classified as risk category C, whereas clotrimazole is classified as risk category B. Fluconazole's risk category classification for the single 150-mg dose is risk category C but category D for all other doses due to case studies of congenital limb deformities with doses of 400 to 800 mg daily during the first trimester.[9] Therefore, topical intravaginal application of clotrimazole or miconazole is generally preferred over oral antifungal therapy with fluconazole in pregnant patients.

Cultural Awareness During Treatment of VVC

As with all gynecologic issues, the practitioner is faced with cultural perceptions of female genitalia. Practitioners are treating an increased number of patients who have undergone female genital mutilation. Female genital mutilation, formerly known as female circumcision, describes the intentional alteration or injury of female genitalia. More than 100 million women and girls, particularly in Africa and the Middle East, have undergone such procedures for cultural and religious reasons.[10] Some authorities suggest using the term "genital cutting" when dealing with patients to avoid appearing judgmental.[11] Women who have undergone this procedure suffer acute and chronic complications. Patients with female genital mutilation may suffer from recurrent VVC due to inadequate drainage of vaginal fluids. Regardless of the practitioner's opinion on female genital mutilation, the practitioner must be sensitive to the patient's feeling and cultural values.

OUTCOME EVALUATION

Whether using a topical or an oral agent, patients should notice relief of itching and discomfort within 1 to 2 days. The volume of discharge should also begin to decrease within a few days. The entire course of therapy should be continued even if symptoms have resolved. If the condition recurs within 4 weeks or more than four times per year, the patient should be further evaluated

Patient Care Process: VVC

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. If patient has experienced previous VVC, determine what medications were utilized and were effective previously.
- Identify allergies to medications and other substances.
- Review the medical history and physical assessment findings.
- Speak with the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Determine whether the patient is taking any substances that could interact with prescribed medications.
- Based on the medical history and lifestyle factors, determine whether the patient has compelling risk factors for VVC.
- Based on physical examination, determine whether the patient's signs and symptoms are consistent with VVC or another vaginal infection, such as a sexually transmitted infection.
- Review relevant laboratory tests, if any available, such as A1C.
- Assess the efficacy, safety, and patient adherence of current and planned pharmacotherapy.
- Identify any significant adverse drug effects or interactions.

Develop a Care Plan:

- Select lifestyle modifications and antifungal therapy that are likely to be effective and safe.
- Choose medications, doses, and dosage forms that are optimal for the patient.

Implement the Care Plan:

- Educate the patient about lifestyle modifications, medication therapy, medication administration, potential adverse effects, how to manage and report adverse effects that occur, and when to anticipate improvement or seek further care.
- Address any patient concerns about VVC and its management.
- Discuss importance of medication adherence and lifestyle modifications to cure VVC and prevent recurrence.
- Determine whether the patient has insurance coverage or whether recommended agents are included on the formulary.

Follow-up: Monitor and Evaluate:

- No monitoring and evaluation is necessary unless unresolved after treatment.
- If unresolved, review medication and lifestyle modification adherence, review physical examination, and consider diagnostic laboratory to evaluate for other types of infection.

for possible non-*Candida* infections, resistant organism, or other complicating factors, along with assessment of need for long-term suppressive therapy.

OROPHARYNGEAL AND ESOPHAGEAL CANDIDIASIS

Oropharyngeal candidiasis (OPC) is a common fungal infection, often associated with immune suppression (ie, HIV infection, diabetes, and malignancies). If left untreated, it will progress to more serious oral disease, such as esophageal candidiasis.

EPIDEMIOLOGY AND ETIOLOGY

The occurrence of oropharyngeal and esophageal candidiasis is an indicator of immune suppression, often developing in infants, the elderly, and the immunocompromised. One-third to one-half of geriatric inpatients develop OPC. Denture stomatitis is present in approximately 40% of denture wearers,[12] more commonly in women than men. Oral candidiasis is the most commonly reported adverse drug event reported by patients receiving inhaled corticosteroids,[13] with the prevalence of esophageal candidiasis reaching 37% among patients treated with inhaled corticosteroids.[14] The incidence of esophageal candidiasis is highest among patients receiving high doses of corticosteroids or those with diabetes.

The prevalence of HIV infection plays a significant role in the incidence of oropharyngeal and esophageal candidiasis. In the 1980s, the incidence of OPC increased fivefold, in association with the spread of HIV infections.[15] Although HIV infection remains a risk factor for candidiasis, the introduction of highly active antiretroviral therapy caused a decline in the incidence of oral candidiasis to 45.9% to 79.1%, varying by geographic location, race, and therapy.[16]

OPC remains the most common opportunistic infection in patients with HIV. For the majority of patients, it is the first manifestation of HIV infection.[18] The incidence of oropharyngeal infection increases with decreasing CD4+ lymphocyte counts and is most often observed when CD4+ counts are less than 200 cells/mm^3 (350 × 106/L). An incidence of 59% is observed in patients with a CD4+ count less than 350 cells/mm^3 (350 × 106/L).[17]

Esophageal candidiasis usually occurs in patients with lower CD4+ counts than those that develop OPC.[21] Although esophageal candidiasis represents the first manifestation of HIV infection in less than 10% of cases, it is the most common acquired immunodeficiency syndrome (AIDS)-defining disease.[18] The CDC classifies esophageal candidiasis as a Stage 3–defining opportunistic infection in HIV.[19] As with OPC, the incidence of esophageal candidiasis increases with decreasing CD4+ counts and, therefore, is a measure of declining CD4+ count or treatment failure.

C. albicans accounts for 80% of cases of OPC and esophageal candidiasis. Over the last 20 years, an increasing incidence of *C. albicans* resistance has been accompanied by an increased incidence of nonalbicans species infections, including *C. glabrata, C. tropicalis, C. krusei*, and *C. parapsilosis*. In patients with cancer and HIV, the prevalence of *C. glabrata* infections or mixed *C. albicans* and *C. glabrata* infection has been increasing.[20] Such infections tend to be more severe and require larger doses of antifungal agents for treatment.

PATHOPHYSIOLOGY

Similar to VVC, the development of OPC occurs when the normal environment is altered. *Candida* organisms frequently colonize the oropharynx and mucous membranes. These organisms do not become pathogenic until the environmental balance is disturbed. This occurs in the setting of broad-spectrum antibiotic use, tissue damage (due to chemotherapy, catheter tubing, trauma, or smoking), hyposalivation, or immune deficiency.

Table 85–4

Risk Factors for Oropharyngeal and Esophageal Candidiasis

Factor	Proposed Mechanism
Extremes of age	Immature immunity in infants and reduced immunity in the elderly
Impaired mucosal integrity	Breaks in the protective barrier allows fungal invasion; often due to radiation, surgery, or mucositis
Dentures	Adherence of fungus to dentures, along with reduced salivary flow under dentures; ill-fitting dentures may impair mucosal integrity
Xerostomia	Reduced cleansing and defense factors of saliva
Use of antibiotics	Altered flora of mucosa allowing fungal overgrowth
Use of steroids	Suppression of immunity
Use of immunosuppressant	Suppression of immunity
HIV infection	Decreased CD4 T lymphocytes
Diabetes mellitus	Elevated glucose levels and defense factors in saliva
Nutritional deficiencies	Altered defense mechanisms, impaired mucosal integrity, or enhanced pathogenic potential of fungus

HIV, human immunodeficiency virus.

RISK FACTORS

Risk factors for OPC can be found in Table 85–4.

CLINICAL PRESENTATION AND DIAGNOSIS

See text boxes for clinical presentation and diagnosis of OPC and esophageal candidiasis.

TREATMENT

Along with selecting an effective treatment, selection of an appropriate antifungal agent requires consideration of location and severity of infection, medication adherence, potential drug interactions, concomitant medical conditions, and presence of sucrose or dextrose. Topical agents require frequent dosing and prolonged contact time with oral mucosa. Rough surfaces of tablets and troches may irritate sensitive mucosa. Patients with **xerostomia** may have inadequate saliva to dissolve troches. Topical agents containing sucrose or dextrose may increase the risk of caries or cause elevated blood sugar in patients with diabetes. Along with being expensive, oral azoles exhibit an increased risk of toxicity and drug interactions due to inhibition of CYP-450.

Because oropharyngeal and esophageal candidiasis are signs of an immunocompromised state, the immune status of the patient should be considered in the therapeutic care plan. For HIV-infected patients, this should also include an evaluation of the patient's antiretroviral therapy because fungal infections may represent immune status deterioration.

Clinical Presentation and Diagnosis of Oropharyngeal Candidiasis

OPC is often a presumptive diagnosis based on signs and symptoms, along with the resolution of them after treatment with antifungal agents.

Symptoms

- Sore, painful mouth, and tongue
- Burning tongue
- **Dysphagia**
- Metallic taste/loss of taste

Signs

Signs vary depending on the type of oropharyngeal candidiasis.

- Diffuse erythema on the surface of buccal mucosa, throat, tongue, and gums
- White patches on tongue, palate, gums, or buccal mucosa; removal of patches reveals erythematous and bloody tissue; ability to remove patches distinguishes OPC from oral hairy leukoplakia
- Angular cheilitis presents with small cracking lesions, erythema, and soreness at the corners of the mouth; associated with vitamin and iron deficiency
- Denture stomatitis presents with flat, red lesions on mucosa beneath dentures, signs of chronic erythema and edema on mucosa
- Hyperplastic OPC presents with discrete, transparent raised lesions on the inner mucosa of the cheek; typically found in men who smoke
- Pseudomembranous OPC presents with yellow-white plaques that may be small and discrete or confluent; the most common form found in HIV patients

Diagnostic Testing

Diagnosis is primarily based on identification of characteristic lesions and confirmed by scraping of lesions to perform a gram-stain. Although rarely necessary, diagnostic testing is possible if a definitive diagnosis is required.

- Cytology, although presence of *Candida* is not diagnostic because colonization is common
- Culture to identify species of yeast or presence of resistance
- Biopsy

Clinical Presentation and Diagnosis of Esophageal Candidiasis

Symptoms

- Fever
- **Odynophagia**
- Dysphagia
- Retrosternal pain

Signs

- Fever
- Hyperemic or edematous white plaques
- Ulceration of esophagus
- Increased mucosal friability
- Narrowing of lumen

Diagnostic Testing

Unlike OPC, diagnosis of esophageal candidiasis is not based solely on clinical presentation, instead requiring endoscopic visualization of lesions and culture confirmation. Due to the invasive nature of these procedures, most practitioners opt to treat the infection presumptively, reserving endoscopic evaluation for patients who fail therapy.

- Cytology and culture to identify species of yeast or presence of resistance
- Barium esophagogram
- Endoscopy revealing whitish plaques with progression to superficial ulceration of the esophageal mucosa
- Mucosal biopsy

For low-risk patients, topical agents are first-line therapy for OPC, although systemic agents may be used for severe or unresponsive cases. Infectious Disease Society of America (IDSA) guidelines recommend clotrimazole troches, 10 mg five times per day, or miconazole mucoadhesive buccal 50 mg tablet for 7 to 14 days for mild infections. Alternatives for mild infections include nystatin suspension or pastilles four times daily.[21] Once-daily oral fluconazole 100 to 200 mg for 7 to 14 days is reserved for moderate-to-severe cases.[21] Two weeks of oral itraconazole 200 mg or posaconazole 400 mg daily, voriconazole 200 mg twice daily, or amphotericin-B suspension four times daily are alternatives, typically reserved for refractory cases. For refractory cases additional therapy options include intravenous echinocandin or intravenous amphotericin-B deoxycholate but are considered second-line due to lack of concentration of drug at the site of infection.

For non–HIV-infected patients who have suppressed immune systems, the practitioner must consider the patient's risk of dissemination. Patients with cell-mediated immune deficiency but near-normal granulocyte function, such as patients with diabetes, solid organ transplant, or solid tumors, are at low risk for dissemination. The risk of dissemination is higher in patients who develop neutropenia, including patients with leukemia or bone marrow transplant. These patients should be treated aggressively to prevent invasive fungal infection.

For the treatment of OPC in HIV-infected individuals, initial episodes can be adequately controlled with topical agents, such as clotrimazole troches, so long as symptoms are not severe and no esophageal involvement is suspected.

Representing a severe extension of OPC, esophageal candidiasis requires systemic antifungal therapy. The significant morbidity associated with esophageal candidiasis warrants aggressive treatment.

Unlike OPC, which can be treated with topical agents, esophageal candidiasis requires systemic antifungal therapy for effective treatment.[18] The IDSA recommends oral fluconazole for 7 to

Patient Care Process: Oropharyngeal Candidiasis

Collect Information:

- Assess the patient's symptoms to determine whether symptoms are consistent with oropharyngeal or esophageal candidiasis.
- Evaluate for risk factors, such as immunocompromised state
- Review the medical history. Does the patient have compelling indications or contraindications for specific antifungal treatment?
- Review any available diagnostic data, including cultures.
- Review available laboratory tests, especially liver function.
- Obtain a thorough history of prescription, nonprescription, and natural drug product use. Is the patient taking any medications that may contribute to candidiasis? Is the patient taking any medications that may interfere with treatment?
- Determine if the patient has any allergies.

Assess the Information:

- If the patient has had oropharyngeal or esophageal candidiasis previously, determine what treatments were helpful to the patient in the past.
- If the patient has had oropharyngeal or esophageal candidiasis previously, determine whether the patient has risk factors for recurrent infection.
- Determine whether long-term suppressive therapy is necessary.
- Evaluate the patient for the potential of adverse drug reactions, drug allergies, or drug interactions.

Develop a Care Plan:

- Select antifungal therapy that is likely to be effective and safe.
- Choose medications, doses, and dosage forms that are optimal for the patient.
- Discuss warning signs to report, include, worsening symptoms or recurrence.

Implement the Care Plan:

- Stress the importance of adherence with the antifungal regimen until complete.
- Provide patient education pertaining to oropharyngeal or esophageal candidiasis and antifungal therapy, including causes, risk factors, medication administration, potential adverse effects, and potential medication interactions.
- Discuss warning signs to report, include worsening symptoms or recurrence.

Follow-up: Monitor and Evaluate:

- Follow-up if symptoms do not resolve within 7 days or if symptoms worsen.
- Follow up on any identifiable precipitating cause, such as an immunocompromised state.

14 days in patients with esophageal candidiasis and moderate-to-severe disease, with an echinocandin or amphotericin-B as alternatives in patients unable to tolerate oral therapy, or with resistant or refractory disease.[21] Itraconazole 200-mg daily, posaconazole 400-mg twice daily, voriconazole 200-mg twice daily, and intravenous fluconazole are considered second-line therapy. If immunocompromised patients experience frequent or severe recurrences, particularly of esophageal candidiasis, chronic maintenance therapy with fluconazole 100 to 200 mg daily should be considered.

Patient Encounter 2, Part 1

A 35-year-old man presents to your clinic complaining of "burning and soreness in my mouth" along with a metallic taste and "this funny white stuff." On initial examination, he has white patches on his tongue, gums, and buccal mucosa. These patches are easily removed, revealing erythematous tissue underneath. Although he has visited the clinic before, his medical records are incomplete. He denies any current or recent medication use or being HIV-positive.

What additional information do you need to know before creating a treatment plan for this patient?

What underlying medical conditions might make him susceptible to fungal infections?

OUTCOME EVALUATION

Patients should notice symptomatic relief within 2 to 3 days of initiating therapy. Complete resolution typically occurs within 7 to 10 days. The entire course of therapy should be continued even if symptoms have resolved. If the condition worsens or does not resolve, the patient should be referred to a specialist for aggressive therapy.

Short courses of oral azoles are associated with gastrointestinal upset, whereas courses lasting longer than 7 to 10 days are associated with increased risk of hepatotoxicity and CYP-450 drug interactions. In patients receiving prolonged therapy lasting more than 3 weeks, baseline and periodic monitoring of liver function tests should be considered.

Immunocompetent patients generally do not require reassessment after treatment. Patients with neutropenia exhibit an increased risk of dissemination of infection and, therefore, should be monitored for signs of systemic fungal infection. Due to an increased risk of recurrence, HIV-positive patients should routinely be evaluated for recurrence at each visit.

Patient Encounter 2, Part 2

How is the treatment care plan altered if the patient has a history of frequent and severe OPC? If the patient is HIV-positive? If the patient is neutropenic?

MYCOTIC INFECTIONS OF THE SKIN, HAIR, AND NAILS

Tinea infections are superficial fungal infections in which the pathogen remains within the keratinous layers of the skin or nails (Table 85–5). Typically, these infections are named for the affected body part, such as tinea pedis (feet), tinea cruris (groin), and tinea corporis (body). Tinea infections are commonly referred to as ringworm due to the characteristic circular lesions. In actuality, tinea lesions can vary from rings to scales and single or multiple lesions.

EPIDEMIOLOGY AND ETIOLOGY

Tinea infections are the second most frequently reported skin condition. The common tinea infections are tinea pedis, tinea corporis, and tinea cruris. Tinea pedis, the most prevalent cutaneous fungal infection, impacts more than 25 million people annually in the United States.

Fungal skin infections are primarily caused by **dermatophytes** such as *Trichophyton*, *Microsporum*, and *Epidermophyton*. *Trichophyton rubrum* accounts for more than 75% of all cases in the United States.[22] To a lesser extent, *Candida* and other fungal species cause skin infections. With tinea infections, the

Table 85–5

Signs, Symptoms, and Risk Factors of Superficial Fungal Infections

Infection	Symptoms, Signs, and Risk Factors
Tinea pedis	• Involves plantar surface and interdigital spaces of foot • Interdigital infections produce itching; presents as fissures, scaling, or macerated skin; can occur between any toes but most often between fourth and fifth toes; may cause foul smell due to superinfection with *Pseudomonas* or diphtheroids • Hyperkeratotic infections present with slivery white scales on a thickened, red base; usually covers entire foot; occasionally may also affect hand • Vesiculobullous tinea pedis presents as pustules or vesicles on soles of feet; associated with maceration, itching, and thickening of sole; may cause lymphangitis and cellulitis; most common during summer months • Ulcerative tinea pedis presents as macerated, denuded, and weeping ulcers on soles; may produce extreme pain and erosion of interdigital spaces; typically complicated by opportunistic gram-negative infections • Risk factors include occlusive footwear, foot trauma, and use of public showers
Tinea manuum	• Infection of the interdigital and palmar surfaces • Presents as white scales in palmar folds; may also develop scales on remainder of palm; may present as singular plaque • More commonly affecting only one hand • Presents with hyperkeratotic skin
Tinea cruris	• Presents with follicular papules and pustules on the medial thigh and inguinal folds • Ringed lesions may extend from inguinal fold over adjacent inner thigh • Lesions usually spare the penis and scrotum, in contrast to candidiasis • Frequency increases during summer • Primarily develops in young men • Risk factors include tight-fitting clothing, excessive sweating, poor hygiene, increased humidity and temperatures • Commonly referred to as "jock itch"
Tinea corporis	• Presents with circular, scaly patch with enlarged border • Lesions may have red papules or plaque in center that clears, leaving hypopigmentation or hyperpigmentation • Itching may be present • Commonly referred to as ringworm of the body • Risk factors include animal to human contact
Tinea versicolor	• Characterized by skin depigmentation but can present as hyperpigmentation, particularly in dark-skinned patients • Typically occurs in areas with sebaceous glands, including neck, trunk, and arms • Depigmentation may persist for years • Primarily develops in young and middle-aged adults • Risk factors include application of oil, greasy skin, high ambient temperature, high relative humidity, tight-fitting clothing, immunodeficiency, malnutrition, hereditary predisposition
Tinea barbae	• Infection of beard area
Tinea capitis	• Infection of the head and scalp • May be asymptomatic initially, then progresses to inflammatory alopecia • "Black dot" alopecia may develop due to breakage of hair at the root • May form kerions (nodular swellings) • Scaling or favus may develop on scalp • Cervical lymphadenopathy is common • Primarily found in infants, children, and young adolescents, often in African American and Hispanic populations • Can be spread from person to person or animal to person
Onychomycosis (tinea unguium)	• Infection of nail plate and bed • Nail becomes opaque, thick, rough, yellow or brownish, and friable; nail may separate from bed • Toenails affected more frequently than fingernails • Prevalence increases with advanced age

causative dermatophyte typically invades the stratum corneum without penetration into the living tissues, leading to a localized infection.

PATHOPHYSIOLOGY

The primary mode of transmission of tinea infections is direct contact with other persons or surface reservoirs. Upon contact, the dermatophytes attach to the keratinized cells, leading to thickening of the cells. Although infection remains localized, bacterial superinfections may develop.

The pathophysiology of onychomycosis depends on the clinical type. With the most common form of onychomycosis, distal lateral subungual, the fungus spreads from the plantar skin. The fungus invades the underside of the nail through the distal lateral nail bed, leading to inflammation of the area. In cases of white superficial onychomycosis, the fungus invades the surface of the nail plate directly. With white superficial onychomycosis, the nail bed and hyponychium are infected secondarily. Proximal subungual onychomycosis infections begin in the cuticle and the proximal nail fold, then penetrate the dorsum of the nail plate.

RISK FACTORS

- Prolonged exposure to sweaty clothing
- Excessive skin folds
- Sedentary lifestyle
- Warm, humid climate
- Use of public pools
- Walking barefoot in public areas
- Skin trauma
- Poor nutrition
- Diabetes mellitus
- Immunocompromised state
- Impaired circulation

Clinical Presentation and Diagnosis of Mycotic Infections

Symptoms and Signs

See Table 83–5.

Diagnostic Testing

- KOH prep
- Wood's ultraviolet lamp
- Microscopic examination
- Fungal cultures
- Periodic acid-Schiff (PAS) staining of nail

Treatment of Skin and Hair Infections

The goals of treatment include the following:

- Providing symptomatic relief
- Resolution of infection
- Preventing spread of infection

TREATMENT

Nonpharmacologic Therapy

- Because fungi thrive in warm, moist environments, the practitioner should encourage patients to wear loose-fitting clothing and socks, preferably garments made of cotton or other fabrics that wick moisture away from the body. Avoid clothing made with synthetic fibers or wool.
- Sweaty or wet clothing should be removed as soon as possible.
- Clean the infected area daily with soap and water.
- The infected area should be dried completely prior to dressing, paying particular attention to skin folds.
- To allow circulation of air, the infected area should not be bandaged.
- For foot infections, cotton socks are recommended, although these should be changed two to three times a day to reduce moisture.
- To prevent spread, towels, clothing, and footwear should not be shared with other persons.
- Wear protective footwear in public showers and pool areas.

Pharmacologic Therapy of Tinea Infections

Since dermatophyte hyphae seldom penetrate into the living layers of the skin, instead remaining in the stratum corneum, most infections can be treated with topical antifungals. Infections covering large areas of the body, infections involving nails or hair, chronic infections, or infections not responding to topical therapy may require systemic therapy. Treatment is typically initiated based on symptoms, rather than on microscopic evaluation. For infections accompanied by inflammation, combination therapy with a topical steroid can be considered (Tables 85–6, 85–7, and 85–8).

Typically, tinea pedis requires treatment one to two times daily for 4 weeks, whereas tinea corporis and tinea cruris require topical treatment one to two times daily for 2 weeks. When applying treatment, the medication should be applied at least 1 inch beyond the affected area. Treatment of infection should continue at least 1 week after resolution of symptoms. Many practitioners opt to initiate therapy with nonprescription clotrimazole, tolnaftate, miconazole, or terbinafine, reserving prescription topical agents, such as naftifine, ciclopirox, and butenafine, for second-line therapy or refractory cases and systemic therapy for refractory cases.

When recommending topical therapy, the selection of vehicle is based on the type of lesion and location of the infection. Solutions and lotions are recommended for hairy areas and oozing lesions, whereas creams and ointments should be avoided in these areas. Creams are better for moderately scaling and nonoozing lesions. For hyperkeratotic lesions, ointments can be considered. The selected formulation should be applied to the affected area after it is cleaned and dried. The medication should be rubbed into the infected area for improved penetration. Because most patients do not rub in sprays and powders, penetration of the epidermis is minimal, making them less effective than other formulations. Sprays and powders should be considered adjuvant therapy with a cream or lotion or as prophylactic therapy to prevent recurrence.[7] For OTC medications, in addition to formulation, it is important to identify the active ingredient desired. Even products with the same brand name may contain different active ingredients. Due to the severity of infection and inflammation,

Table 85–6

Available Topical Antifungal Agents

Medication	Rx/OTC	Cream/Ointment	Gel	Lotion	Spray/Solution	Powder
Butenafine	OTC	X				
Ciclopirox	Rx	X		X	Lacquer and shampoo	
Clotrimazole	OTC	X		X	X	X
Econazole	Rx	X				
Efinaconazole	Rx				X	
Haloprogin	Rx	X			X	
Ketoconazole	Rx/OTC	X			Shampoo	
Miconazole	OTC	X		X	X	X
Naftifine	Rx	X	X			
Nystatin	Rx	X		X		X
Oxiconazole	Rx	X		X		
Sertaconazole	Rx	X				
Sulconazole	Rx	X				
Tavaborole	Rx				X	
Terbinafine	OTC	X	X		X	
Tolnaftate	OTC	X		X	X	

tinea capitis does not adequately respond to topical agents; therefore, oral agents for 6 to 8 weeks are recommended. Griseofulvin has long been considered the treatment of choice due to its ability to achieve high levels within the stratum corneum.[23] Terbinafine and itraconazole have also demonstrated effectiveness.[23] Due to its lipophilicity, itraconazole achieves high dermal concentrations that are maintained for 4 weeks after discontinuation of therapy.[24]

Treatment of Onychomycosis

For onychomycosis, a chronic infection that rarely remits spontaneously, adequate treatment is essential to prevent spread to other sites, secondary bacterial infections, cellulitis, or gangrene.

Due to the chronic nature and impenetrability of nails, topical agents have low efficacy rates for treating onychomycosis. Oral agents that can penetrate the nail matrix and nail base, such as itraconazole and terbinafine, are more effective than ciclopirox lacquer, efinaconazole solution, or tavaborole solution. Itraconazole (200 mg twice daily for 1 week per month or 200 mg daily for 12 weeks) and terbinafine (250 mg daily for 12 weeks) demonstrate mycological cure rates of 71% and 77%, respectively, whereas the cure rate range from 29% to 36% for ciclopirox, approximately 55% for efinaconazole, and 35% for tavaborole.[25] For patients with liver disease or who are unable to use oral agents, ciclopirox lacquer, efinaconazole solution, and tavaborole solution remain reasonable alternatives, despite requiring 48 weeks of therapy. Due to low efficacy, griseofulvin should only be considered second-line therapy with therapy continued for 4 months for fingernail infections or 6 months for toenail infections.

There is a small risk of developing congestive heart failure with itraconazole therapy due to its negative inotropic effects.[26] Itraconazole should not be administered to patients with ventricular dysfunction such as congestive heart failure. The Food and Drug Administration (FDA) also released warnings that itraconazole and terbinafine are associated with serious hepatic toxicity, including liver failure and death. Liver failure associated with these medications has occurred in patients with no preexisting liver disease or serious underlying medical conditions. Treatment with itraconazole or terbinafine for prolonged periods requires laboratory monitoring of liver function tests before initiation of therapy and at monthly intervals.

Cultural Awareness When Treating Mycotic Infections

Awareness of cultural beliefs related to feet and hands is essential when treating patients with fungal infections. In Arab countries, showing the bottom of the foot is a grave insult. The foot is

Table 85–7

Dosing of Topical Agents for Tinea Infections and Onychomycosis

Agents	Topical Dosing Frequency
Butenafine	Once daily
Ciclopirox	Twice daily; at bedtime (lacquer)
Clotrimazole	Twice daily
Econazole	Once daily
Efinaconazole	Once daily (nail solution)
Haloprogin	Twice daily
Ketoconazole	Once daily
Miconazole	Twice daily
Naftifine	Once daily (cream); twice daily (gel)
Oxiconazole	Twice daily
Sertaconazole	Twice daily
Sulconazole	Twice daily
Tavaborole	Once daily (nail solution)
Terbinafine	Twice daily
Tolnaftate	Two to three times daily

Table 85–8

Dosing of Systemic Therapy for Tinea Infections

Medication	Adult Dosing	Pediatric Dosing
Fluconazole	150 mg/week	6 mg/kg/week
Griseofulvin	0.5–1 g/day	10–20 mg/kg/day
Itraconazole	200 mg twice daily	Not studied
Ketoconazole	200–400 mg/day	3.3–6.6 mg/kg/day
Terbinafine	250 mg/day	< 25 kg: 125 mg/day; 25–35 kg: 187.5 mg/day; > 35 kg: 250 mg/day

Patient Care Process: Mycotic Infections—1

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. If patient has experienced previous tinea infections, determine the location of that infection and what medications were utilized and were effective previously.
- Identify allergies to medications and other substances.
- Review the medical history and physical assessment findings.
- Speak with the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Determine whether the patient is taking any substances that could interact with prescribed medications.
- Based on the medical history and lifestyle factors, determine whether the patient has compelling risk factors for tinea infections.
- Based on physical examination of affected area, determine whether the patient's signs and symptoms are consistent with a superficial fungal infection.
- Review relevant laboratory tests, if any are available.
- Assess the efficacy, safety, and patient adherence of current and planned pharmacotherapy.
- Identify any significant adverse drug effects or interactions.

Develop a Care Plan:

- Select lifestyle modifications and antifungal therapy that are likely to be effective and safe.
- Choose medications, doses, and dosage forms that are optimal for the patient.

Implement the Care Plan:

- Educate the patient about lifestyle modifications, medication therapy, medication administration, potential adverse effects, and how to manage and report adverse effects that occur.
- Address any patient concerns about the tinea infection and its management.
- Discuss importance of medication adherence and lifestyle modifications to cure tinea pedis, cruris, or corporis and prevent fungal infection recurrence.
- Determine whether the patient has insurance coverage or whether recommended agents are included on the formulary.

Follow-up: Monitor and Evaluate:

- No monitoring and evaluation is necessary for short-course therapy unless unresolved. For courses lasting longer than 6 weeks in children, baseline alanine aminotransferase (ALT) and aspartate aminotransferase (AST) measurements are recommended, along with complete blood count (CBC) at 6 weeks.
- If unresolved, review medication and lifestyle modification adherence, review physical examination, and consider diagnostic laboratory to evaluate for other types of infection.

Patient Care Process: Mycotic Infections—2

Collect Information:

- Assess the patient's symptoms to determine whether self-treatment with OTC antifungal therapy is appropriate. Exclusions for self-treatment include infection of nails or hair, unsuccessful initial treatment, worsening condition, signs of secondary bacterial or systemic infection, large infected areas, or chronic medical conditions such as diabetes, immunosuppression, or impaired circulation.
- Review any available diagnostic data, including cultures and KOH preps.
- Obtain a thorough history of prescription, nonprescription, and natural drug product use.
- Any allergies?

Assess the Information:

- If the patient has had a mycotic infection previously, determine what treatments were helpful to the patient in the past.
- Determine whether long-term prophylactic therapy is necessary to prevent recurrence.
- Determine whether the patient has prescription coverage.

Develop a Care Plan:

- Evaluate the patient for the potential for adverse drug reactions, drug allergies, and drug interactions.
- Select lifestyle modifications and antifungal therapy that are likely to be effective and safe.
- Choose medications, doses, and dosage forms that are optimal for the patient.

Implement the Care Plan:

- Educate the patient on lifestyle modifications that will prevent recurrence, including keeping the area dry, wearing shower shoes, washing clothing in hot water, using drying powders, avoiding sharing towels or clothing, and wearing loose-fitting clothing.
- Provide the patient education pertaining to mycotic infections and antifungal therapy, including causes, medication application or administration, length of therapy, how to avoid spread of infection or recurrence, and potential adverse effects.
- Discuss dietary modifications that are necessary with oral agents.
- Discuss medications that may interact with antifungal therapy, particularly with oral agents used for nail infections.
- Discuss warning signs to report such as recurrent or difficult-to-cure infections, infections with malodorous discharge or bleeding.
- Stress the importance of adherence with the antifungal regimen.

Follow-up: Monitor and Evaluate:

- Follow-up if unresolved or worsens with treatment.

considered the dirtiest part of the body. As such, patients from these countries may be hesitant to show their feet to the practitioner. In other countries, the open palm "high five" gesture is considered insulting. When treating patients with infections on the hand, the practitioner should refrain from making this gesture while discussing the patient's hand infection.

OUTCOME EVALUATION

For infections of the skin, patients should notice relief of symptoms, including pruritus, scales, and inflammation, within 1 to 2 weeks. Therapy should be continued at least 1 week after complete resolution of symptoms. If the condition worsens on topical therapy, the patient should be treated with oral therapy.

For onychomycosis, relief of symptoms is slow. The infected nail will need months to grow out. The practitioner should advise the patient not to become frustrated by the slow resolution. Despite the slow progress, the antifungal agent is curing the infection. The practitioner should also advise the patient that even after the infection is cured, the nail may not look "normal."

Abbreviations Introduced in This Chapter

AIDS	Acquired immunodeficiency syndrome
CDC	Centers for Disease Control and Prevention
HIV	Human immunodeficiency virus
KOH	Potassium hydroxide
OPC	Oropharyngeal candidiasis
OTC	Over-the-counter
PAS	Periodic acid-Schiff test
VVC	Vulvovaginal candidiasis

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86

Invasive Fungal Disease

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Differentiate epidemiologic differences and host risk factors for acquisition of primary and opportunistic invasive fungal diseases.
2. Recommend appropriate empiric or targeted antifungal therapy for the treatment of invasive fungal diseases.
3. Describe the components of a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for invasive fungal infections.
4. Evaluate the role of antifungal prophylaxis in the prevention of opportunistic fungal diseases.

INTRODUCTION

Invasive fungal infections or invasive mycoses are general terms for diseases caused by the invasion of living tissue by fungi. In contrast to superficial mycoses (see Chapter 85), invasive fungal infections are less common but are of greater medical concern because of their disproportionately higher severity and mortality. Approximately 1.5 million people die each year from the 10 most common invasive fungal infections, which is higher than World Health Organization mortality estimates for tuberculosis (1.4 million) or malaria (1.2 million).[1] However, these numbers likely underestimate the actual mortality burden of invasive fungal infections considering that the four most common infections (cryptococcosis, invasive candidiasis, invasive aspergillosis [IA], and *Pneumocystis jiroveci* pneumonia) are often underdiagnosed and not reportable diseases to public health agencies (Table 86–1).

Invasive fungal diseases are broadly categorized as either primary or opportunistic mycoses. **KEY CONCEPT** Primary invasive fungal diseases develop following exposure to fungal spores or conidia in the soil that, when disturbed, can become aerosolized and inhaled leading to infection, even in an immunocompetent patient exposed to a sufficient inoculum. Because these fungi are in specific soil types in select geographic areas, they are also referred to as endemic fungi. In the United States, three species (*Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis/Coccidioides posadasii*) account for most of these infections (see Table 86–1).

KEY CONCEPT In contrast, opportunistic fungal diseases are most frequently encountered in the setting of compromised host immune defenses and are caused by a wider spectrum of less virulent fungal species that rarely cause infection in healthy patients (see Table 86–1). Hence, the spectrum, severity, and outcome of opportunistic fungal diseases are strongly influenced by the degree, type, and severity of host immunosuppression. As a rule, opportunistic fungal diseases are difficult to diagnose, but often fatal if not diagnosed early and treated aggressively.

Occasionally, opportunistic fungal diseases may be associated with outbreaks in nonimmunocompromised patients if fungi are inadvertently inoculated into patients from contaminated drug solutions or medical devices. In 2012, an outbreak of fungal meningitis and joint infections ($n = 751$ cases) in 20 states was eventually traced by the Centers for Disease Control and Prevention and state health departments to contaminated preservative-free methylprednisolone solution compounded by a pharmacy that was distributed to multiple doctors' offices. These contaminated steroid solutions were administered as epidural and articular injections in patients with chronic back or joint pain. The dematiaceous mold eventually linked to the fungal meningitis cases, *Exserohilum rostratum*, had rarely been described as a human pathogen prior to the outbreak.[2]

PRIMARY (ENDEMIC) MYCOSES

EPIDEMIOLOGY AND ETIOLOGY

Endemic mycoses are capable of infecting otherwise healthy individuals. In immunocompromised patients, endemic fungal infections present with more severe manifestations or can reactivate with life-threatening consequences. Because initial symptoms of an endemic fungal infection are nonspecific and produce symptoms indistinguishable from other slowly progressing infections (tuberculosis), a careful patient history concerning travel and activities that may have resulted in exposure to endemic fungi is essential for early diagnosis.

Two of the most common endemic fungal infections (histoplasmosis and North American blastomycosis) are found in overlapping regions in the eastern and central river basins of the United States (Figure 86–1). *H. capsulatum* var. *capsulatum*, the causative fungus of histoplasmosis, grows heavily in soil contaminated with bird or bat excreta, which serves to enhance sporulation of the fungus.[3,4] Infections have been associated with activities that disturb soil contaminated with this excreta, including cave

Table 86–1

Invasive Mycoses

Primary (Endemic) Invasive Fungi
Histoplasma capsulatum[a]
Coccidioides immitis/Coccidioides posadasii[a]
Blastomyces dermatitidis[a]

Opportunistic Invasive Fungi
Yeast
- *Candida* species (*C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, and others)[a]
- *Cryptococcus neoformans*[a]
- *Trichosporon* spp. and others

Mold
- Hyalohyphomycoses (non-dematiaceous)
  - *Aspergillus fumigatus*, *Aspergillus terreus*, *Aspergillus flavus*, and other species[a]
  - *Fusarium solani* and *Fusarium oxysporum*
  - *Mucorales* (formally *zygomycosis*) (*Mucor*, *Absidia*, *Rhizopus*, *Cunninghamella*, and *Rhizomucor*)
  - *Penicillium* species
- Phaeohyphomycoses (dematiaceous)
  - *Pseudallescheria boydii* (*Scedosporium* spp.)
  - Bipolaris
  - Alternaria
  - *Exserohilum rostratum*

Other
- *Pneumocystis jiroveci* (formerly *P. carinii*)[a]

[a]Most common.

Patient Encounter 1, Part 1: Endemic Fungal Infection

A 32-year-old man from Cincinnati, Ohio presents with influenza-like symptoms, including mild fever and persistent cough, 2 months after working on renovating a structure on his property. The patient has had persistent symptoms 3 weeks despite a recent 2-week course of amoxicillin/clavulanate. He is otherwise healthy and does not take any chronic medications. Chest computed tomography (CT) found mediastinal and hilar lymphadenopathy as well as multiple pulmonary nodules.

What information is suggestive that this patient may have an endemic fungal infection?

What is the most likely endemic fungal pathogen based on this patient's area of residence?

exploration (spelunking), working in or demolishing chicken coops or older buildings, or work in campsites in heavily wooded areas. For blastomycosis, decaying organic matter, warm humid conditions, and proximity to water or frequent rainfall support growth of this fungus. Outbreaks of blastomycosis have been most frequently associated with occupational or recreational activities around the major waterways such as the Great Lakes region, where soil concentrations of *B. dermatitidis* are elevated.[4]

Coccidioidomycosis differs from histoplasmosis and blastomycosis, as the fungus is associated with arid to semiarid climates, hot summers, low altitude, alkaline soil, and sparse flora. Hence the fungus is found in the Southwestern region of the United States stretching from Western Texas to Southern California (see Figure 86–1).[5] Epidemics of coccidioidomycosis have been reported in California following dust storms and earthquakes, including cycles of intense drought and rain, which favor the growth of the fungus and dispersal of its spores, called arthroconidia.

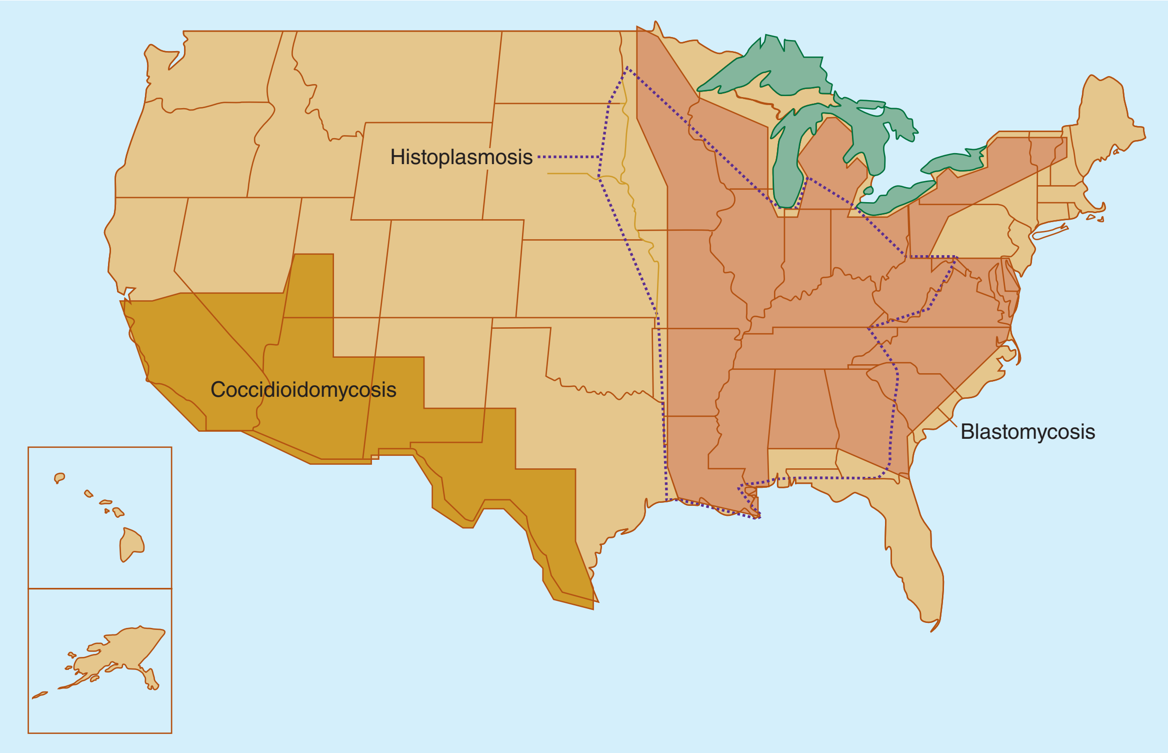

FIGURE 86–1. Geographic localization of primary (endemic) fungi in the United State.

PATHOPHYSIOLOGY

Endemic fungi share several characteristics that contribute to their pathogenicity in humans. All endemic fungi exhibit temperature-dependent dimorphism, meaning they can propagate as either yeast (single cells that reproduce by budding into daughter cells) or molds (multicellular filamentous fungi that reproduce through the production of conidia or spores). At environmental temperatures (25–30°C [77–86°F]), *H. capsulatum*, *B. dermatitidis*, and *C. immitis* grow in the mold form, producing 2- to 10-μm round- to oval-shaped (*Histoplasma* and *Blastomyces*) or barrel-shaped **conidia** (*Coccidioides*) that are dispersed throughout the environment and in air currents. At physiologic temperatures, the conidia germinate into yeast (*Histoplasma* and *Blastomyces*) or specialized cell forms called spherules (*Coccidioides*) that are resistant to killing by alveolar macrophages and neutrophils in the lung.

Control of infection by the host requires the development of antigen-specific T-lymphocyte response that enhances macrophage fungicidal activity and formation of a **granuloma** to contain the fungus.[6] Not surprisingly, patients with T-cell–mediated immune deficiency (eg, acquired immunodeficiency syndrome [AIDS] patients and transplant recipients requiring immunosuppressive therapy) or suppressed cellular immunity due to drug therapy (eg, chemotherapy, high-dose corticosteroids, or tumor necrosis–α blockers such as infliximab) are at higher risk for reactivation of fungal disease.

The most common route of infection for endemic fungi is the respiratory tract, where conidia aerosolized from contaminated soil are inhaled into the lung. Once in the lung, conidia are phagocytosed but not destroyed by macrophages and neutrophils in the alveoli and bronchioles. Within 2 to 3 days, conidia germinate into yeast resistant to phagocytosis and killing by macrophages and neutrophils (Figure 86–2A and B). For *C. immitis*, germination of the arthroconidia results in the formation of a sac-like structure called a spherule filled with endospores (Figure 86–2C). Spherules then rupture to release large numbers of endospores, which are the propagating form of the infection. Control of infection in the lungs requires the formation of a granuloma to contain the fungus. However, patients exposed to an overwhelming inoculum or a lower inoculum exposure in the setting of suppressed T-cell–mediated immunity can result in a potentially fatal infection that disseminates outside the lung to the skin and oral mucosa, adrenal glands, bone, spleen, thyroid, gastrointestinal (GI) tract, heart, and central nervous system (CNS).

CLINICAL PRESENTATION AND DIAGNOSIS

Histoplasmosis and coccidioidomycosis frequently present with mild self-limiting, influenza-like or mild lower respiratory tract–like illness 1 to 3 weeks after the inhalation of conidia. The clinical presentation of blastomycosis can range from asymptomatic infection to acute or chronic pneumonia that develops weeks after exposure, to a full-blown disseminated disease.

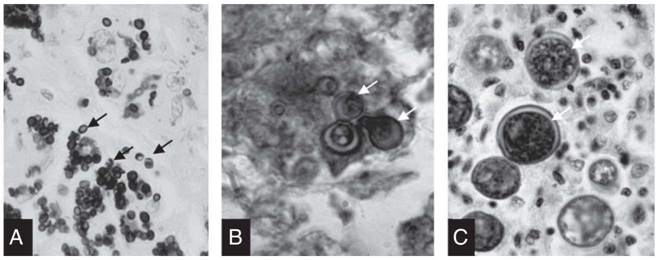

FIGURE 86–2. Histopathology of endemic mycoses in tissue. **A:** Histoplasmosis (yeast). **B:** Blastomycoses (broad-based budding yeast). **C:** Coccidioidomycoses (spherules with endospores).

Severe endemic fungal disease often presents with a clinical history of persistent pneumonia despite multiple courses of antibiotic therapy that is accompanied by fever, chills, cough, arthralgia, night sweats, and weight loss. This clinical presentation is often indistinguishable from other chronic infections such as pulmonary tuberculosis. Therefore, the diagnosis of endemic fungal infection is often prompted by a patient history of prolonged infectious symptoms, travel or residence in an endemic area, and/or participation in activities that result in exposures to soil contaminated by endemic fungi.

Radiological findings

- Chest radiographs often reveal either diffuse or nodular infiltrates in the lung, accompanied by enlargement of the hilar and/or mediastinal lymph nodes.
- Fulminant pneumonia may be seen with high-inoculum exposures, resulting in diffuse lung infiltrates that progress to **acute respiratory distress syndrome** (ARDS) and respiratory failure.

Signs and Symptoms

- Rheumatologic symptoms such as severe arthritis, **pericarditis**, and **erythema nodosum** may be seen in 10% to 30% of patients with endemic fungi.[3-5]
- Dissemination outside the lung is common in patients with suppressed cellular immunity and frequently produces signs of progressing infection.
- Ulcerative oral and cutaneous lesions may also arise with any endemic fungal infection.
- Verrucose (wart-like) skin lesions on sun-exposed areas on the face are particularly suggestive of progressing blastomycosis and frequently mistaken for skin cancer.
- Dissemination of the fungi to bone marrow may result in anemia or thrombocytopenia.
- Hepatomegaly, splenomegaly, and adrenal insufficiency can also occur with the dissemination of the endemic fungi to these internal organs.
- Seizures, meningeal signs, and **hydrocephalus** may occur with the dissemination of the infection to the CNS and signify a poor prognosis.

Definitive diagnosis of an endemic fungal infection requires growth of the fungus from body fluids or tissue, or evidence of cellular or tissue invasion in clinical samples by histopathology. However, cultures may only be positive in the setting of high-inoculum exposures, pneumonia, or disseminated disease. Serologic detection of antibodies is helpful in the diagnosis and management of patients with histoplasmosis or coccidioidomycosis but lacks specificity for the diagnosis of *B. dermatitidis*.[4] In general, a fourfold rise in antibody or complement fixation titers of *Histoplasma* or *Coccidioides*, or any titer greater than 1:16, suggests active infection. However, many clinicians still consider titers as low as 1:8 as evidence of active disease because undetectable titers may be present in one-third of all active infections. Enzyme-linked immunosorbent assays (ELISAs) have been developed for direct detection of *Histoplasma* antigens in serum and urine. Serial antigen testing can also provide a means for assessing response of histoplasmosis to antifungal therapy and detection of relapsing disease.[3]

TREATMENT

KEY CONCEPT The approach to antifungal therapy in patients with endemic fungal infections is determined by the severity of clinical presentation, the patient's underlying immunosuppression, and potential toxicities and drug interactions associated with antifungal treatment. Immunocompetent patients with mild disease following exposure to *H. capsulatum* or *C. immitis* often experience a benign course of infection that does not require antifungal therapy. Persons of Filipino or African descent have a higher risk for dissemination with *C. immitis*, and this may also be taken into consideration for more aggressive treatment.[5] Approximately 9% of patients exposed to coccidioidomycosis (defined by positive IgM or IgG serology) develop pneumonia requiring hospitalization, and 1% may develop infections of the CNS, which are difficult to treat if not incurable.[5]

Current guidelines suggest that patients with mild histoplasmosis or coccidioidomycosis may be initially followed in the outpatient setting with serial antigen or serologic studies to confirm resolving infection. Patients without clinical improvement within the first month can be treated with oral itraconazole for 6 to 12 weeks (Table 86–2).[3,5] Broader spectrum triazoles such as voriconazole and posaconazole, and possibly isavuconazole, appear to have clinically useful activity against endemic fungi but have limited data to recommend their routine first-line use. Fluconazole treatment (6–12 mg/kg/day; 400–800 mg/day) is associated with somewhat higher relapse rates than itraconazole but has fewer GI adverse effects and drug interactions compared to itraconazole. Echinocandins and flucytosine are not clinically useful agents for the treatment of endemic mycoses.

Patients with symptoms persisting longer than 2 weeks, greater than 10% weight loss, extensive pneumonia, or serologic titers greater than 1:8 of histoplasmosis or coccidioidomycosis are candidates for immediate antifungal therapy. Any patient with underlying immunosuppression should also receive immediate antifungal therapy. The following signs and symptoms are

Table 86–2

Common Treatment Regimens for Endemic Fungal Infections

Mycosis	Recommended Treatment Regimens	Comments
Histoplasmosis		
Mild to moderate	Observation or itraconazole 200 mg three times daily for 3 days, then two times daily for 6–12 weeks.	
	Fluconazole 12 mg/kg/day PO for 6–12 weeks adjusted for renal function.[a]	Fluconazole has a higher rate of relapse than itraconazole but is better tolerated by many patients than itraconazole. Echinocandins are not clinically effective against endemic mycoses.
Severe, including CNS disease or immunocompromised host	Amphotericin B 0.7 mg/kg/day IV or liposomal amphotericin B 3–5 mg/kg/day for 12 weeks or until clinically stable.	Liposomal amphotericin B better tolerated than conventional formulations, especially for CNS disease. Patients initially treated with amphotericin B–based regimens are transitioned to itraconazole or fluconazole once they are clinically stable. Corticosteroid therapy should be considered in hypoxic patients with acute pulmonary infection. Itraconazole is less effective for CNS infections.
Blastomycosis		
Mild to moderate	Itraconazole 200 mg three times daily for 3 days, then two times daily for 6–12 months.	
Severe, including CNS disease or immunocompromised host	Amphotericin B 0.7 mg/kg/day or liposomal amphotericin B 3–5 mg/kg/day IV until patient is clinically stable, then itraconazole (non-CNS) or fluconazole 12 mg/kg/day orally adjusted for renal function.[a]	
Coccidioidomycosis		
Mild to moderate, including noncomplicated pneumonia	Observation or itraconazole 200 mg three times daily for 3 days, then two times daily for 3–6 months. OR Fluconazole 6–12 mg/kg/day (400–800 mg daily) daily adjusted for renal function[a] for 3–6 months.	Itraconazole demonstrated trend toward superiority over fluconazole in a randomized controlled trial for progressive, nonmeningeal coccidioidomycosis; however, fluconazole is better tolerated than itraconazole.
Diffuse pneumonia or disseminated infection	Amphotericin B 1–1.5 mg/kg/day with dose and frequency decreased as improvement occurs. Patient then transitioned to triazole therapy. OR Liposomal amphotericin B formulation 3–5 mg/kg/day. Patient then transitioned to triazole therapy.	Fluconazole 800–1000 mg/day adjusted for renal function[a] is often recommended after initial amphotericin B therapy for meningitis.

[a] CrCl > 50–90 mL/min (0.83–1.50 mL/s), 100% of dose; CrCl 10–50 mL/min (0.17–0.83 mL/s), 50% of dose; CrCl < 10 mL/min (0.17 mL/s) 50%.

CNS, central nervous system; IV, intravenous; PO, oral.

Patient Encounter 1, Part 2: Endemic Fungal Infection

Patient Management

The patient's serum titer for histoplasmosis returns as greater than 1:16. Based on the information presented, select an appropriate treatment plan for the patient's infection.

Should the patient receive antifungal therapy now? What factors need to be considered?

indicators of severe disease that require hospitalization and initial treatment with systemic amphotericin B (see Table 86–2).

- Hypoxia indicated by a partial pressure of oxygen less than 80 mm Hg (10.6 kPa)
- Hypotension (systolic blood pressure < 90 mm Hg)
- Impaired mental status
- Anemia (hemoglobin < 10 g/dL [100 g/L or 6.2 mmol/L])
- Leukopenia (< 1×10^3/mm^3 [1×10^9/L])
- Elevated hepatic transaminases (> 5 times upper limit of normal) or bilirubin (> 2.5 times upper limit of normal)
- Coagulopathy (impaired clotting ability)
- Evidence of dissemination, including cutaneous manifestations
- Meningitis

All patients with blastomycosis require antifungal treatment, even though patients with mild disease can be managed as outpatients with oral itraconazole.[7] Patients with evidence of severe pulmonary disease or dissemination require initial treatment in the hospital with amphotericin B–based regimens until they are clinically stable. Subsequently, they can complete a 6- to 12-month treatment course as outpatients with oral triazoles.[4] Methylprednisolone (0.5–1 mg/kg daily IV) may be administered during the first 1 to 2 weeks of antifungal therapy if the patient develops hypoxemia or significant respiratory distress.

OUTCOME EVALUATION

Response to antifungal therapy may be slow in patients with a prolonged history of infection or severe manifestations. However, gradual improvements in symptoms and reduction in fever are indicators of response to treatment. For histoplasmosis and coccidioidomycosis, decreasing antigen titers or serology are indicative of response to antifungal therapy.[3,5]

Antifungals used for the treatment of endemic mycoses can be associated with many clinically significant drug interactions and toxicities, especially with the prolonged treatment courses required for endemic mycoses. Itraconazole is available as a capsule formulation that should be taken with food and a cyclodextrin-solubilized solution taken without food. The liquid formulation of itraconazole has several advantages over the capsule: it has a better oral bioavailability and does not require the low gastric pH that is required for dissolution and absorption of the capsule. However, the oral solution is somewhat dilute requiring large volume doses, has an unpalatable aftertaste (an issue when taking months of therapy), and has a much higher rate of GI intolerance. Therefore, the capsule formulation is often preferred, provided patients are not on acid suppression therapy (ie, proton pump inhibitors, histamine antagonists, or antacids). Acidic beverages, such as orange or apple juice, or cola can improve the absorption of itraconazole capsules.

Fluconazole is well tolerated and available in both IV and oral formulations that have good bioavailability. Posaconazole is formulated as a micronized suspension that is best absorbed when taken with high-fat meals and in divided doses up to 800 mg/day. A delayed-release tablet formulation of posaconazole with improved bioavailability (permitting substantially lower daily dosages) and fewer gastric pH-associated drug interactions is also available and is the preferred oral treatment formulation of posaconazole in most patients unless the patient cannot swallow the tablet.[8] An IV formulation of posaconazole is also available for patients who cannot take oral formulations. Absorption of voriconazole is not affected by gastric pH but is generally administered 1 hour prior to or 2 hours after eating. Isavuconazole is available in both an IV and oral prodrug formulation that is not affected by gastric pH or food.[9]

Drug interactions are an important concern in patients taking long-term triazole therapy. Itraconazole, voriconazole, and isavuconazole are substrates of the cytochrome P450 (CYP) 3A4 enzyme. Coadministration of itraconazole, voriconazole, and, to a lesser extent, fluconazole, posaconazole, and isavuconazole with inducers of this CYP 3A4 enzyme (eg, rifampin, phenytoin, and phenobarbital) increase drug clearance resulting in ineffective plasma and tissue concentrations of the drug.[10] In general, coadministration of the broader spectrum triazoles (itraconazole, voriconazole, posaconazole, and isavuconazole) with these inducers should be avoided. Itraconazole, voriconazole, posaconazole, and, to a lesser extent, isavuconazole are also potent inhibitors of CYP 3A4, which predisposes these agents to a large number (estimated > 2000) of clinically significant pharmacokinetic drug–drug interactions (such as those with calcineurin inhibitors, chemotherapeutics, antiretrovirals, and statins).[10]

All patients should have their medication profile carefully reviewed prior to initiating and stopping triazole antifungals, preferably with the aid of a computerized drug interaction database. Even in the absence of drug interactions, serum drug levels of triazoles can be unpredictable.[11] Serum drug concentration monitoring or therapeutic drug monitoring (TDM) has been recommended in patients receiving itraconazole, voriconazole, and posaconazole suspension for documented infections, or when inadequate serum concentrations are suspected because of altered absorption or drug interactions.[11] Suspected toxicities, especially CNS adverse effects (such as visual disturbances, dizziness, or hallucinations) during voriconazole therapy,[12] may also be indicative of excessive drug levels that can be detected with TDM (Table 86–3).

All triazole antifungals carry the potential for rash, photosensitivity, and hepatotoxicity. In general, hepatotoxicity is mild and reversible, presenting as asymptomatic increases in liver transaminases, and less frequent increases in total bilirubin. Fulminant hepatic failure is less common and typically mediated by immunologic mechanisms. Therefore, serial monitoring of liver function is recommended in all patients receiving triazole antifungals. Long-term therapy with itraconazole has also been associated with reversible adrenal suppression and cardiomyopathy due to negative inotropic effects of the drug. Long-term therapy with voriconazole can be associated with severe phototoxic reactions and cutaneous erythema in sun-exposed skin, which may not be preventable with sunscreen alone. This phototoxic reaction has been linked to a high risk for developing squamous cell carcinoma or melanoma.[13] Patients should be instructed to avoid sun exposure while on voriconazole therapy and have frequent

Table 86–3

Recommendations for Antifungal Therapeutic Drug Monitoring

Drug	Indication for Monitoring	Time of First Measurement (days)	Target Conc. for Efficacy (mcg/mL or mg/L)	Target Conc. for Safety (mcg/mL or mg/L)
Flucytosine	Routine during the first week of therapy, renal insufficiency, or poor clinical response	3–5	Peak > 20 (155 μmol/L)	Peak < 50 (387 μmol/L) to reduce risk of marrow toxicity
Itraconazole	Routine during first week of therapy, GI dysfunction, suspected drug interactions	4–7	Prophylaxis > 0.5 (0.7 μmol/L); therapy trough > 1–2 (1.4–2.8 μmol/L)	Some evidence to suggest trough > 4 (5.7 μmol/L) increased adverse effects
Voriconazole	Lacking response, GI dysfunction, suspected drug interactions, pediatrics,[a] IV to oral switch, unexplained neurological changes	4–7	Prophylaxis trough > 0.5 (0.7 μmol/L); therapy trough 1–2 (2.9–5.7 μmol/L)	Trough < 6 (17.2 μmol/L) to reduce risk of CNS toxicities
Posaconazole	Lacking response, GI dysfunction, potent acid suppression therapy (ie, proton pump inhibitor), suspected drug interactions	4–7	Prophylaxis trough > 0.5 (0.7 μmol/L); therapy trough 0.5–1.5 (0.7–2.1 μmol/L)	Not established Delayed-release tablet formulation preferred for most patients because of fewer pH drug interactions and improved bioavailability. IV formulation is available for patients who cannot take oral therapy
Isavuconazole	Lacking response, suspected drug interactions, mucormycosis	4–7	Not established, in clinical trials to the average trough concentration surpassed 2 (5.7 μmol/L)	Not established, in clinical trials the average trough concentration surpassed 2 (5.7 μmol/L)

[a] Pediatric patients display accelerated linear clearance of voriconazole. Therefore, higher daily voriconazole dosing (7 mg/kg every 12 hours) is recommended to achieve similar exposures to adults. Some children may require doses as high as 12 mg/kg every 12 hours to achieve similar serum drug exposures to adults. Therefore, therapeutic drug monitoring is recommended.

GI, gastrointestinal; IV, intravenous.

skin examinations by a dermatologist. Long-term voriconazole therapy may also predispose patients to periostitis, or inflammation of tissue surrounding bone due to fluoride toxicity from chronic voriconazole exposure, (fluoride toxicity) that present with nonspecific joint, shoulder, and limb pain that can be diagnosed by X-ray and serum analysis of fluoride levels.[14] Alopecia, chapped lips, brittle nails, and cognitive difficulties have also been reported with longer term voriconazole therapy, especially at higher doses.[15] Peripheral neuropathy may develop in 3% to 17% of patients on long-term triazole therapy and is most frequently reported with itraconazole and voriconazole.[16]

Amphotericin B remains the mainstay of treatment of patients with severe endemic fungal infections. The conventional deoxycholate formulation of the drug can be associated with substantial infusion-related adverse effects (chills, fever, nausea, rigors, and, in rare cases, hypotension, flushing, respiratory difficulty, and arrhythmias). As-needed premedications with low doses of acetaminophen and diphenhydramine, and less frequently nonsteroidal anti-inflammatory agents hydrocortisone or meperidine (if rigors are present), are used to reduce acute infusion-related reactions. Venous irritation associated with the drug can also lead to thrombophlebitis; hence, central venous catheters are the preferred route of administration in patients receiving more than a week of therapy.

The most severe adverse effect associated with amphotericin B therapy is nephrotoxicity, which occurs through direct effects on glomerular filtration (constriction of the afferent arterioles in the kidney tubule) and damage of the distal tubular membrane.[17] Generally, nephrotoxicity with amphotericin B is reversible, provided the drug is stopped. However, treatment interruptions can be problematic in patients with severe infections. Precipitous decreases in glomerular filtration may occur in patients with marked dehydration or during aggressive diuresis. Infusion of normal saline before and after amphotericin B, a practice known as “sodium loading,” can blunt precipitous decreases in renal perfusion pressure and slow the rate of decline in the glomerular filtration rate but may not be tolerated in patients with poor cardiac function. Administration of amphotericin B by continuous infusion reduces the glomerular but not distal tubular toxicity and is generally not advocated because of unproven efficacy. Amphotericin B–associated nephrotoxicity can be delayed by avoiding the use of other drugs with known tubular toxicity such as aminoglycosides, calcineurin inhibitors, cisplatin, or foscarnet. The initial manifestation of tubular toxicity is in patients with severe wasting of potassium and magnesium in the urine. Therefore, patient electrolytes must be carefully monitored, and potassium and magnesium supplementation is always necessary. Hypokalemia and hypomagnesaemia frequently precede decreases in glomerular filtration (increased serum creatinine), especially in patients who are adequately hydrated.[17] Continued tubular damage eventually results in decreases in renal blood flow and glomerular filtration through tubuloglomerular feedback mechanisms that further constrict the afferent arteriole.

During the 1990s, amphotericin B was reformulated into three different lipid-based formulations (Abelcet, AmBisome, and Amphotec) that have reduced rates of nephrotoxicity compared with the conventional deoxycholate formulation (Fungizone). Two of the formulations that are currently available (Abelcet and AmBisome) have lower rates of infusion-related reactions. Although these lipid formulations are generally considered to be as effective as conventional amphotericin B deoxycholate, they are not dosed equivalently to the standard formulation (see Table 86–2).

PROPHYLAXIS

Primary **prophylaxis**, before development of infection, is generally not recommended for endemic fungi. Antifungal prophylaxis is generally recommended in specific situations, including the following:

1. Patients with HIV infection [and with $CD4^+$ cell counts less than 150 cells/mm^3 (150×10^6/L) (histoplasmosis)] living in regions with high endemic case rates (> 10 cases per 100 patient-years), or any patient with positive IgM or IgG antibodies. The recommended regimen is itraconazole 200 mg daily.
2. Secondary prophylaxis or suppressive therapy with itraconazole 200 mg daily is recommended to prevent the recurrence of blastomycosis in immunosuppressed patients if immunosuppression cannot be reversed.[4]
3. In patients with prior CNS disease, fluconazole or voriconazole are preferred over itraconazole and posaconazole due to the lower penetration of itraconazole and posaconazole into the CNS.[5]

OPPORTUNISTIC MYCOSES

KEY CONCEPT Commensal or environmental fungi that are typically harmless can become invasive mycoses when the host immune defenses are impaired. Host immune suppression and risk of opportunistic mycoses can be broadly classified into three categories:

1. A reduction in the number or quality of neutrophils
2. Deficits in **cell-mediated immunity**
3. Disruption of the skin, gut, and/or microbiologic barriers

A reduction in the number of neutrophils (neutropenia) resulting from neoplastic diseases, cytotoxic chemotherapy, marrow transplantation, or bone marrow aplasia is among the most common risk factors for opportunistic mycoses. Functional neutrophil defects may be seen in certain disease states (eg, advanced diabetes mellitus and chronic granulomatous disease) or with high-dose corticosteroid therapy. Deficits in T-cell–mediated immunity associated with HIV infection, high-dose corticosteroid therapy, calcineurin inhibitors, other immunosuppressive drugs, chemotherapy, transplantation, bone marrow failure, and other immunodeficiencies are increasingly prevalent with the prolonged survival of transplant patients or other chronically immunosuppressed populations.

Immune deficits arising from the disruption of the skin GI/genitourinary barriers can also predispose patients to fungal diseases. The most common types of barrier disruptions include surgery or infections/perforations of the abdominal viscus, use of central venous and urinary catheters, parenteral nutrition, and mucositis associated with cytotoxic chemotherapy and antibiotic therapy. Broad-spectrum antibacterial therapy, which is common in high-risk hematology patients and the critically ill patient in the ICU, disrupts the protective microbiologic flora of the gut allowing overgrowth of *Candida* species that can translocate to the bloodstream and invade internal organs.

In general, opportunistic mycoses are difficult to diagnose and are frequently treated empirically before diagnosis is proven. **KEY CONCEPT** Deciding when to initiate antifungal therapy and what opportunistic pathogens to cover is a decision governed largely by the immune deficits of the host, local epidemiology and experience, or clinical or diagnostic clues suggestive of incipient infection.

INVASIVE CANDIDIASIS

EPIDEMIOLOGY AND ETIOLOGY

Candida species are the most common opportunistic fungal pathogens encountered in hospitals, ranking as the third to fourth most common cause of nosocomial bloodstream infections in **ICUs** in the United States and the eighth most common cause of bloodstream infections overall.[18] The incidence of nosocomial candidiasis has increased steadily since the early 1980s, with the widespread use of central venous catheters, broad-spectrum antimicrobials, and other advancements in the supportive care of critically ill patients. In the 1980s, *C. albicans* accounted for more than 80% of all bloodstream yeast isolates cultured from patients. By the late 2000s, this relative frequency of *C. albicans* had decreased to less than 50% in national surveys of bloodstream infections with increasing proportion of infections caused by non-*albicans* species.[19] Because of the inherent resistance (eg, *C. glabrata, C. krusei*, and more recently *C. auris*) of many of the non-*albicans* species, the introduction of fluconazole in the early 1990s is often cited as the key element driving the shift in the microbiology of invasive candidiasis. **KEY CONCEPT** Familiarity with the local epidemiology and frequency of non-albicans *Candida* species in the institution or intensive care unit (ICU) is essential before selecting **empiric** antifungal therapy for invasive candidiasis, as fluconazole is not recommended for the treatment of *C. glabrata* and *C. krusei infections*, and echinocandin resistance among *C. glabrata* is increasing in some centers. *C. auris* is an emerging, multidrug-resistant fungal pathogen for which therapeutic options are limited.

CLINICAL PRESENTATION AND DIAGNOSIS

Invasive candidiasis encompasses several infectious syndromes broadly categorized as candidemia or deep-seated infections, which most frequently affect the kidney, eye, or bones but may also affect heart valves, the CNS, and other organs, including the spleen and liver.[20] A major difficulty in the diagnosis of invasive candidiasis in high-risk patients is distinguishing colonization from true infection. *Candida* frequently colonizes the urine, sputum, and skin and wounds, especially in patients receiving broad-spectrum antibacterial therapy. However, isolation of *Candida* from these sites frequently does not indicate true infection. For example, *Candida* in the urine can be an indication of renal candidiasis or an obstructing fungus ball; however, it must be distinguished from more common benign colonization of the urinary tract, especially in patients with chronic indwelling urinary catheters. Similarly, *Candida* species isolated for respiratory samples (sputum, bronchoalveolar lavage) are nearly always indicative of colonization and not true *Candida* pneumonia, which is a rare clinical entity.

Approximately one-third of all patients with true invasive candidiasis fall within three groups at the time of diagnosis: (a) patients with uncomplicated candidemia in the absence of deep-seated candidiasis, most frequently arising from an infected catheter; (b) candidemia associated with deep-seated candidiasis, most frequently arising from the GI tract or secondary seeding from a separate infection site; and (c) deep-seated candidiasis without candidemia.[21]

Invasive candidiasis is most frequently diagnosed by growth of yeast in blood cultures. Blood cultures successfully detect infection in most patients with candidemia alone, fewer patients with mixed deep-seated disease and intermittent candidemia, and virtually no patients who have infection limited to deep tissues at the time of culture. As a result, it is estimated that half of all episodes of invasive candidiasis are not detected by blood cultures alone. Therefore, a blood culture positive for *Candida* is always considered strong evidence of infection, but a negative blood culture cannot rule out the possibility of invasive candidiasis, especially in patients with multiple underlying risk factors. The development of new diagnostic tools that do not exclusively rely on microbiological isolation of *Candida* has become a major research focus for improving the diagnosis of the infection, especially deep-seated disease.[20]

Serodiagnostic tests have been developed for the detection of *Candida* cell wall antigens, or nucleic acids of *Candida* species, in the hope of improving the detection of invasive disease missed by blood cultures. Currently, the most frequently used test is the Fungitell (1→3)-β-D-glucan test, Associates of Cape Cod, Inc. False-positive results may occur, however, in patients with Gram-negative bacteremia, certain gauze dressing or dialysis membranes, or patients heavily colonized with *Candida* species. Additionally, the presence of other fungal pathogens that produce (1→3)-β-D-glucan as a cell wall component, such as *Aspergillus*, may also lead to a positive Fungitell (1→3)-β-D-glucan test result. More recently the development and Food and Drug Administration (FDA) approval of the T2 Magnetic Resonance–based T2Candida Panel has made possible the rapid, direct, and culture-independent detection of *Candida* species, although this test is not available in all institutions.[22]

Laboratory identification of *Candida* in clinical samples must be performed to the species level whenever possible, as *Candida* species differ considerably in their susceptibility to antifungal agents (Figure 86–3A). Rapid discrimination of *C. albicans* from common non-albicans *Candida* species can be accomplished by the germ tube test, which presumptively identifies *C. albicans* by the early formation (< 4 hours) of a hyphae-like structure when the yeast is incubated in serum at 37°C (98.6°F). Definitive species identification, however, may require an additional 48 to 72 hours after the organism is isolated on agar but can be accelerated with fluorescent in situ hybridization (FISH) of *Candida* species–specific DNA sequences. Matrix-assisted laser desorption/ionization time of flight (MALDI-TOF), polymerase chain reaction (PCR)–based methodologies, and magnetic resonance–based technologies have shown some promise in the early identification of *Candida* species in whole blood specimens in as little as 1 hour, which could shorten the time to earlier diagnosis.

C. albicans remains the most common cause of invasive candidiasis and is the most virulent of *Candida* species but is most susceptible to commonly used antifungals, including fluconazole.[23] Like *C. albicans*, *C. tropicalis* is a relatively virulent species associated with the highest mortality rates but has similar susceptibility profiles as *C. albicans*. *C. parapsilosis* is a less virulent species seen frequently in neonates and adults with central venous catheters. However, many *C. parapsilosis* isolates form thick biofilms on prosthetic materials and catheters that make the organism difficult to eradicate. *C. parapsilosis* is generally susceptible to most antifungals, including fluconazole, although mean inhibitory concentrations (MICs) for echinocandins are higher for other *Candida* species. *C. krusei* is uniformly resistant to fluconazole, although most isolates retain susceptibility to voriconazole and posaconazole. *C. auris* is an emerging highly virulent, multidrug-resistant pathogen that has been associated with infection outbreaks in hospitals and nursing homes.[24] Almost all *C. auris* isolates are resistant to fluconazole, 50% are resistant to voriconazole, 30% are resistant to amphotericin B, and 5% are resistant to echinocandins.[25] Additionally, a major problem with *C. auris* is frequent misidentification by automated systems used by many clinical microbiological laboratories, potentially resulting in the patient getting the wrong treatment. Therefore, specialized methods have been proposed for the detection and identification of *C. auris* in healthcare facilities.[24]

C. glabrata may present as a breakthrough infection on fluconazole prophylaxis and is becoming increasingly resistant to echinocandins.[18] Although *C. glabrata* is generally less virulent than other *C. albicans*, infections with this organism are typically seen

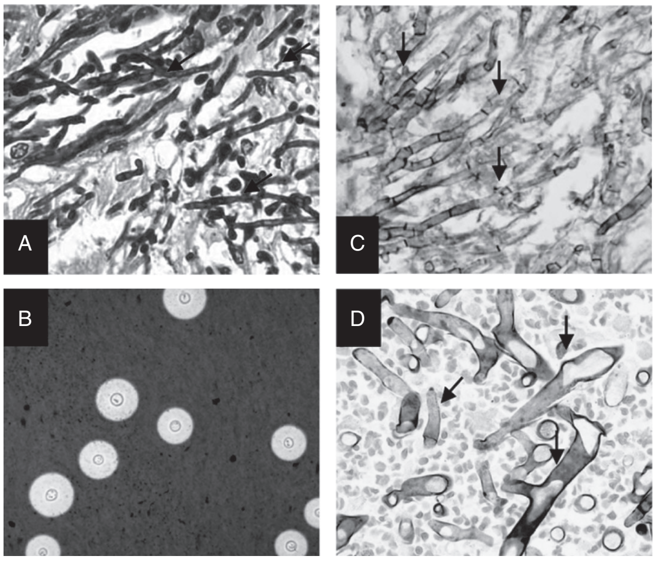

FIGURE 86–3. Opportunistic mycoses in clinical samples. **A:** Candidiasis (tissue). **B:** Cryptococcosis (India ink stain of CSF). **C:** Aspergillosis (tissue). **D:** Mucormycosis (tissue).

Patient Encounter 2, Part 1: Invasive Candidiasis

A 65-year-old man with chronic liver disease is recovering in the ICU after becoming septic secondary to a severe case of spontaneous bacterial peritonitis and develops fever while receiving broad-spectrum antibacterial therapy (meropenem 2 g every 8 hours and vancomycin 1 g every 12 hours). The patient has a central venous catheter and a Foley catheter. Blood cultures are negative at the time, but the patient has yeast growing in the sputum and urine. A serum (1→3)-β-D-glucan test is positive at 80 pg/mL (80 ng/L). Laboratory studies reveal a white blood cell count of 17,500 cells/mm^3 $(17.5 \times 10^9/L)$.

What are this patient's risk factors for developing an invasive fungal infection?

What evidence suggests this patient has an invasive fungal infection despite negative blood cultures?

If antifungal therapy is empirically started in this patient, what information should be considered?

in older patients with poor performance status, and therefore mortality remains high. The marginal dose-dependent susceptibility of *C. glabrata* to fluconazole and increasing echinocandin resistance[26,27] has fueled a growing clinical need for susceptibility testing of this species, as some isolates may demonstrate resistance to multiple antifungal classes. Generally, fluconazole-resistant strains of *C. glabrata* should be assumed to be cross-resistant to other triazoles.

TREATMENT

Seven antifungals (amphotericin B, fluconazole, voriconazole, isavuconazole, caspofungin, micafungin, and anidulafungin) have been studied as monotherapy in prospective, randomized comparative clinical trials for the treatment of invasive candidiasis. In a patient-level meta-analysis of several of these trials, increased patient age, elevated APACHE II score, use of immunosuppressive therapy, and infection with *Candida tropicalis* were independent risk factors for mortality[28] (see Table 86–4). On the other hand, removal of central venous catheters in patients with candidemia and treatment with an echinocandin were variables associated with reduced patient mortality. It is also recommended that all patients with candidemia should undergo an eye examination to rule out *Candida* endophthalmitis, which can be sight threatening if not recognized early and may require direct installation of antifungal therapy for adequate treatment.[21] **KEY CONCEPT** Based on these findings and treatment guidelines endorsed by the Infectious Diseases Society of America, echinocandins are recommended as the preferred initial treatment for invasive bloodstream candidiasis, even in less "critically-ill" patients.[21] Timely initiation of antifungal therapy for invasive candidiasis is critical, as any delay in the initiation of antifungal therapy once a patient has a positive blood culture increases the potential for metastatic seeding of organs and mortality. Clinically stable patients can be transitioned to oral fluconazole or other triazoles once the infecting isolate has been identified and susceptibility is known.[29]

The efficacy of echinocandins for deep-tissue candidiasis is less well established compared to bloodstream infections, and higher failure rates were reported for infections located in anatomical sites where echinocandin penetration is limited (ie, meninges, endophthalmitis, urine).[30] For other forms of deep-tissue candidiasis, triazoles or lipid amphotericin B formulation may be preferable as initial therapy until diagnosis and culture results are available, depending on the suspected organs involved and the clinical severity of illness.[21] Frequently patients are transitioned to oral triazole therapy once stable because of the long-treatment courses that are often required (4–6 weeks minimum) for deep-seated infections.

An important caveat for echinocandin treatment is that cryptococcosis, endemic fungi, or other rare yeast (eg, *Trichosporon* species) occasionally produce fungemia in lymphopenic patients that may initially be mistakenly assumed to be *Candida*. Therefore, initial treatment with a lipid amphotericin B formulation may be judicious in profoundly lymphopenic patients (ie, $CD4^+$ < 250/mm^3 [250 × 10^6/L]) with yeast in blood cultures until fungal identification is confirmed, as echinocandins have poor activity against non-*Candida* yeast.

Echinocandins (ie, caspofungin, micafungin, or anidulafungin), voriconazole, or lipid amphotericin B formulation are often administered as empiric treatment for *Candida* spp. in patients with prolonged neutropenia (ie, absolute neutrophil count < 500 PMN/mm^3 [500 × 10^6/L] for > 7 days) with fever[21] (See Table 86–4). Fluconazole may be an acceptable option in patients expected to have short duration of neutropenia (< 2 weeks) not receiving systemic antifungal prophylaxis with a triazole. Lipid amphotericin B formulations, an echinocandin, or voriconazole are preferred if the patient has or is expected to have prolonged neutropenia (ie, > 2 weeks) because of the increased risk of mold infections. If patients are receiving fluconazole prophylaxis, breakthrough infections with *C. glabrata,* and less frequently *C. krusei*, are possible and should be initially treatable with an echinocandin or amphotericin B.

Urinary candidiasis is a term for group of syndromes that can range from benign colonization (candiduria) in the bladder to invasive disease of the renal parenchyma. Isolation of *Candida* in the urine from nonneutropenic patients does not require antifungal therapy, as transient clearance of *Candida* from the urine has no demonstrable clinical benefit.[21] Patients should receive 7 to 14 days of antifungal therapy for urinary candidiasis if they are (a) symptomatic, (b) have clinical or laboratory evidence of infection, (c) are neutropenic, (d) are low-birth-weight infants; (e) will undergo urologic manipulations, or (f) have renal allografts. Removal of urinary tract instruments, including Foley catheters and stents, is essential to prevent relapse. The preferred therapy is fluconazole 200 mg daily, although IV amphotericin B deoxycholate 0.3 to 1 mg/kg/day is also effective. Other antifungal agents (except for flucytosine) do not achieve appreciable concentrations in the urine and therefore should not be considered first-line treatments for urinary candidiasis.[30] Irrigation with amphotericin B is not effective for infections above the bladder and should not be used in higher risk patients except for its use as a diagnostic tool for confirming a localized infection of the bladder. *Candida* infections of the renal parenchyma secondary to metastatic seeding from the bloodstream are treated in a similar fashion to candidemia.

Oral candidiasis (thrush) is not an invasive disease and can be treated with topical azoles (clotrimazole troches), oral fluconazole, or oral polyenes (such as nystatin or oral amphotericin B). Orally administered and absorbed azoles (fluconazole, voriconazole, or itraconazole solution), amphotericin B suspension, IV echinocandins, or IV amphotericin B are recommended for refractory or recurrent infections.

Although more severe than mucocutaneous candidiasis, esophageal candidiasis typically does not evolve into a life-threatening infection unless the esophagus is ruptured. However, topical

Patient Encounter 2, Part 2: Invasive Candidiasis

The patient was started on caspofungin 50 mg/day following a 70 mg loading dose but 4 days later has persistent fever and develops hypotension. Blood cultures are now growing a germ tube–negative yeast. Laboratory studies revealed a white blood cell count of 16,300/mm^3 (16.3 × 10^9/L), aspartate aminotransferase 147 IU/L (2.44 μkat/L), alanine aminotransferase 72 IU/L (1.2 μkat/L), alkaline phosphatase 303 IU/L (5.05 μkat/L), and normal bilirubin. Serum creatinine is currently stable at 1.2 mg/dL (106 μmol/L).

What factors suggest empiric antifungal therapy should be changed in this patient?

What other procedures should be recommended in this patient to improve management and response to antifungal therapy?

Table 86–4

Therapeutic Approach to Opportunistic Invasive Fungal Infections

Mycoses	Recommended Treatment Regimens	Comments
Candidiasis		
Catheter-related and acute hematogenous	Echinocandin[a] **OR** Fluconazole 12 mg/kg loading dose, then 6–12 mg/kg/day IV every 24 hours (400–800 mg/day) adjusted for renal function[b] **OR** Voriconazole 6 mg/kg every 12 hours IV for 1 day, then 3 mg/kg every 12 hours IV *Second line:* Lipid amphotericin B formulation 3–5 mg/kg /day IV[c] **OR** Amphotericin B 0.7 mg/kg/day IV **OR** Amphotericin B + fluconazole	Treat for 14 days after the last positive blood culture and resolution of signs and symptoms; catheter should be removed whenever possible. Patients can be switched to oral fluconazole when clinically stable if isolate is susceptible. Echinocandins and amphotericin B are preferred agents for fluconazole-resistant species. Voriconazole appears to be effective against fluconazole-resistant *C. krusei*.
Empirical therapy in neutropenic patient	Fluconazole 6–12 mg/kg/day (low risk) adjusted for renal function[b] **OR** Liposomal amphotericin B 3 mg/kg IV every 24 hours **OR** Echinocandin **OR** Amphotericin B 0.7 mg/kg IV every 24 hours	Antifungals with coverage of *Aspergillus* spp. should be used in higher risk patients or prolonged neutropenia (ie, > 2 weeks).
Urinary candidiasis	Fluconazole 200 mg IV or orally for 7–14 days **OR** Amphotericin B 0.3 mg/kg/day IV for 1–7 days	Asymptomatic candiduria does not require therapy.
Cryptococcosis		
Pulmonary Isolated	Fluconazole 6 mg/kg/day IV or PO for 6–12 months adjusted for renal function[b]	
Severe Pulmonary Infection and Meningitis	*Induction:* Amphotericin B 1 mg/kg/day IV + flucytosine 100 mg/kg/day orally divided every 6 hours for 2 weeks adjusted for renal function[c] *Consolidation:* Fluconazole 6–12 mg/kg/day for 10 weeks adjusted for renal function[b] *Second line:* Fluconazole + flucytosine for 2 weeks, then fluconazole for 10 weeks adjusted for renal function[b,c] **OR** Amphotericin + fluconazole for 2 weeks, then fluconazole for 10 weeks adjusted for renal function[b] **OR** Liposomal amphotericin B 5 mg/kg/day IV for 2 weeks, then fluconazole for 10 weeks adjusted for renal function[a]	Therapeutic drug monitoring is required for safe use of flucytosine, see Table 84–3. Echinocandins have no activity against cryptococci. Use of flucytosine–amphotericin B combination therapy was associated with faster CSF sterilization and improved survival. Similar benefits were not observed with combination fluconazole–amphotericin B regimens.
Aspergillosis	Voriconazole 6 mg/kg IV every 12 hours × 2 doses, then 4 mg/kg IV every 12 hours Voriconazole 4 mg/kg oral every 12 hours **OR** Isavuconazole 200 mg (372 mg of isavuconazonium prodrug) every 8 hours for two days, then 200 (372 mg isavuconazonium prodrug) daily ***ALTERNATIVES*** Lipid formulations of amphotericin B **OR** Echinocandin[a] **OR** Posaconazole 300 mg every 12 hours IV day 1, then 300 mg IV daily Posaconazole delayed-release tablet 300 mg twice daily, day 1, then 300 mg daily Posaconazole suspension 200 mg by mouth four times daily for 14 days, then 400 mg PO twice daily **OR** Combination therapy, typically echinocandin plus triazole	Voriconazole can be administered as oral therapy in patients taking oral medications. However, patients with suspected aspergillosis should initially be started on IV therapy. Therapeutic drug monitoring should be considered in patients receiving voriconazole (any formulation) or posaconazole suspension, see Table 84–3. Posaconazole tablets and IV formulations have less pharmacokinetic variability but some patients may still benefit from TDM. Combination therapy with triazole and echinocandin associated with improved survival in patients with galactomannan-diagnosed infection. *A. terreus* and *A. flavus* should be considered resistant to amphotericin B.

[a] Anidulafungin 200 mg loading dose day 1, then 100 mg daily, caspofungin 70 mg loading dose day 1, then 50 mg daily; or micafungin 100 mg daily.

[b] Fluconazole renal dosing adjustments: CrCl > 50–90 mL/min (0.83–1.50 mL/s), 100% of dose; CrCl 10–50 mL/min (0.17–0.83 mL/s), 50% of dose; CrCl < 10 mL/min (0.17 mL/s) 50%.

[c] Flucytosine renal dosing adjustments: CrCl > 50–90 mL/min (0.83–1.50 mL/s), 25 mg/kg every 12 hours; CrCl 10–50 mL/min (0.17–0.83 mL/s), 25 mg/kg every 12–24 hours; CrCl < 10 mL/min (0.17 mL/s) 25 mg/kg every 24 hours. Therapeutic drug monitoring is required for safe use of flucytosine (see Table 84–3).

CSF, cerebrospinal fluid; IV, intravenous; PO, oral; TDM, therapeutic drug monitoring.

therapy is ineffective. Triazole antifungals (fluconazole, itraconazole solution, or voriconazole), echinocandins, or IV amphotericin B (in cases of unresponsive infections because of antifungal resistance, most commonly to fluconazole) are effective treatment options. Parenteral therapy should be used in patients who are unable to take oral medications.

OUTCOME EVALUATION

The outcome of invasive candidiasis is influenced by the timely administration of appropriately dosed antifungal therapy appropriate for the *Candida* species isolated, as well as early source control (eg, removal of infected catheters) that reduces the risk of progression to sepsis. To ensure appropriate and cost-effective use of diagnostics and treatments for invasive candidiasis, some institutions have devised "*Candida* treatment bundles" to ensure logical evidence-based interventions in the management of invasive candidiasis and support antifungal stewardship. Examples of elements of treatment bundles for invasive candidiasis are highlighted at the end of the chapter (see Patient Care Process section).

PROPHYLAXIS

Prophylaxis for invasive candida infections has been evaluated in high-risk populations such as those with neutropenia, hematopoietic stem cell transplant, or nonneutropenic patients requiring hospitalization in an intensive care unit. Fluconazole (400 mg/day) has been studied as a prophylactic regimen to prevent invasive candidiasis in patients with prolonged (> 2 weeks) neutropenia.[21] Placebo-controlled, prospective randomized trials performed in the 1990s demonstrated that fluconazole was effective in reducing the frequency, morbidity, and, in some trials, mortality due to invasive candidiasis in neutropenic patients if administered until marrow recovery. However, the major limitation with fluconazole is its lack of mold coverage needed for high-risk patients with prolonged (ie, > 3 weeks) neutropenia. Itraconazole, voriconazole, posaconazole, and the echinocandin micafungin have demonstrated a benefit in reducing the incidence of invasive candidiasis when used for prophylaxis in hematopoietic cell transplant recipients until engraftment; however, all of the drugs have limitations with respect to prolonged administration in high-risk patients. Therefore, the approach toward antifungal prophylaxis is often institution-specific depending on the patient population, epidemiology of invasive fungal infections, and options for outpatient IV drug therapy.

Use of antifungal prophylaxis for invasive candidiasis in nonneutropenic patients remains an area of controversy. Fluconazole prophylaxis has been shown to reduce the incidence but not necessarily mortality associated with invasive candidiasis in select high-risk transplant populations (eg, liver, pancreatic, or small-bowel transplantation) or subsets of ICU patients at high risk of infection (ie, neonatal intensive care).[21] Because prophylaxis can result in excessive antifungal use in lower risk patients, many experts have advocated **preemptive** (ie, starting therapy based on biomarkers of infection such as serum β-glucan) or empirical (symptoms of infection) treatment approaches in this population instead of routine prophylaxis.

A multiinstitutional prospective randomized trial of administering empirical fluconazole (800 mg/day versus placebo) in ICU patients with persistent fever failed to demonstrate significant benefits in reducing the incidence or mortality associated with invasive candidiasis.[31] Similarly, recent multiinstitutional studies that focused on ICU patients identified as "high risk" for invasive candidiasis that administered either caspofungin[32] or micafungin[33] failed to demonstrate any mortality benefit. Therefore, many questions persist regarding the optimal approach for preventing or preemptive treating invasive candidiasis in nonneutropenic ICU patients.

CRYPTOCOCCOSIS

EPIDEMIOLOGY

Cryptococcus neoformans is an encapsulated yeast that can infect normal hosts but has historically been associated with severe infections in immunocompromised patients. *C. neoformans* is divided into two varieties based on serotype: *C. neoformans* var. *neoformans* (serotypes a and d) that is associated with infections in immunocompromised patients, and *C. neoformans* var. *gattii* (serotypes b and c) that is associated with infections in healthy hosts. *C. neoformans* var. *gattii* is found predominantly in tropical and subtropical climates with eucalyptus trees and has been linked to infectious outbreaks around Vancouver Island and the US Pacific Northwest. *C. neoformans* var. *neoformans* is found worldwide and is associated with pigeon droppings and other avian excreta. Before the AIDS pandemic, cryptococcosis was a relatively uncommon disease but became a leading cause of meningitis among HIV-infected patients. Although the incidence of cryptococcal meningitis has declined in developed countries with the widespread use of highly active antiretroviral therapy (HAART), *C. neoformans* remains an important pathogen in the developing regions with high rates of AIDS and in immunocompromised patients, including transplant and cancer patients, who may present with initially indolent pulmonary forms of the infection.

CLINICAL PRESENTATION AND DIAGNOSIS

C. neoformans is acquired primarily through inhalation of the desiccated yeast particles found in the environment. Inhaled cells reach distal alveolar spaces where they gradually rehydrate and form a polysaccharide capsule that is resistant to phagocytosis. Defects in cellular immunity allow reconstitution of the protective capsule and multiplication of yeast in the lungs. Although alveolar macrophages phagocytose the yeast, containment and killing require a coordinated response between innate and adaptive humoral (complement and anticryptococcal antibodies) and T-cell–mediated host responses.[6] Deficiencies in host cell–mediated immunity allow the yeast to survive as a **facultative** intracellular pathogen in macrophages as they migrate from the lung to draining lymph nodes, leading to dissemination via the bloodstream to the meninges.

Unlike most opportunistic fungi, true virulence factors have been identified for *C. neoformans*. The capsules, including the soluble polysaccharides released from the yeast cells during infection, impair phagocytosis and binding of anticryptococcal antibodies. Primary cryptococcal infection begins in the lung, presenting as a mildly symptomatic or asymptomatic infection that resolves spontaneously or undergoes encapsulation in noncalcified lung nodules. These isolated nodules may be detected on chest X-rays during routine workup and aspirated or removed because of concerns for lung cancer.

In the immunocompromised host, infection of the lung may present with more diffuse, bilateral, and interstitial disease that mimics the presentation of *P. jiroveci (carinii)* pneumonia (PCP). Dissemination to other organs, particularly the CNS, eye, and possibly the skin, is more likely to occur in patients with severe deficits in cell-mediated immunity. Fever, cough, dyspnea, and pleural pain are common at presentation, with accompanying hypoxemia that can rapidly evolve to acute respiratory failure.

Because the features of diffuse pulmonary cryptococcosis overlap with other opportunistic pathogens, early diagnosis requires bronchoalveolar lavage or transbronchial biopsy, which can effectively diagnose 80% to 100% of cases.[34] The clinical course of diffuse cryptococcal pneumonia can be as severe as PCP, with mortality rates approaching 100% in untreated patients by 48 hours.

C. neoformans readily disseminates from the lung to the CNS, specifically the leptomeninges, and occasionally the parenchyma of the brain. The clinical characteristics of cryptococcal meningitis differ somewhat, however, between patients with and without underlying AIDS. In patients without AIDS, disease presentation is more insidious, and symptoms such as dizziness, irritability, decreased comprehension, and unstable gait may present many weeks to months before the diagnosis is established. Patients with AIDS generally present much later in the course of disease with severe meningoencephalitis.[34] The most common signs and symptoms on presentation are fever, headache, **meningismus**, photophobia, mental status changes, and seizures. CT or more tissue-sensitive imaging techniques such as magnetic resonance imaging (MRI) may reveal cerebral edema, multiple areas of enhanced nodules, or a single mass lesion (cryptococcoma). Examination of the cerebrospinal fluid (CSF) often reveals increased opening pressure upon lumbar puncture, but glucose, protein, and leukocyte levels can be normal.[34]

LABORATORY DIAGNOSIS

Clinical diagnosis is confirmed by cultures from the blood, CSF, or other clinically relevant fluids or tissue. *C. neoformans* can be directly visualized in the CSF when stained with India Ink, which is excluded by the yeast capsule (Figure 86–3B). However, infection is most frequently diagnosed by the detection of cryptococcal antigen in either serum or CSF, which has high sensitivity and specificity (> 95%) and correlates with fungal burden.[34] A positive serum antigen test of greater than 1:4 strongly suggests cryptococcal infection, and greater than or equal to 1:8 is indicative of active disease. Antigen titers in serum are positive in 99% of patients with cryptococcal meningitis and often exceed 1:2048 in patients with AIDS.[34] However, the time course of cryptococcal antigen elimination is unknown, and a positive test result can persist for many years. Changes in the CSF cryptococcal antigen titers have limited value in the monitoring of drug therapy for cryptococcal meningitis, although it is expected that a decrease should be seen after 2 or more weeks of antifungal therapy.[34]

TREATMENT

Cryptococcal meningitis is fatal if left untreated. Because pneumonia frequently precedes dissemination of disease and subsequent meningitis, all patients with culture-, histopathology-, or serology-proven disease should receive antifungal therapy. In patients with isolated pulmonary cryptococcosis, fluconazole is generally considered to be the therapy of choice (see Table 86–2).[34] Alternatively, itraconazole, voriconazole, or combination therapy (fluconazole plus flucytosine) has also been used with some success, but these regimens are generally considered inferior to amphotericin B and are recommended only for persons unable to tolerate or unresponsive to standard treatment. Echinocandins do not have activity against *C. neoformans*.

Disseminated or CNS cryptococcosis requires a more aggressive treatment approach. Pretreatment predictors of a poor prognosis include the following:

- Progressive underlying disease or immune dysfunction
- Abnormal mental status at the time of presentation
- Increased opening pressure on lumbar puncture (> 260 mm H_2O [2.55 kPa])
- High fungal burden as reflected by a CSF antigen titer (in AIDS patients) of greater than 1:2048

Clinical trials performed by the National Institute of Allergy and Infectious Diseases (NIAID) and Mycoses Study Group have defined the standard treatment regimen for cryptococcal meningitis consisting of 2 weeks of induction antifungal therapy with combination amphotericin B (0.7 mg/kg/day) plus flucytosine (100 mg/kg/day) for cryptococcal meningitis, followed by consolidation therapy with fluconazole (400 mg daily) for 8 weeks (see Table 86–2).[34] However, other combinations of either fluconazole plus flucytosine or fluconazole plus amphotericin B were sometimes recommended due to difficulties in obtaining flucytosine (especially in developing countries) due to both the high cost of the medication and toxicity (such as myelosuppression, hepatic dysfunction, renal dysfunction, and cardiac toxicity) (see Table 86–2).

KEY CONCEPT In a landmark study addressing which combination is best for cryptococcal meningitis, significantly fewer deaths were observed in patients receiving amphotericin B plus flucytosine compared to patients receiving amphotericin B alone, or a combination of amphotericin B plus fluconazole.[35] Notably, the amphotericin B–flucytosine combination was associated with more rapid clearance of yeast from the CSF versus other regimens.

PROPHYLAXIS

Fluconazole (200 mg/day) is recommended as maintenance therapy for life in patients with persistent underlying immune dysfunction to prevent recurrent cryptococcal meningitis.[34] Available data suggest it is safe to discontinue maintenance therapy in AIDS patients who have had a sustained immunologic response on effective antiretroviral therapy (ie, $CD4^+$ count greater than 100 cells/microliter [100×10^6/L] with undetectable or very low viral RNA) if they have received at least 12 months of antifungal therapy.[34] Occasionally, initiation of HAART can result in the reactivation of a subclinical, immunologic manifestation of cryptococcal infection (or other opportunistic infections). Manifestations of this **immune reconstitution inflammatory syndrome (IRIS)** may include exacerbations of meningitis or necrotizing pneumonia. Antifungal therapy plus a nonsteroidal anti-inflammatory agent or prednisone has been used successfully in patients with cryptococcal-associated IRIS.[36] However, there are few studies that have evaluated treatment options for the control of IRIS. To avoid this potential complication, initiation of HAART is typically delayed by 2 to 10 weeks.

INVASIVE ASPERGILLOSIS

EPIDEMIOLOGY

KEY CONCEPT Invasive mold infections, most frequently due to *Aspergillus* species but occasionally caused by *Fusarium* spp. or Mucorales, may cause infection in patients undergoing intensive cancer chemotherapy required for hematologic malignancies, and prolonged immunosuppression following hematopoietic and solid organ transplantation.[37] The four most common *Aspergillus* species that cause invasive infection in humans are *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus terreus*, and *Aspergillus niger*. Of these four species, *A. fumigatus* accounts for most infections. However, identification of *Aspergillus* mold in culture to the species level when cultures are available is still important because *Aspergillus terreus* and *Aspergillus flavus* display relatively higher MICs

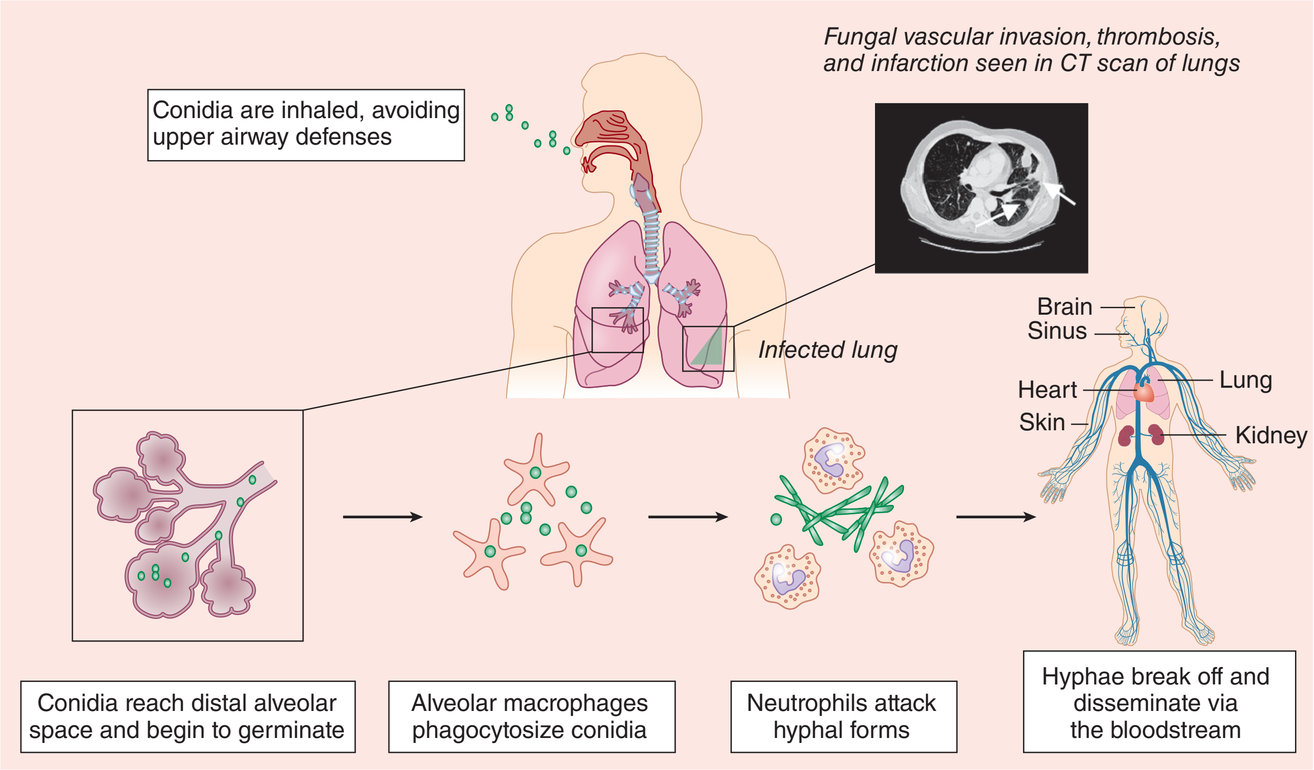
Conidia are inhaled, avoiding upper airway defenses
Fungal vascular invasion, thrombosis, and infarction seen in CT scan of lungs
Infected lung
Brain
Sinus
Heart
Skin
Lung
Kidney
Conidia reach distal alveolar space and begin to germinate
Alveolar macrophages phagocytosize conidia
Neutrophils attack hyphal forms
Hyphae break off and disseminate via the bloodstream

FIGURE 86–4. Pathogenesis of invasive aspergillosis (IA).

(resistance) to amphotericin B. Additionally, less common mold infections such as fusariosis and mucormycosis often present with similar clinical and radiographic features as aspergillosis but require different treatment approaches due to their inherent resistance to many antifungal agents. Early and accurate diagnosis of IA improves the outcome of infection, reducing mortality rates by 30% to 50% with the timely administration of effective antifungal therapy.[37]

CLINICAL PRESENTATION AND DIAGNOSIS

The pathogenesis of IA is defined largely by the underlying immune dysfunction of the host. The most common route of acquisition for *Aspergillus* is through the respiratory tract. Conidia dispersed in air currents are continuously inhaled through the sinuses and mouth and penetrate down to distal alveolar spaces (see Figure 86–4). Most conidia are rapidly phagocytosed and removed by resident macrophages and neutrophils in the upper and lower respiratory tract.[6] However, macrophage function may be suppressed following transplantation, cytotoxic chemotherapy, or in patients who have received high-dose corticosteroid therapy. Conidia that escape phagocytosis begin to germinate into hyphal forms that invade blood vessels or contiguous tissues or bone (in sinuses), resulting in hemorrhage and/or infarction and coagulative necrosis. Once in the bloodstream, viable hyphal fragments can break off and disseminate to distal organs, including the brain. Control of the infection at this stage requires development of an adaptive T-helper cell type 1 (TH1) or type 17 (TH17) response to enhance the fungicidal activity of neutrophils against hyphal elements.[6] Patients with dysregulated, suppressed T-cell–mediated immunity, or prolonged neutropenia are unable to control fungal growth and are at high risk for dissemination of the infection to other organs, including the brain. Without early diagnosis and antifungal therapy, IA in persistently immunosuppressed patients is uniformly fatal.

Signs and symptoms of IA are often subtle in the immunocompromised host. Fever is common but nonspecific for infection and may be accompanied by pleuritic chest pain, cough, hemoptysis, and/or friction rub.[37] Neurologic signs, including seizures, hemiparesis, and stupor, may be present in patients with dissemination to the brain. Cutaneous plaques or papules characterized by a central necrotic ulcer or eschar occur in up to 10% of patients with disseminated disease; however, concomitant blood cultures are often negative. Chest radiographs cannot detect early forms of disease and may remain negative in up to 10% of patients within 1 week of death. Nodular lesions detected by high-resolution computed tomography (HRCT), along with fever, are often the first indication of invasive pulmonary aspergillosis in severely immunocompromised patients. CT images of the lung often reveal wedge-shaped or nodular lesions, surrounded by intermediate attenuation called the "halo sign" (Figure 86–5). These early lesions on CT scans represent hemorrhage and

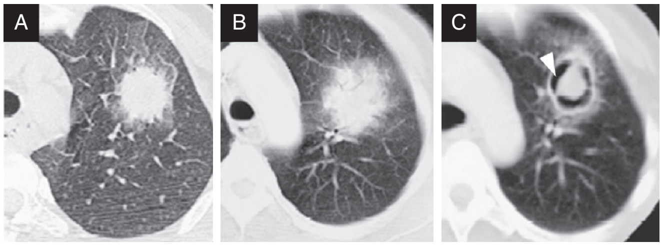

FIGURE 86–5. Radiographic evolution of invasive pulmonary aspergillosis in a neutropenic patient. **A:** Early halo sign of ground glass opacity surrounding nodular lesions. **B:** Nonspecific infiltrate of increased diameter. **C:** Air-crescent sign observed with neutrophil recovery, cavitation of infected lung in walled off cavity with air (*arrowhead*).

Patient Encounter 3: Invasive Aspergillosis

A 37-year-old woman with acute myeloid leukemia who received autologous hematopoietic stem cell transplantation presents to the clinic 36 days after transplant with complaints of fever. On laboratory examination, she is noted to have an alanine aminotransferase of 153 IU/L (2.54 μkat/L), aspartate aminotransferase 127 IU/L (2.11 μkat/L), and total bilirubin of 1.8 mg/dL (31 μmol/L). The patient has an absolute neutrophil count of 770 (770×10^6/L). Her current medications include tacrolimus 5 mg twice daily (most recent level: 15 ng/mL [15 mcg/L; 18.3 nmol/L]), prednisone 10 mg daily, levofloxacin 500 mg daily, fluconazole 200 mg/day, and valacyclovir 500 mg twice daily. A CT scan of the chest reveals a single dense pleural-based lung nodule in the left lung. A serum galactomannan test is reported to be positive (index 0.8, positive when > 0.5). The primary service wishes to start isavuconazole.

What are the patient's risk factors and signs that suggest she has an invasive fungal infection?

What potential advantages are there to choosing isavuconazole as opposed to voriconazole?

If the patient's infection appears to resolve and he continues to take isavuconazole for months while tapering immunosuppression, what are some of the toxicities potentially associated with prolonged isavuconazole therapy?

edema surrounding an infarcted blood vessel. Despite "effective" antifungal therapy, lesions on CT scan may continue to increase in size in neutropenic patients until neutrophil counts recover, at which time they begin to cavitate, forming the "air-crescent sign" on chest radiographs, indicative of resolving infection. Immunocompromised patients on fluconazole with progressive sinus or pulmonary disease by radiography should be considered to have a possible mold infection and receive antifungal therapy directed (at minimum) against *Aspergillus* species.

LABORATORY DIAGNOSIS

Like other invasive mycoses, definitive diagnosis of aspergillosis requires histopathologic evidence of hyphal invasion in tissue (see Figure 86–3C and D). However, procedures needed to establish a definitive diagnosis by sampling of suspicious lesions (eg, fine needle aspiration or open-lung thoracoscopic biopsy) are not feasible in many patients with underlying thrombocytopenia secondary to hematologic malignancies or chemotherapy. Even if **hyphae** are observed in tissue, histopathology alone cannot distinguish *Aspergillus* from other angioinvasive septate molds, such as *Fusarium*, which have different patterns of antifungal susceptibility (see Table 86–1). Therefore, respiratory and/or wound cultures (if cutaneous or sinus/hard palate lesions are present) are important factors in the modification of empiric antifungal therapy.

Respiratory cultures, including sputum, bronchial washings, or bronchoalveolar lavage, have a low sensitivity for diagnosis of IA but a higher positive predictive value in severely immunocompromised patients. Therefore, a negative bronchoalveolar lavage culture does not rule out invasive pulmonary aspergillosis, but a positive culture in a high-risk patient (eg, allogeneic hematopoietic cell transplant patients) indicates pulmonary aspergillosis in at least 60% to 80% of such patients. Blood cultures have little diagnostic value for IA but may reflect true disease with *A. terreus*. Patients with limited lung involvement or on prophylactic or empiric antifungal therapy may continue to be culture negative for *Aspergillus* species, despite the appearance of progressing disease. Therefore, negative cultures are never the sole indication for stopping antifungal therapy in patients with suspected or proven aspergillosis.

Considerable effort has been focused in the last decade to develop non–culture-based laboratory methods (antigen detection, PCR) for the diagnosis of IA. The hope is that these surrogate tests could detect early evidence of *Aspergillus* infection before significant target organ damage eventually detected by CT scans occurs. Currently, most centers use an ELISA-based assay for the detection of a polysaccharide component of the *Aspergillus* cell wall called galactomannan. Although several large prospective studies have found that the sensitivity and specificity of the assay approaches 90% in neutropenic patients with hematologic malignancies, the median time span between galactomannan detection and clinical signs and symptoms of IA averages less than 6 days. The sensitivity of the galactomannan may be enhanced if the test is performed on bronchial lavage fluid collected during bronchoscopy. Other factors such as patient immune status (higher sensitivity in neutropenic versus nonneutropenic patients) antibacterial therapy, antifungal prophylaxis, and diet may affect the sensitivity and specificity of the galactomannan test.[37] For example, false-positive results are reported more frequently in pediatrics, following the ingestion of certain cereals, pastas, nutritional supplements, or soy sauce. Piperacillin–tazobactam therapy was also associated with false-positive galactomannan tests in the past, but more recent studies have suggested that galactomannan contamination of the antibiotic is now uncommon.[39]

Increasing galactomannan levels are a harbinger of breakthrough infection, and declining galactomannan concentrations are an early indicator of response to treatment. However, antifungal therapy is rarely stopped in patients once the serum galactomannan becomes negative, especially in persistently immunosuppressed patients. Hence, the galactomannan test and other non–culture-based strategies, such as serum β-glucan, which can also be detected during *Aspergillus* infection, serve as complementary methods to confirm results from microbiologic, histopathologic, and radiographic investigations directed toward diagnosing IA.[40]

In the past, antifungal susceptibility testing was not routinely recommended for *Aspergillus* spp. in treatment guidelines because of limited data to support the recommendation. *Aspergillus terreus* and *A. flavus* were the major concerns because of their intrinsic resistance to amphotericin B. However, more recently multi-triazole-resistant *Aspergillus fumigatus* spp. have been reported in China, Canada, the United States, and several European countries, with especially high levels in the Netherlands and the United Kingdom.[38] These trends suggest that MIC testing (when isolates can be grown from patient) may be increasingly necessary to confirm susceptibility to first-line antifungal treatments.

TREATMENT

Four comparative randomized controlled clinical trials have evaluated antifungal therapies for the treatment of diagnosis-proven IA. Voriconazole or isavuconazole are considered in consensus treatment guidelines to be the first-line antifungal for IA (see Table 86–2), as voriconazole has been shown to be associated with improved patient survival as compared to amphotericin B.[36] However, patients who are intolerant to triazoles, have ongoing hepatotoxicity issues, or have received voriconazole or posaconazole prophylaxis in the recent past may initially be treated with a liposomal amphotericin B formulation. Lipid amphotericin B formulations are recommended over echinocandins because of their better coverage of Mucorales molds, which sometimes break through on *Aspergillus*-active therapy because of their intrinsically higher resistance to voriconazole and other antifungals. Echinocandins are not typically recommended as a frontline monotherapy regimen for invasive aspergillosis due to poorer responses rates in nonrandomized trials compared to triazoles.[41] Once the infection has stabilized and diagnosis is clarified, patients can be transitioned back to an intravenous or oral triazole for the completion of therapy.

Isavuconazole is a newer triazole unique from other agents because it is administered as a prodrug, isavuconazonium, which is rapidly cleaved in vivo to the active drug (isavuconazole) and an inactive prodrug cleavage product (BAL8728). In a phase 3 trial, patients with proven or probable aspergillosis treated with isavuconazole achieved similar clinical response rates as a standard voriconazole regimen, but with significantly fewer hepatic, skin, and visual adverse effects.[9] Isavuconazole has also been reported to be as effective as amphotericin B–based treatment for mucormycosis. Therefore, isavuconazole appears to be a promising alternative to voriconazole for the treatment of IA.

Multiple studies in vitro and in animal models, as well as small clinical studies, have suggested that administration of an echinocandin with a triazole such as voriconazole may be synergistic and improve survival in IA over monotherapy, but prospective clinical studies, until recently, have been lacking. A multicenter, randomized clinical trial comparing voriconazole–anidulafungin combination therapy to voriconazole monotherapy for proven or probable aspergillosis reported a trend in improved 6-week survival for patients randomized to combination therapy, that was significant among a post hoc analyzed group of patients whose disease was diagnosed with galactomannan antigen but not culture (reflecting patients with earlier diagnosed disease).[39] Nevertheless, the failure of the study to meet its primary endpoint objective raises lingering questions about the efficacy of combination therapy, and many clinicians reserve the use of combination regimens for patients with extensive disease (ie, multifocal or bilateral pneumonia, disseminated infection) or in cases of suspected breakthrough infection.

PROPHYLAXIS

Primary antifungal prophylaxis against *Aspergillus* is recommended in guidelines for some groups of patients with baseline risk of IA that approaches or exceeds 10%. These subgroups typically include patients with acute myeloid leukemia undergoing remission induction chemotherapy, or allogeneic hematopoietic stem cell transplants with graft-versus-host disease. Depending on the institution and local epidemiology, other groups of patients may also be considered candidates for prophylaxis. **KEY CONCEPT** Posaconazole was shown in two prospective randomized trials to reduce Aspergillus-associated death in patients with acute high-risk leukemia and reduce mold infections in patients with graft-versus-host disease following hematopoietic stem cell transplantation. Similar data are available for voriconazole, HSCT, but no significant advantage was observed compared to standard fluconazole prophylaxis plus intensive galactomannan monitoring in the hematopoietic stem cell transplant patients.[42]

Patient Care Process

Collect Information:

- Review the medical history, physical assessment findings, and recent laboratory results of the patient to assess current immunological status and organ function.
- Perform a medication history for use of prescription and nonprescription medications. Identify allergies to medications and other substances.

Assess the Information:

- Analyze patient's medication profile for potential drug interactions with triazole antifungals using an updated computerized drug interaction database.
- Confirm prescribed antifungal therapy is the appropriate spectrum for likely fungal pathogen(s).
- Review whether modifiable risk factors affecting treatment outcome (eg, timely administration of antifungal therapy, catheter removal in patients with invasive candidiasis) have been addressed.
- Ensure prescribed antifungal dose is appropriate for patient age, weight, renal, and/or hepatic function.

Develop a Care Plan:

- Confirm prescribed antifungal therapy is the appropriate spectrum for likely fungal pathogen(s).
- Ensure prescribed antifungal dose is appropriate for patient age, weight, renal, and/or hepatic function.
- Prepare a strategy for therapeutic drug monitoring (TDM) for antifungals with unpredictable pharmacokinetics (eg, itraconazole, voriconazole, and posaconazole suspension).
- Anticipate how antifungal therapy can be modified when culture results become available, intolerance to the drug of first choice, or if there is consideration of switching from IV to oral therapy.

Implement the Care Plan:

- Educate the patient about potential for medication adverse effects, importance of taking medications correctly, and potential for drug interactions.
- Review TDM results, microbiology and susceptibility information if available, and treatment response parameters to ensure patient is on correct antifungal at the best dose.
- Streamline antifungal therapy if possible and/or switch to oral therapy if patient is clinically stable.

Follow-up: Monitor and Evaluate:

- Monitor patient clinical, laboratory, and radiographic parameters to assess effectiveness and safety of therapy.
- Reevaluate potential for serious drug interactions.
- Consider TDM if patient has changes to medication profile, change in clinical status, or new-onset toxicity.

OUTCOME EVALUATION

Response to antifungal therapy in invasive molds is slow and difficult to judge by clinical signs alone. Resolution of fever and eventual clearing of CT scans (in the case of lung infections) are indications of response to antifungal therapy. Toxicity associated with antifungal therapy is similar in these patients as in those described earlier. Patients who develop breakthrough infections on voriconazole should also undergo a careful clinical workup for other invasive mold pathogens such as mucormycosis (see Table 86–1), which are not susceptible to voriconazole. In most cases, antifungal therapy may be continued until immunosuppression has resolved.

Abbreviations Introduced in This Chapter

AIDS	Acquired immunodeficiency syndrome
ARDS	Acute respiratory distress syndrome
CNS	Central nervous system
CrCl	Estimated creatinine clearance
CSF	Cerebrospinal fluid
CT	Computed tomography
CYP	Cytochrome P450 isoenzyme
ELISA	Enzyme-linked immunosorbent assay
FISH	Fluorescent in situ hybridization
HAART	Highly active antiretroviral therapy
HRCT	High-resolution computed tomography
IA	Invasive aspergillosis
ICU	Intensive care unit
IRIS	Immune reconstitution inflammatory syndrome
IV	Intravenous
MALDI-TOF	Matrix-assisted laser desorption/ionization time of flight
MIC	Minimum inhibitory concentration
NIAID	National Institute of Allergy and Infectious Diseases
PCP	*Pneumocystis jiroveci (carinii)* pneumonia
PCR	Polymerase chain reaction
PMN	Polymorphonuclear cell
TDM	Therapeutic drug monitoring

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Human Immunodeficiency Virus Infection

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and Fidelia Bernice

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the routes of transmission for human immunodeficiency virus (HIV) and its natural disease progression.
2. Identify typical and atypical signs and symptoms of acute and chronic HIV infection.
3. Identify the desired therapeutic outcomes for patients living with HIV.
4. Recommend appropriate first-line pharmacotherapy interventions for patients with HIV infection.
5. Describe the components of a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for HIV infection.
6. Educate patients about the disease state, appropriate lifestyle modifications, and drug therapy required for effective treatment.

INTRODUCTION

Human immunodeficiency virus (HIV) is the virus that causes acquired immunodeficiency syndrome (AIDS). HIV primarily targets CD4$^+$ T-lymphocytes, which are critical to proper immune system function. If left untreated, most patients experience a prolonged asymptomatic period followed by rapid, progressive immunodeficiency. AIDS is defined by a CD4$^+$ cell count below 200 cells/mm^3 (200 × 10^6/L), a CD4$^+$ cell percentage of total lymphocytes less than 14% (0.14), or the presence of one of the Centers for Disease Control and Prevention (CDC) AIDS-defining conditions, such as pneumocystis pneumonia, and Kaposi sarcoma, and HIV-related encephalopathy.[1]

Fortunately, significant progress in research and drug development over the past several decades has drastically improved both the length and quality of life of persons living with HIV (PLWHIV), transforming HIV into a chronic, manageable disease state. Current efforts can now focus on care connection and retention, long-acting therapies and regimen simplification strategies, and novel prevention strategies.

EPIDEMIOLOGY

As of 2019, approximately 38 million people globally are living with HIV, of which 1.7 million were newly infected and an estimated 7.1 million unaware of their infection. Approximately 70% of these cases are in sub-Saharan Africa and globally, women and girls accounted for 48% of all new HIV infections in 2019. In 2019, approximately 690,000 people worldwide died from AIDS-related illnesses, which is a 39% decrease since 2010.[2]

In the United States, at the end of 2018, an estimated 1 million adults and adolescents (persons aged 13 years and older) were living with diagnosed HIV infection. From 2014 to 2018, the number of diagnoses among male and female adults and adolescents decreased, while diagnoses for transgender male-to-female and transgender female-to-male increased. The highest rate of diagnoses per age-group was in those aged 25 to 29 years; the highest rate by race/ethnicity was in Blacks and African Americans. Male-to-male sexual contact accounted for the highest percentage of diagnoses by transmission category.[3]

ETIOLOGY, TRANSMISSION, AND PATHOPHYSIOLOGY

Etiology

HIV is a retrovirus and member of the genus *Lentivirus*. Human infection is believed to have originated from a type of chimpanzee in Central Africa. There are two molecularly and serologically distinct but related types of HIV: HIV-1 and HIV-2. HIV-1 is the most widespread, whereas HIV-2 is found predominantly in West Africa. This distinction is important as certain antiretrovirals cannot be used to treat HIV-2.

Transmission

HIV is primarily transmitted by sexual contact, by contact with blood or blood products, and from mother to child during gestation, delivery, or breastfeeding. Specifically, HIV is transmitted through certain body fluids—blood, semen, preseminal fluid, rectal fluids, vaginal fluids, and breast milk—which requires contact with a mucous membrane, damaged tissue, or be directly injected into the bloodstream. The risk of acquiring HIV varies depending on the type and frequency of exposure or behavior, such as injection drug use (needle or equipment sharing), unprotected sexual intercourse with high-risk individuals, and the presence of other sexually transmitted infections (STIs) (eg, *chlamydia*, *gonorrhea, and syphilis*).

The most common method for transmission of HIV is receptive anal and vaginal intercourse, with the highest probability of transmission being with receptive anal intercourse (138 infections per 10,000 exposures).[4] Parenteral transmission of HIV primarily occurs through injection drug use by sharing contaminated needles or injection-related supplies and accounts for about 1 in 15 diagnoses in the United States.[3] Less than 1% of all cases of HIV infection occur as a result of transfusions of contaminated blood,

blood products, or infected transplant organs.[3] Occupational HIV transmission is extremely rare, with the average risk of infection after a needle stick of cut exposure estimated at 0.23%.[5] Across all of the aforementioned modes, the probability of transmission increases when the infected partner (or source) has a high level of viral replication and subsequent high viral load. Transmission risk is also heightened when the uninfected partner has ulcerative disease, compromised mucosal surfaces, or (in men) has not been circumcised.

Perinatal infection (also known as vertical transmission or mother-to-child transmission [MTCT]) can occur during gestation, at or near delivery, and during breastfeeding. In the absence of specific interventions, the risk of MTCT up to and including delivery ranges from 15% to 30%. Breastfeeding can further increase the risk by 5% to 15%.[6] Risk increases significantly with increasing maternal viral load. It is important to treat women living with HIV during pregnancy regardless of the clinical stage of disease or CD4 count and to retain them for postpartum care.

Pathophysiology

Understanding the life cycle of the virus is important to recognize how antiretroviral drugs are combined for optimal therapy (**Figure 87–1**). Once HIV enters the body, a surface envelope glycoprotein, gp120, binds to CD4 receptors found on the surface of dendritic cells, T-lymphocytes, monocytes, and macrophages. This binding triggers a conformational change that allows further binding to other chemokine receptors on the cell surface (C-C chemokine receptor type 5 (CCR5) and/or C-X-C chemokine receptor type 4 (CXCR4)). Greater than 95% of newly infected patients have viruses that preferentially use CCR5 to enter the cell, and most patients with advanced disease have viruses that preferentially use CXCR4 to enter the cell.

After the virus has attached to CD4 and chemokine receptors, another viral glycoprotein, gp41, assists with viral fusion to the cell and internalization of the viral contents. The viral contents include single-stranded ribonucleic acid (RNA), an RNA-dependent deoxyribonucleic acid (DNA) polymerase (also known as **reverse transcriptase**), and other enzymes. Using the single-stranded viral RNA as a template, reverse transcriptase synthesizes a complementary strand of DNA. The single-stranded viral RNA is removed from the newly formed DNA strand by ribonuclease H, and reverse transcriptase completes the synthesis of double-stranded DNA. The viral reverse transcriptase enzyme is highly error-prone and many mutations occur in the conversion of RNA to DNA, allowing HIV to rapidly develop drug resistance under selective pressure.

Chronic infection is established when the double-stranded DNA migrates to the host cell nucleus and is integrated into the host cell DNA by the viral enzyme **integrase**. Viral replication begins when the host CD4 cell becomes activated in the presence of antigens or cytokines. Host RNA polymerase transcribes viral DNA into genomic RNA and messenger RNA. After exiting the nucleus, the messenger RNA is translated into viral proteins using the host cell's ribosomes. The HIV **protease** enzyme cleaves large polypeptides into smaller functional proteins which, along with the viral genome, are assembled into immature virions along the

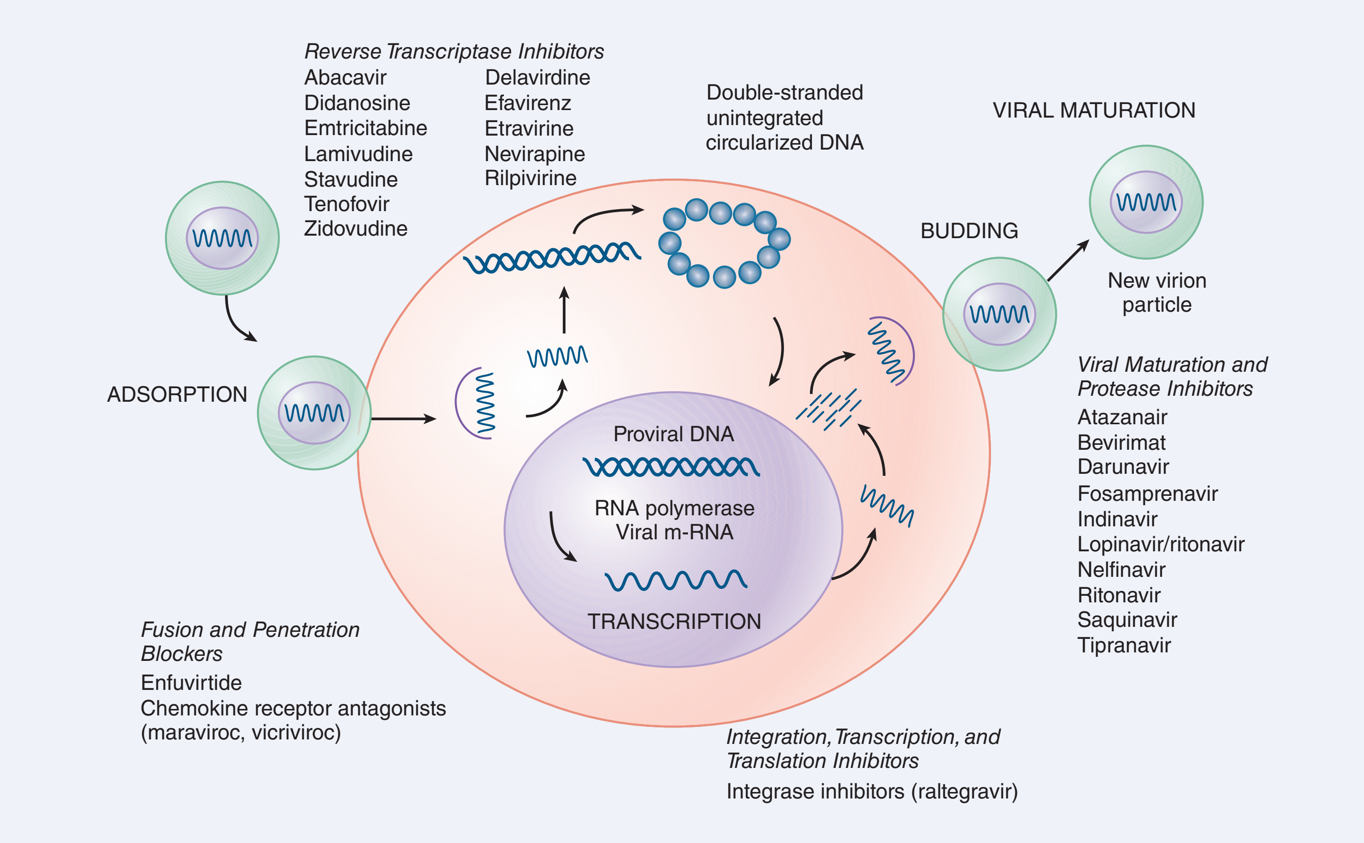
Reverse Transcriptase Inhibitors
Abacavir
Didanosine
Emtricitabine
Lamivudine
Stavudine
Tenofovir
Zidovudine
Delavirdine
Efavirenz
Etravirine
Nevirapine
Rilpivirine
Double-stranded unintegrated circularized DNA
VIRAL MATURATION
BUDDING
New virion particle
ADSORPTION
Viral Maturation and Protease Inhibitors
Atazanair
Bevirimat
Darunavir
Fosamprenavir
Indinavir
Lopinavir/ritonavir
Nelfinavir
Ritonavir
Saquinavir
Tipranavir
Proviral DNA
RNA polymerase
Viral m-RNA
TRANSCRIPTION
Fusion and Penetration Blockers
Enfuvirtide
Chemokine receptor antagonists (maraviroc, vicriviroc)
Integration, Transcription, and Translation Inhibitors
Integrase inhibitors (raltegravir)

FIGURE 87–1. Life cycle of HIV and targets for antiretroviral drugs. (From Anderson PL, Kakuda TN, Fletcher CV. Human immunodeficiency virus infection. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill; 2014; with permission.)

internal side of the cell's lipid bilayer. As the virion buds from the cell, it acquires a lipid envelope and surface proteins from the host cell. After budding, the virus continues final assembly and maturation, which then goes on to infect new CD4 cells. During the early stages of infection, approximately 10 billion virions can be produced each day. Most of the cells containing these viruses will be lysed as a result of budding virions, cytotoxic T-lymphocyte destruction, or apoptosis. However, HIV will be protected within some cells (macrophages, T cells in lymph nodes), which can stay dormant for years.

The initial immune response against HIV is relatively effective; however, it is unable to completely clear the infection, and the patient enters a latent, asymptomatic, or mildly symptomatic stage lasting 5 to 15 years. During this time, a high rate of viral replication can be seen in the lymph nodes but ultimately can occur in all sites of the body including protected sites such as the central nervous system (CNS) and genitalia. Replication is evident by a rise in circulating, detectable viral RNA, or viremia. It should be noted that this is a vulnerable period, whereby the infected, asymptomatic individual is often at high risk for transmitting the virus. Eventually, immune deficiency occurs when the body is no longer able to replenish helper T cells at a rate equal to that at which HIV is destroying them resulting in a progressive decline in the number of circulating CD4 lymphocytes.

KEY CONCEPT The goal of therapy is to maximally and durably suppress HIV replication to restore and preserve immune system function and minimize morbidity and mortality.

CLINICAL PRESENTATION AND DIAGNOSIS

HIV testing may involve blood draws, finger pricks, or oral swabs. Certain modalities are used only for screening, while others are required for confirmatory diagnosis. Accuracy of the tests is contingent upon both the specimen type and the target for detection. Antigen tests detect a HIV capsid protein called p24, which is highly specific and typically the first marker to rise following infection. As antibodies develop, typically 3 to 12 weeks after infection, p24 antigen concentrations wane. Nucleic acid tests detect viral RNA and provide a quantifiable result but are less routinely used for diagnosis due to cost.

Patients who are newly infected with HIV may be asymptomatic or present with nonspecific, or "flu-like" signs and symptoms such as fever, myalgias, arthralgias, lymphadenopathy, pharyngitis, and rash. This phase is known as acute, or primary, HIV infection and occurs as the body's natural response to infection. Symptoms last for an average of 14 days following transmission. Providers should consider the possibility of HIV infection in any patient with these findings and inquire about recent high-risk sexual encounters or other high-risk exposures. In acute infection, HIV RNA concentrations in blood and the genital tract are very high, increasing the risk of transmission to others. These patients will generally have plasma HIV RNA concentrations greater than 10^6 copies/mL (10^9 copies/L) in the absence of detectable anti-HIV antibodies. Therefore, both rapid and antibody-only based HIV tests may render a false negative result during acute infection. Increased infectiousness coupled with undiagnosed HIV infection in these patients may account for a substantial proportion of sexual HIV transmission.

If patients are not identified during acute infection, most people with HIV will recover from the initial symptoms and enter a phase of chronic, asymptomatic infection. During this period of clinical latency, the virus is active but reproduces at low levels. Over time, the virus will overwhelm the immune system and patients may progress to AIDS. If not diagnosed in the acute infection phase, patients may present later in the infectious course with nonspecific symptoms such as myalgias, fatigue, unexplained weight loss, thrush, or symptoms associated with opportunistic infections.

Diagnosis of HIV begins with a fourth generation combination immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen. No further testing is required for specimens that are nonreactive. Specimens that are reactive on the initial immunoassay should be tested with an antibody immunoassay that differentiates HIV-1 from HIV-2 antibodies. Positive results of both the fourth generation immunoassay and differentiation tests confirm the diagnosis of HIV. Nonreactive or indeterminate specimens on the HIV-1/HIV-2 antibody differentiation immunoassay should be tested with an HIV-1 nucleic acid test (NAT). Positive testing results indicate the need for HIV medical care that includes additional testing such as HIV viral load and CD4 count to stage the disease and establish baseline values around which treatment goals are centered. At-home, HIV-1 test kits (eg, Home Access HIV-1 Test System, OraQuick) allow patients to self-collect blood or oral swab samples and obtain confidential results in the privacy of their home. Individuals with positive tests should contact a healthcare provider for follow-up testing. In the United States, 1 in 7 patients living with HIV are not aware of their status, thus identifying infected patients and providing referral into HIV care is critical for preventing HIV transmission.[7] Accordingly, the US CDC recommends that patients aged 13 to 64 years in all healthcare settings undergo opt-out HIV testing, meaning a separate consent form for testing is not needed after the patient has been informed that testing will be completed, at least once as part of routine care. For patients in the high-risk groups mentioned previously, HIV testing should be performed on an annual basis, and pregnant women should be tested with each pregnancy.[8]

KEY CONCEPT HIV treatment response and disease progression are determined by the following: (a) the CD4 T-lymphocyte count (CD4 count) and percentage and (b) plasma HIV RNA (viral load). The CD4 percentage is followed because the absolute count may fluctuate and does not necessarily indicate a change in the patient's condition.

TREATMENT

KEY CONCEPT The goals of treatment are to maximally and durably suppress viral replication, restore and preserve immune function, reduce HIV-associated morbidity and prolong the duration and quality of survival, and prevent disease transmission. Elimination or cure of HIV is not possible with currently available therapies. Instead, maximal suppression of viral replication (defined as plasma HIV RNA concentrations undetectable by the most sensitive assay available) is the most important indicator of response to drug therapy and serves to prevent transmission to others. After the initiation of combination antiretroviral therapy (ART) (cART), a rapid decline to undetectable plasma HIV RNA in 12 to 24 weeks is a predictor of improved clinical outcomes.[9] Routine viral load testing is recommended to ensure a sustained response.

KEY CONCEPT Degree of immune function preservation is also correlated with decreased viral replication and is measured by CD4 T-cell counts. The CD4 count is the best predictor of progression to AIDS and helps clinicians determine when to initiate opportunistic infection prophylaxis. At CD4 T-cell counts of 200 cells/mm^3 (200×10^6/L) and lower, patients require chemoprophylaxis

Clinical Presentation and Diagnosis of HIV

Patients with acute HIV infection may display nonspecific, flu-like symptoms. Patients with chronic HIV infection may present with these same nonspecific symptoms and/or opportunistic infections.

Signs and Symptoms of Acute or Primary HIV

Patients may present with fever, fatigue, lymphadenopathy, pharyngitis, myalgias, arthralgias, diarrhea and/or rash. These symptoms typically subside within days to weeks. Some patients may remain asymptomatic.

Signs and Symptoms of AIDS

Patients may experience signs and symptoms similar to acute HIV but may seem exaggerated and prolonged. They may also experience weight loss, recurring fever or night sweats, hepatosplenomegaly, thrush, or neurologic symptoms (such as meningoencephalitis, aseptic meningitis, peripheral neuropathy, facial palsy, cognitive impairment, or psychosis).

Opportunistic Infections

Depending on the severity of immunosuppression (the CD4 count), patients may present with the following opportunistic infections (grouped by CD4 count):

- _Any CD4 count_
  - _Mycobacterium tuberculosis_ disease*
  - Bacterial pneumonia (commonly _Streptococcus pneumoniae, Haemophilus influenzae_)**
  - Herpes simplex virus disease**
  - Varicella zoster virus disease
  - Bacterial enteric disease (most commonly _Salmonella, Campylobacter_, and _Shigella_)**
  - Syphilis
  - Bartonellosis
- _Less than 200 cells/mm^3 (200×10^6/L)_
  - Coccidioidomycosis**
  - _Pneumocystis jiroveci_ pneumonia (PCP or PJP)*
  - Oropharyngeal and esophageal* candidiasis
  - Kaposi sarcoma* or human herpesvirus-8 disease
- _Less than 150 cells/mm^3 (150×10^6/L)_
  - Disseminated histoplasmosis*
- _Less than 100 cells/mm^3 (100×10^6/L)_
  - _Toxoplasma gondii_ encephalitis*
  - Cryptosporidiosis**
- _Less than 50 cells/mm^3 (50×10^6/L)_
  - Disseminated _Mycobacterium avium_ complex disease*
  - Cytomegalovirus disease (CMV)**
  - Cryptococcosis**

*AIDS-defining condition.
**AIDS-defining condition if certain criteria are met.

for opportunistic infections. Table 87–1 details the monitoring points of HIV treatment for plasma HIV RNA and CD4 T-cell counts. In addition to these parameters, basic blood chemistry tests, liver function tests (LFTs), complete blood counts, and lipid profiles should be monitored every 3 to 12 months in patients receiving ART.[9]

Eight classes of drugs are available to treat HIV infection: nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), nonnucleoside reverse transcriptase inhibitors (NNRTI), integrase strand transfer inhibitors (INSTI), protease inhibitors (PIs), a fusion inhibitor, a CCR5 antagonist, a CD4 post-attachment inhibitor, and a gp120 attachment inhibitor. Pharmacokinetic enhancers or "boosters" including ritonavir and cobicistat may be added to a regimen in order to slow the metabolism and thus enhance efficacy of certain antiretroviral agents. **KEY CONCEPT** Generally, cART consists of three or more active drugs at any CD4

Table 87–1

Monitoring End Points for CD4 T-Cell Counts and HIV RNA

CD4$^+$ T Cell Count		Plasma HIV-1 RNA	
When to Monitor?	**Why?**	**When to Monitor?**	**Why?**
Initial diagnosis	Assess immune function and urgency to initiate cART Assess need for OI prophylaxis	Entry to care or before initiating cART	Establish baseline Provide prognostic information May impact treatment selection
3 months after cART initiation	Assess degree of immune reconstitution	2–8 weeks after starting or modifying cART due to treatment failure	Confirm adequate initial response to regimen
Every 3–6 months	Monitor success of treatment and need for OI prophylaxis in patients receiving cART Assess urgency to initiated cART and need for OI prophylaxis in untreated patients	4–8 weeks after modifying cART in virally suppressed patients	Confirm effectiveness of switch therapy
		Every 3–6 months	Confirm continuous viral suppression in patients receiving cART

Patient Encounter 1, Part 1: Treatment Initiation

A 23-year-old African American man presents to your clinic with complaints of weight loss, nausea and vomiting, fatigue, and rash. During a detailed social history, you learn that for the past 5 years, he has had many unprotected sexual encounters with men and women. His last HIV test was 2 years ago which was negative. He does not use IV drugs but does smoke marijuana. Based on his presentation and risk factors today, you decide to perform general STI as well as HIV testing.

PMH: Seizure disorder and previously treated for gonorrhea 3 years ago

FH: Mother—coronary artery disease, lung cancer; Father—HTN, type II diabetes

SH: Full-time college student, part-time retail store clerk; sexual history as above with no condom use. He reports moderate (three to four times weekly) marijuana use.

Meds: Multivitamin daily, carbamazepine 400 mg twice daily

Allergies: Latex (rash)

ROS: Positive for weight loss, decreased appetite; Negative for shortness of breath, cough, chest pain, nausea, vomiting, diarrhea

PE:

Within normal limits

VS: BP 120/65 mm Hg, P 75 beats/min, RR 18 breaths/min, T 37.5°C

HEENT: Thrush, lymph nodes (+) lymphadenopathy

CV: RRR, normal S1, S2; no murmurs, rubs, gallops

Abd: Soft, nontender, nondistended; (+) bowel sounds, no hepatosplenomegaly

Rectal: Deferred

Labs: Sodium 140 mEq/L (140 mmol/L), potassium 4.0 mEq/L (4.0 mmol/L), chloride 102 mEq/L (102 mmol/L), bicarbonate 25 mEq/L (25 mmol/L), blood urea nitrogen 10 mg/dL (3.57 mmol/L), creatinine 0.7 mg/dL (62.9 μmol/L), WBC $8 \times 10^3/\text{mm}^3$ (8×10^9/L), hemoglobin 11.4 g/dL (114 g/L or 7.07 mmol/L), hematocrit 32% (0.32), platelets $79 \times 10^3/\text{mm}^3$ (79×10^9/L), neutrophils 45% (0.45), bands 9% (0.09), lymphocytes 20% (0.20), monocytes 1% (0.01), eosinophils 1% (0.01), basophils 0% (0.00)

What information is suggestive of HIV?

What are the risk factors present for having HIV?

What is the likely time frame of this patient's HIV infection?

How can the diagnosis of HIV be made in this patient?

What additional laboratory measurements would be useful?

count, which increases the durability of viral suppression and decreases the potential for the development of resistance. Traditional treatment regimens include at least three drugs: two NRTIs given with an INSTI, a PI (plus a pharmacokinetic enhancer), or an NNRTI. Data now also support the use of select two-drug regimens for initial or consolidation therapy under certain circumstances. Combination regimens suppress HIV viral loads in 80% to 90% of patients in clinical trials.[9] Therefore, monotherapy with any agent or the use of NRTIs without another drug class are not recommended treatment options. Enfuvirtide, a fusion inhibitor, and ibalizumab, a post-attachment inhibitor, are only Food and Drug Administration (FDA)-approved for use in treatment-experienced patients when other options are not available due to drug resistance. Figure 87–1 details the mechanisms of action of the drug classes within the life cycle of HIV.

KEY CONCEPT Patient adherence is a key component to treatment success. In patients living with HIV, drug therapy is required indefinitely, as the virus begins to replicate at high levels when medications are stopped. Combination therapy used in the past for HIV was exceedingly complicated for patients with multiple daily doses, varying food restrictions, and large pill burdens. Advances in delivery and formulations now make possible once- or twice-daily dosing with fewer pills per day. Refer to Table 87–2 for a list of single-tablet HIV regimens. These advances, however, do not replace the need for patient counseling by a trained pharmacist and a multidisciplinary approach to promoting adherence.

Nonpharmacologic Interventions

All patients should be counseled initially and repeatedly on ways to prevent viral transmission. In 2016, only 51% of people living with HIV in the United States had maximally suppressed viral loads.[9] Nonsuppressed individuals can still transmit the virus to sexual partners or those with whom they share needles or other drug equipment. In contrast, patients with an undetectable viral load nearly eliminate the risk of sexual transmission to their partners. In instances where both partners are living with HIV, safe sex and needle practices reduce the risk of superinfection with differing strains of HIV and the transmission of other sexually transmitted infections (STIs). General guidelines for preventing viral transmission include using condoms with a water-based lubricant for vaginal or anal intercourse, using condoms without lubricant or dental dams for oral sex, and avoiding the use of shared, nonsterile equipment used to prepare, inject, or inhale

Table 87–2

Complete Single Pill Regimens

Atripla	Efavirenz + tenofovir disoproxil fumarate + emtricitabine
Biktarvy	Bictegravir + tenofovir alafenamide + emtricitabine
Complera	Rilpivirine + tenofovir disoproxil fumarate + emtricitabine
Delstrigo	Doravirine + tenofovir disoproxil fumarate + lamivudine
Dovato	Dolutegravir + lamivudine
Genvoya	Elvitegravir + cobicistat + tenofovir alafenamide + emtricitabine
Juluca	Dolutegravir + rilpivirine
Odefsey	Rilpivirine + tenofovir alafenamide + emtricitabine
Stribild	Elvitegravir + cobicistat + tenofovir disoproxil fumarate + emtricitabine
Symfi/Symfi Lo	Efavirenz + tenofovir disoproxil fumarate + lamivudine
Symtuza	Darunavir + cobicistat + tenofovir alafenamide + emtricitabine
Triumeq	Dolutegravir + abacavir + lamivudine

drugs. Treating other STIs in patients living with HIV may also help to prevent HIV transmission. The presence of STIs increases genital tract HIV viral load and, correspondingly, the risk of HIV transmission to sexual partners.

KEY CONCEPT Nutrition and dietary counseling should also be included in the care of the HIV patient, as poor nutrition leads to poorer outcomes and complicates treatment. ART itself may introduce nutritional considerations, including drug–food interactions, gastrointestinal (GI) adverse effects that may affect appetite and limit dietary intake, weight gain, lipid abnormalities, and fat redistribution. The American Dietetic Association currently recommends assessing HIV-infected patients for their level of nutritional risk and involving a registered dietician as part of the clinical team for optimal nutrition care.[10]

Further, the coordination of care and management of mental and psychosocial determinants of health, such as active substance abuse, depression, and anxiety, are paramount in the success of HIV control.

Pharmacologic Therapy for Antiretroviral-Naïve Patients

Two expert panels publish guidelines for the treatment of HIV-infected individuals. Although the recommendations are quite similar, slight differences do exist between the Department of Health and Human Services (DHHS) Guidelines[9] and the International Antiviral Society—USA (IAS-USA) Panel Recommendations.[11] The DHHS Guidelines are updated frequently, and current and archived versions are available online at www.aidsinfo.nih.gov. Due to the intense research and constant modifications to therapeutic approaches in the treatment of HIV, the majority of the treatment algorithms and recommendations presented herein follow the most up-to-date information found in the June 2021 DHHS recommendations.

KEY CONCEPT ART is recommended in all patients living with HIV (regardless of CD4 count), as soon as possible following diagnosis, in order to reduce the morbidity and mortality associated with HIV infection and prevent HIV transmission. This recommendation, updated in 2015, supercedes previous stipulations that were based on CD4+ cutoffs, and now reflect the proven benefit of ART in all patients, irrespective of disease severity. Patients should understand the importance of adherence and commit to ART indefinitely. Urgency is heightened in patients with AIDS-defining conditions, acute or recent HIV infection, and who are pregnant.[9] Once the decision is made to initiate treatment, the regimen is selected based on patient-specific factors such as baseline viral load and CD4 count, comorbidities, individual preferences, anticipated adherence, and medication accessibility. **KEY CONCEPT** Currently, based on high their potency and strong safety profiles, all of the preferred regimens for initial treatment contain an INSTI in combination with one or two NRTIs. The recommended agents are shown in Table 87–3.

Drug resistance testing should be performed at diagnosis and again prior to initiating treatment if treatment is deferred (see "Pharmacologic Therapy for Antiretroviral-Experienced Patients" section for further discussion of drug resistance testing). The results of resistance testing may dictate which drugs or drug classes are preferred, as approximately 10% to 17% of ART-naive patients will have drug-resistant virus.[9] This initial resistance pattern often involves the NRTIs or NNRTIs but may involve other drug classes. In general, INSTI-based regimens have the advantage of avoiding many complex drug–drug interactions and toxicities seen with NNRTIs and PIs. If transmitted INSTI resistance is a concern, integrase resistance testing must be specified as standard HIV genotyping only includes the protease and reverse transcriptase genes.

Table 87–3

Recommended Initial ART Regimen Options for Most Patients Living with HIV, Regardless of Pre-ART Viral Load or CD4 Cell Count[8]

INSTI-Based Regimen:

Bictegravir/tenofovir alafenamide/emtricitabine (AI)

Dolutegravir/abacavir/lamivudine *(Only for patients who are HLA-B*5701 negative)* (AI)

Dolutegravir + tenofovir alafenamide OR tenofovir disoproxil fumarate + emtricitabine OR lamivudine (AI)

Dolutegravir/lamivudine (*except for patients with HIV RNA >500,000 copies/mL, HBV coinfection, or are pending HIV genotypic resistance testing for reverse transcriptase or HBV testing)* (AI)

ART, Antiretroviral therapy; HIV, human immunodeficiency virus.

Rating of Recommendations: A = Strong; B = Moderate.

Rating of Evidence: I = data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observations cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies.

If abacavir is included in a regimen, patients should undergo human leukocyte antigen (HLA)-B*5701 testing prior to initiation to assess the risk of abacavir hypersensitivity, a multiorgan clinical syndrome that often presents soon after treatment initiation. Studies suggest a slightly higher risk in White patients (5%–8%) in comparison to Black patients (2%–3%).[9] Patients who test positive for the allele are at high risk of developing this reaction and should not be prescribed abacavir.[9] An abacavir allergy should also be documented in the patient's medical record to prevent future administration. Those patients with a negative test may receive abacavir but should still be counseled and monitored for the development of hypersensitivity. Tenofovir alafenamide (TAF) is a new prodrug formulation of tenofovir that achieves high intracellular conentations and significantly lower plasma exposure. This pharmacokinetic difference presumably explains why TAF is associated with less nephrotoxicity and impact on bone mineral density than its predecessor tenofovir disoproxil fumarate (TDF) and may be preferable from a toxicity standpoint.

In patients who cannot tolerate the recommended initial regimens for most patients living with HIV, or have a compelling reason to choose a different agent, the following alternative regimens are recommended (Table 87–4).[9]

PI-based regimens, particularly containing darunavir, may be preferable in patients in whom adherence is a concern or drug resistance results are pending given the high overall resistance barrier of this class, though drug interactions, the need for boosting agents, and toxicities must also be considered. NNRTI-based regimens are associated with lower pill burden and decreased incidence of long-term adverse effects (eg, dyslipidemia) in comparison with some PI-based regimens. However, this class also has a low threshold for drug resistance (the K103N mutation causes high-level cross-class resistance), and patient adherence is a critical consideration. Regimens with demonstrated efficacy but limited by other factors such as toxicities or pill burden are also provided in the guidelines. One of these regimens should only be selected if a first-line or alternate regimen is intolerable or the patient has a compelling reason to avoid drugs in a first-line or alternate regimen. The guidelines also include a list of therapies *not recommended* for initial treatment due

Table 87–4

Recommended Initial cART Regimen Options in Certain Clinical Situations

PI-Based Regimens:

Darunavir/cobicistat OR darunavir/ritonavir + tenofovir alafenamide OR tenofovir disoproxil fumarate + emtricitabine OR lamivudine (AI)

Atazanavir/cobicistat OR atazanavir/ritonavir + tenofovir alafenamide OR tenofovir disoproxil fumarate + emtricitabine OR lamivudine (BI)

Darunavir/cobicistat OR Darunavir/ritonavir + abacavir/lamivudine *(Only for patients who are HLA-B*5701 negative)* (BII)

NNRTI-Based Regimens:

Doravirine/tenofovir disoproxil fumarate/lamivudine (BI) or doravirine/tenofovir alafenamide/emtricitabine (BIII)

Efavirenz 600 mg + tenofovir disoproxil fumarate + emtricitabine OR lamivudine (BI)

Efavirenz 400 mg/tenofovir disoproxil fumarate/lamivudine (BI)

Efavirenz 600 mg + tenofovir alafenamide/emtricitabine (BII)

Rilpivirine/(tenofovir alafenamide OR tenofovir disoproxil fumarate)/emtricitabine (If HIV RNA < 100,000 copies/mL and CD4 > 200 cells/mm^3) (BI for TDF, BII for TAF)

INSTI-Based Regimen:

Elvitegravir/cobicistat/(tenofovir alafenamide OR tenofovir disoproxil fumarate)/emtricitabine (BI) Raltegravir + tenofovir alafenamide OR tenofovir disoproxil fumarate + emtricitabine OR lamivudine (BI for TDF, BII for TAF/FTC)

cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; RNA, ribonucleic acid.

Rating of Recommendations: A = Strong; B = Moderate.

Rating of Evidence: I = data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observations cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III Expert opinion.

to suboptimal potency, significant toxicity, or other pharmacological concerns. It is also noteworthy that certain drug combinations may require dosage adjustments due to pharmacokinetic changes. Drug formulations, commonly prescribed doses, and other considerations for single agent and combination tablets are provided in Tables 87–5 and 87–6.

Pharmacologic Therapy for Antiretroviral-Experienced Patients

KEY CONCEPT Ongoing viral replication, whether at low levels (plasma HIV RNA < 200 copies/mL) in the face of adequate drug concentrations or at higher levels due to inconsistent systemic concentrations (or low concentrations in sanctuary sites, eg, male and female genital fluids, cerebrospinal fluid, or lymph nodes), will eventually lead to resistance to the prescribed medications. To avoid further progression of resistant mutations, drug resistance testing should be performed and then a failing regimen should be discontinued as soon as possible.[9] The goal of therapy for patients with antiretroviral resistance is to reestablish virologic suppression or plasma HIV RNA lower than the limit of detection of the assay (typically < 40 copies/mL [40 × 10^3 copies/L]).

Treatment considerations for antiretroviral-experienced patients are much more complex than for patients who are naïve to therapy. Prior to changing therapy, the reasons for treatment failure should be identified. A comprehensive review should be performed of the patient's severity of disease, antiretroviral treatment history, adherence to therapy, intolerance or toxicity, concomitant drug therapies, comorbidities, and results of current and past HIV resistance testing. If patients fail therapy due to poor adherence, the underlying reasons must be determined and addressed prior to initiation of a new regimen. Reasons for poor adherence may include problems with medication access, active substance abuse, depression and/or denial of the disease, and a lack of education on the importance of 100% adherence to therapy. Medication intolerance or toxicity can be remedied with therapy for the adverse event, exchanging the drug causing the toxicity with another in the same class, or changing the entire regimen. Pharmacokinetics or systemic drug exposure can be optimized by ensuring maximal drug absorption (taking the drug with or without food can alter exposure by up to 30%) and avoiding interactions with concomitant prescription or nonprescription medications and dietary supplements.

Patient Encounter 1, Part 2

After receiving the diagnosis of HIV and assessing his laboratory values and willingness to initiate therapy, the patient from Part 1 and his medical team decide to start antiretroviral therapy.

What is the guidance for when to start therapy in a treatment-naïve patient?

What are the recommended regimens according to the DHHS Guidelines?

What is the potential for drug interactions with each of the recommended regimens?

Which concomitant medication complicates initiating therapy in this patient and what are possible ways to manage such drug interactions?

What adverse effects does the patient need to be counseled on with each of the recommended regimens?

Drug interactions between different antiretroviral agents and between antiretrovirals and concomitant medications should be evaluated for each patient to avoid under- and/or overexposure of either therapy. KEY CONCEPT NNRTIs, PIs, certain INSTIs, and maraviroc are metabolized by CYP-450 enzymes. In addition, NNRTIs, PIs, and cobicistat are inhibitors and/or inducers of this enzyme system. Some of the antiretrovirals are substrates, inhibitors, and/or inducers of transporters such as P-glycoprotein (P-gp) and, therefore, may lead to drug interactions. Information provided in Table 87–7 describes the drug interaction potential of each antiretroviral. Due to ever-changing drug interactions, the regularly updated DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1–Infected Adults and Adolescents are a recommended source of specific drug interactions.[9]

It is reasonable to expect maximal viral suppression in patients with limited drug exposure. However, this may not be feasible for patients with prior exposure to multiple medications. In antiretroviral-experienced patients, a reasonable goal is to minimize toxicity, preserve immune function and prevent clinical progression.

Several issues need to be considered in choosing a salvage regimen for HIV infection. Knowing prior medication exposure can assist in identifying which drugs to avoid. However, direct HIV resistance testing can better identify the resistance and susceptibility patterns of the major viral strains. Two types of HIV

Table 87–5

Summary of Currently Available, Commonly Used Antiretroviral Products[a]

Generic Name [Abbreviation] (Trade Name)	Dosage Forms	Commonly Prescribed Doses	Dose Adjustments	Food Restrictions	Significant Adverse Events
Nucleoside (Tide) Reverse Transcriptase Inhibitors					
Abacavir (Ziagen)	300-mg tablet; 20-mg/mL oral solution	300 mg twice daily or 600 mg once daily	Child Pugh Class A: 200 mg twice daily Child Pugh Class B or C: contraindicated	None (alcohol increases abacavir conc. by 41%)	Potentially fatal hypersensitivity reaction (rash, fever, malaise, nausea, vomiting, shortness of breath, sore throat, loss of appetite)—HLA B*5701 test before treatment
Emtricitabine (Emtriva)	200-mg capsule; 10-mg/mL oral solution	200 mg daily; 240 mg oral solution daily	**CrCl (mL/min [mL/s]):** **Capsule:** **Solution:** 30–49 [0.50–0.82] 200 mg every 48 hours 120 mg every 24 hours 15–29 [0.25–0.49] 200 mg every 72 hours 80 mg every 24 hours < 15/HD [0.25/HD] 200 mg every 96 hours 60 mg every 24 hours Dose after dialysis on dialysis days	None	Minimal
Lamivudine (Epivir)	150- and 300-mg tablets, 10-mg/mL oral solution	150 mg twice daily or 300 mg once daily	**CrCl (mL/min [mL/s]):** **Dose:** 30–49 [0.50–0.82] 150 mg every day 15–29 [0.25–0.49] 150 mg, then 100 mg every day 5–14 [0.08–0.24] 150 mg, then 50 mg every day < 5/HD [0.08/HD] 50 mg, then 25 mg every day	None	Minimal
Tenofovir disoproxil fumarate (Viread)	150-, 200-, 250-, 300-mg tablet; 40 mg per 1 g powder	300 mg once daily	**CrCl (mL/min [mL/s]):** **Dose:** 30–49 [0.50–0.82] 300 mg every 48 hours 10–29 [0.17–0.49] 300 mg twice weekly ESRD/HD 300 mg every 7 days	Powder taken with food	Asthenia, headache, diarrhea, renal insufficiency, decreased bone mineral density
Tenofovir alafenamide (Vemlidy) *Of note, only FDA labeled for HBV infection, not HIV*	25-mg tablet	25 mg once daily	Do not use with CrCl < 15 mL/min (0.25 mL/s)	With food	Headache
Zidovudine (Retrovir)[b]	100-mg capsule, 300-mg tablet, 10-mg/mL IV solution, 10-mg/mL oral solution	300 mg twice daily	100 mg three times daily or 300 mg once daily in severe renal impairment (CrCl < 15 mL/min [0.25 mL/s]) or HD	None	Bone marrow suppression: macrocytic anemia or neutropenia; GI intolerance, headache, insomnia, asthenia

Nonnucleoside Reverse Transcriptase Inhibitors					
Doravirine (Pifeltro)	100-mg tablets	100 mg once daily If taken with rifabutin: Increase doravirine to 100 mg twice daily (every 12 hours) while on rifabutin	No dosage adjustments recommended	None	Rash; Sleep disorders, dizziness, altered sensorium, depression, suicidality; weight gain
Efavirenz (Sustiva)	50-, 200-mg capsules or 600-mg tablet	600 mg daily at or before bedtime	Use with caution in patients with hepatic impairment	Take on an empty stomach high-fat/calorie meals increases C_{max} of capsule 39% and C_{max} of tablet 79%	Rash; CNS symptoms (insomnia, irritability, lethargy, dizziness, vivid dreams) usually resolve in 2 weeks; increased LFTs; false-positive cannabinoid test; teratogenic in monkeys
Etravirine (Intelence)	25-, 100-, 200-mg tablets	200 mg twice daily following a meal	No dosage adjustment for Child Pugh Class A or B. Has not been evaluated for Class C	Take following a meal. Fasting decreases systemic exposure by 50%.	Rash, nausea
Nevirapine (Viramune, Viramune XR)[b]	200-mg tablet, 100 and 400-mg XR tablet or 50-mg/5-mL oral suspension	200 mg once daily for 14 days; then 200 mg twice daily. For XR tablet, lead-in with 200 mg once daily of IR tablet followed by 400 mg daily XR tab not recommended for initiation in the following groups unless benefit outweighs the risk: 1) adult females with CD4 cell counts > 250 cells/mm^3 2) adult males with CD4 cell counts > 400 cells/mm^3	Use with caution in patients with hepatic impairment; avoid use with moderate to severe hepatic impairment	No food restrictions	Rash including Stevens–Johnson syndrome; symptomatic hepatitis, including fatal hepatic necrosis
Rilpivirine (Edurant)	25-mg tablet	25 mg daily	No dosage adjustment for Child Pugh Class A or B. Has not been evaluated for Class C; use with caution in severe or end-stage renal impairment	Take with food (a normal- to high-calorie meal) Absorption dependent on gastric pH-special considerations needed when coadministered with antacids	Rash; depressive disorders
Protease Inhibitors					
Atazanavir (Reyataz)	150-, 200-, 300-mg capsules, 50-mg oral packet	Atazanavir 300 mg + ritonavir 100 mg or cobicistat 150 mg OR atazanavir 400 mg daily If taken with efavirenz in treatment of naïve patients only: atazanavir 400 mg daily + ritonavir 100 mg daily (do not use with	Child-Pugh Class C: Not recommended Treatment-naïve patients on hemodialysis: atazanavir 300 mg + ritonavir	Take with food (AUC increases 30%); pH-sensitive dissolution—special considerations needed when coadministered with antacids	Indirect hyperbilirubinemia; prolonged PR interval (asymptomatic first-degree AV block); use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation; hyperglycemia; fat maldistribution; increased bleeding episodes in patients with hemophilia

(*Continued*)

Table 87–5

Summary of Currently Available, Commonly Used Antiretroviral Products[a] (*Continued*)

Generic Name [Abbreviation] (Trade Name)	Dosage Forms	Commonly Prescribed Doses	Dose Adjustments	Food Restrictions	Significant Adverse Events
		efavirenz in treatment of experienced patients)	100 mg daily; treatment-experienced patients on hemodialysis: Not recommended		
Darunavir (Prezista)	75-g, 150-mg, 600-mg, 800-mg tablets, 100-mg/mL oral suspension	Darunavir 600 mg twice daily + ritonavir 100 mg twice daily in treatment experienced patients with at least one darunavir resistance-associated substitution OR if genotypic testing is not possible Darunavir 800 mg daily + ritonavir 100 mg or cobicistat 150 mg daily in treatment naïve patients	Use with caution in patients with hepatic impairment	Take with food	Skin rash (has a sulfonamide moiety, Stevens–Johnson and erythema multiforme have been reported); diarrhea, nausea; headache; hyperlipidemia; transaminase elevation; hyperglycemia; fat maldistribution; possible increased bleeding episodes in patients with hemophilia
Ritonavir (Norvir)	100-mg tablet or capsule, 80-mg/mL solution (contains 43% alcohol)	100–200 mg/dose when used as pharmacokinetic enhancer	No dosage adjustment in mild hepatic impairment No data for moderate-to-severe impairment; use with caution	Take with food to improve tolerability	GI intolerance, nausea, diarrhea; paresthesias; hyperlipidemia; hepatitis; asthenia; taste perversion; hyperglycemia; fat maldistribution; increased bleeding in hemophiliacs
Fusion Inhibitors					
Enfuvirtide (Fuzeon)	Injectable, in lyophilized powder Each single-use vial contains 108 mg of enfuvirtide to be reconstituted with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL	90 mg (1 mL) subcutaneously twice daily	No dosage recommendation	N/A	Local injection site reaction (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) in most patients; increased rate of bacterial pneumonia; < 1% hypersensitivity reaction (rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases); do not rechallenge

CD4 Post-attachment Inhibitor						
Ibalizumab (Trogarzo)	200 mg/1.33 mL (150 mg/mL) in a single dose vial	2 g IV as a single dose over 30 minutes followed by a maintenance dose of 800 mg IV over 15 minutes every 14 days thereafter	No renal or hepatic dose adjustments (has not been studied)	N/A	Scr abnormalities; rash; diarrhea	
Fostemsavir (Rukobia)	600-mg extended release tablet	600 mg twice daily	No renal or hepatic dose adjustments (has not been studied)	None	Increased AST/ALT; Increased serum creatinine	
Chemokine Receptor Antagonists (CCR5 Antagonists)						
Maraviroc (Selzentry)	25-, 75-, 150-, 300-mg tablets; 20 mg/mL oral solution	150 mg twice daily when given with strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except tipranavir/ritonavir) 300 mg twice daily when given with NRTIs, enfuvirtide, tipranavir/ritonavir, nevirapine and other drugs that are not potent P450 inhibitors 600 mg twice daily when given with CYP3A inducers, including efavirenz, rifampin, etc. (without a CYP3A inhibitor)	Patients with CrCl < 30 mL/min (0.83 mL/s) with a CYP3A inhibitor: Use contraindicated		No food restrictions	Abdominal pain; cough; dizziness; musculoskeletal symptoms; pyrexia; rash; upper RTI; hepatotoxicity; orthostatic hypotension
Integrase Inhibitors						
Dolutegravir (Tivicay)	10-,25-50 mg tablet; 5 mg soluble tablet (Tivicay PD)	50 mg daily if treatment naïve 50 mg twice daily if coadministered with efavirenz, fosamprenavir, tipranavir/ritonavir, rifampin OR if INSTI-experienced with known or suspected INSTI resistance If coadministered with etravirine, must add lopinavir/ritonavir, atazanavir/ritonavir or darunavir/ritonavir	Use with caution if CrCl < 30 mL/min (0.83 mL/s) No dosage adjustment for Child Pugh Class A or B Not recommended in Class C/has not been studied		Separate dose from polyvalent cations (eg, Ca, Mg, Al, Fe, Zn) OR may coadminster dolutegravir with calcium or iron supplements when taken together with food	Insomnia, depression, suicidality (primarily in patients with preexisting psychiatric conditions), headache; increased serum creatinine; increased CPK/rhabdomyolysis; hepatotoxicity in person coinfected with HBV or HCV; weight gain

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[a]Note, this is not a comprehensive list of all available antiretroviral agents but represents the agents most commonly used based on guideline recommendations.

[b]Agents that may be utilized less commonly, still noteworthy at the time of publication.

ART, antiretroviral therapy; AUC, area under the time-concentration curve; AV, atrioventricular; C_{max}, maximum concentration; CrCl, creatinine clearance; ESRD, end-stage renal disease; HD, hemodialysis; INSTI, integrase strand transfer inhibitor; LFT, liver function test; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; UGT, uridine diphosphate-glucuronsyltransferase.

Adapted from Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents [online]. Department of Health and Human Services. June 3, 2021. Available from: https://files.aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.

Table 87–6

Summary of Currently Available, Commonly Used Combination Tablet Antiretroviral Agents[a]

Generic Name [Abbreviation] (Trade Name)	Dosage Forms	Commonly Prescribed Doses	Dose Adjustments	Food Restrictions	Significant Adverse Events
Nucleoside (Tide) Reverse Transcriptase Inhibitor Combination Tablets					
Zidovudine + lamivudine (Combivir)[b]	Zidovudine 300 mg + lamivudine 150-mg tablet	One tablet twice daily	Do not use with CrCl < 50 mL/min (0.83 mL/s)	None	Bone marrow suppression: macrocytic anemia or neutropenia; GI intolerance, headache, insomnia, asthenia
Abacavir + lamivudine + zidovudine (Trizivir)[b]	Abacavir 300 mg + lamivudine 150 mg + zidovudine 300-mg tablet	One tablet twice daily	Do not use with CrCl < 50 mL/min (0.83 mL/s)	None	Bone marrow suppression: macrocytic anemia or neutropenia; GI intolerance, headache, insomnia, asthenia Potentially fatal hypersensitivity reaction (rash, fever, malaise, nausea, vomiting, shortness of breath, sore throat, loss of appetite)—HLA B*5701 test before treatment
Abacavir + lamivudine (Epzicom)	Abacavir 600 mg + lamivudine 300-mg tablet	One tablet daily	Do not use with CrCl < 50 mL/min (0.83 mL/s)	None	Potentially fatal hypersensitivity reaction (rash, fever, malaise, nausea, vomiting, shortness of breath, sore throat, loss of appetite)—HLA B*5701 test before treatment
Tenofovir disoproxil fumarate + lamivudine (Cimduo)	Tenofovir disoproxil fumarate 300 mg + lamivudine 300 mg	One tablet daily	Do not use with CrCl < 50 mL/min (0.83 mL/s)	None	Asthenia, headache, diarrhea, renal insufficiency, decreased bone mineral density
Tenofovir disoproxil fumarate + emtricitabine (Truvada)	Tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg	One tablet daily	**CrCl (mL/min [mL/s]):** **Dose**: 30–49 [0.50–0.82] One tablet every 48 hours 10–29 [0.17–0.49], ESRD/HD Not recommended	None	Asthenia, headache, diarrhea, renal insufficiency, decreased bone mineral density
Tenofovir alafenamide + emtricitabine (Descovy)	Tenofovir alafenamide 25 mg + emtricitabine 200 mg	One tablet daily	**CrCl (mL/min [mL/s]):** **Dose**: <30 [0.5] Not recommended ESRD on HD One tablet once daily after HD	None	Headache
Nonnucleoside Reverse Transcriptase Inhibitor Combination Tablets					
Tenofovir disoproxil fumarate + emtricitabine + efavirenz (Atripla)[b]	Tenofovir disoproxil fumarate 300 mg Emtricitabine 200 mg Efavirenz 600 mg	One tablet daily	Do not use in patients with CrCl < 50 mL/min (0.83 mL/s)	High-fat/high-caloric meals increase peak plasma concentrations of efavirenz capsules by 39% and efavirenz tablets by 79%; take on empty stomach	Rash; CNS symptoms (insomnia, irritability, lethargy, dizziness, vivid dreams) usually resolve in 2 weeks; increased LFTs; false-positive cannabinoid test; teratogenic in monkeys, asthenia, headache, diarrhea, renal insufficiency, decreased bone mineral density
Tenofovir disoproxil fumarate + emtricitabine + rilpivirine (Complera)[b]	Tenofovir disoproxil fumarate 300 mg Emtricitabine 200 mg Rilpivirine 25 mg	One tablet daily with a meal	Do not use in patients with CrCl < 50 mL/min (0.83 mL/s)	Take with food (preferably high-fat meal), avoid acid suppression	Rash; depressive disorders, asthenia, headache, diarrhea, renal insufficiency, decreased bone mineral density

Tenofovir alafenamide + emtricitabine + rilpivirine (Odefsey)	Tenofovir alafenamide 300 mg Emtricitabine 200 mg Rilpivirine 25 mg	One tablet daily with a meal	Do not use in patients with CrCl < 30 mL/min (0.5 mL/s)	Take with food (preferably high-fat meal), avoid acid suppression	Rash; depressive disorders, headache
Tenofovir disoproxil fumarate + lamivudine + doravirine (Delstrigo)	Tenofovir disoproxil fumarate 300 mg Lamivudine 300 mg Doravirine 100 mg	One tablet daily If taken with rifabutin: One tablet once daily plus additional 1 tablet doravirine 100 mg 12 hours later while on rifabutin	Use not recommended in patients with CrCl < 30 mL/min (0.5 mL/s) Child-Pugh Class C: No dose adjustments provided (has not been studied)	None	Rash; Sleep disorders, dizziness, altered sensorium, depression, suicidality; weight gain, asthenia, headache, diarrhea, renal insufficiency, decreased bone mineral density
Tenofovir disoproxil fumarate + lamivudine + efavirenz (Symfi, Symfi Lo)	Tenofovir disoproxil fumarate 300 mg Lamivudine 300 mg Efavirenz 400 mg (Symfi Lo) or 600 mg (Symfi)	Once tablet daily	Do not use in patients with CrCl < 50 mL/min (0.83 mL/s) or ESRD on HD	Take on an empty stomach, (preferably at bedtime)	Rash; CNS symptoms (insomnia, irritability, lethargy, dizziness, vivid dreams) usually resolve in 2 weeks; increased LFTs; false-positive cannabinoid test; teratogenic in monkeys, asthenia, headache, diarrhea, renal insufficiency, decreased bone mineral density
Protease Inhibitor Combination Tablets					
Atazanavir + cobicistat (Evotaz)	Evotaz: 300 mg atazanavir plus 150-mg cobicistat tablet	One tablet daily Do not use with abacavir and lamivudine if pre-antiretroviral therapy HIV RNA ≥ 100,000 copies/mL	Use is not recommended in hepatic impairment Hemodialysis: Not recommended	Take with food (AUC increases 30%); pH-sensitive dissolution—special considerations needed when coadministered with antacids	Indirect hyperbilirubinemia; prolonged PR interval (asymptomatic first-degree AV block); use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation; hyperglycemia; fat maldistribution; increased bleeding episodes in patients with hemophilia
Darunavir + Cobicistat (Prezcobix)	Prezcobix: 800 mg darunavir + 150 mg cobicistat tablet	One tablet daily Do not use with abacavir and lamivudine if pre-antiretroviral therapy HIV RNA ≥ 100,000 copies/mL	Use with caution in patients with hepatic impairment	Take with food	Skin rash (has a sulfonamide moiety, Stevens–Johnson and erythema multiforme have been reported); diarrhea, nausea; headache; hyperlipidemia; transaminase elevation; hyperglycemia; fat maldistribution; possible increased bleeding episodes in patients with hemophilia
Darunavir + cobicistat + emtricitabine + tenofovir alafenamide (Symtuza)	Darunavir 800 mg + cobicistat 150 mg + emtricitabine 200 mg + tenofovir alafenamide 10 mg	One tablet once daily	Do not use in patients with CrCl < 30 mL/min (0.5 mL/s) ESRD on HD: One tablet once daily after HD on HD days Child-Pugh Class C: Not recommended	Take with food	As above, additionally asthenia, headache, diarrhea, renal insufficiency, decreased bone mineral density

(*Continued*)

Table 87–6

Summary of Currently Available, Commonly Used Combination Tablet Antiretroviral Agents[a] (*Continued*)

Generic Name [Abbreviation] (Trade Name)	Dosage Forms	Commonly Prescribed Doses	Dose Adjustments	Food Restrictions	Significant Adverse Events
Lopinavir + ritonavir (Kaletra)[b]	Lopinavir 100 mg + ritonavir 25-mg tablet, Lopinavir 200 mg + ritonavir 50-mg tablet, lopinavir 400 mg + ritonavir 100-mg/5-mL oral solution (contains 42% alcohol)	Two 200/50-mg tablets or 5 mL twice daily, four 200/50-mg tablets once daily; with efavirenz or nevirapine: three tablets or 6.5 mL twice daily	Use with caution in patients with hepatic impairment Avoid once-daily dosing in HD	Take with food (AUC increases 48%–80%)	Nausea, vomiting, diarrhea; asthenia; hyperlipidemia; LFT elevation; hyperglycemia; fat maldistribution; increased bleeding episodes in hemophiliacs
Integrase Inhibitor Combination Tablets					
Dolutegravir + rilpivirine (Juluca)	Dolutegravir 50 mg + rilpivirine 25 mg	One tablet once daily in patient virologically suppressed on a stable antiretroviral regimen for ≥ 6 months with no history of treatment failure and no resistance to dolutegravir or rilpivirine If taken with rifabutin: One tablet once daily plus additional rilpivirine 25-mg tablet once daily while on rifampin	Use with caution if CrCl < 30 mL/min (0.83 mL/s) No dose adjustments for Child Pugh Class C	Administer with a normal-to-high calorie meal. Separate dose from polyvalent cations (eg, Ca, Mg, Al, Fe, Zn) OR may coadminster Juluca with calcium or iron supplements when taken together with food	Insomnia, depression, suicidality (primarily in patients with preexisting psychiatric conditions), headache; increased serum creatinine; increased CPK/rhabdomyolysis; hepatoxicity in person coinfected with HBV or HCV; weight gain, rash
Dolutegravir + Lamivudine (Dovato)	Dolutegravir 50 mg + lamivudine 300 mg	One tablet once daily	Do not use in patients with CrCl < 50 mL/min (0.83 mL/s) Not recommended in Child-Pugh Class C (has not been studied)	Separate dose from polyvalent cations (eg, Ca, Mg, Al, Fe, Zn) OR may coadminster Dovato with calcium or iron supplements when taken together with food	Insomnia, depression, suicidality (primarily in patients with preexisting psychiatric conditions), headache; increased serum creatinine; increased CPK/rhabdomyolysis; hepatoxicity in person coinfected with HBV or HCV; weight gain

Bictegravir + emtricitabine + tenofovir alafenamide (Biktarvy)	Bictegravir 50 mg + emtricitabine 200 mg + tenofovir alafenamide 25 mg	One tablet daily	Use not recommended if CrCl < 30 mL/min (0.83 mL/s)	Separate dose from polyvalent cations (eg, Ca, Mg, Al, Fe, Zn) OR may coadminster Biktarvy with calcium or iron supplements when taken together with food	Increased serum creatinine; weight gain; diarrhea, nausea; insomnia, depression, suicidality (primarily in patients with preexisting psychiatric conditions)
Elvitegravir + cobicistat + tenofovir disoproxil fumarate + emtricitabine (Stribild)[b]	Elvitegravir 150 mg + cobicistat 150 mg + tenofovir disoproxil fumarate 300 mg + emtricitabine 200-mg tablet	One tablet daily	CrCl < 70 mL/min (1.17 mL/s) at initiation of therapy: Not recommended CrCl < 50 mL/min (0.83 mL/s) during therapy: Continued use is not recommended	Take with food; separate dose from polyvalent cations (eg, Ca, Mg, Al, Fe, Zn)	Nausea; diarrhea; proteinuria; increased serum creatinine, dyslipidemia, weight gain, insomnia, depression, suicidality
Elvitegravir + cobicistat + tenofovir alafenamide + emtricitabine (Genvoya)	Elvitegravir 150 mg + cobicistat 150 mg + tenofovir alafenamide 25 mg + emtricitabine 200-mg tablet	One tablet daily	Do not use if CrCl < 30 mL/min (0.5 mL/s) ESRD on HD: One tablet once daily, administer after HD on HD days	Take with food	Nausea; diarrhea; proteinuria; increased serum creatinine, dyslipidemia, weight gain, insomnia, depression, suicidality
Abacavir + lamivudine + Dolutegravir (Triumeq)	Abacavir 600 mg Lamivudine 300 mg Dolutegravir 50 mg	One tablet daily	Do not use if CrCl < 50 mL/min (0.83 mL/s) No dosage adjustment for Child Pugh Class A or B Not recommended in Class C/has not been studied		Insomnia, depression, suicidality (primarily in patients with preexisting psychiatric conditions), headache; increased serum creatinine; increased CPK/rhabdomyolysis; hepatoxicity in person coinfected with HBV or HCV; weight gain, HLA B*5701 test before treatment

[a]Note, this is not a comprehensive list of all available antiretroviral agents but represents the agents most commonly used based on guideline recommendations.

[b]Agents that may be utilized less commonly, still noteworthy at the time of publication.

ART, antiretroviral therapy; AUC, area under the time-concentration curve; AV, atrioventricular; C_{max}, maximum concentration; CrCl, creatinine clearance; ESRD, end-stage renal disease; HD, hemodialysis; INSTI, integrase strand transfer inhibitor; LFT, liver function test; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; UGT, uridine diphosphate-glucuronsyltransferase.

Adapted from Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents [online]. Department of Health and Human Services. June 3, 2021. Available from: https://files.aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.

Table 87–7

Notable Drug–Drug Interaction Potential

Antiretroviral Agent	Mechanism of Drug Interaction
Nucleoside (tide) reverse transcriptase inhibitors	
Abacavir	UGT1A1 Substrate
Tenofovir alafenamide	P-gp substrate
Tenofovir disoproxil fumarate	P-gp substrate
Non-nucleoside reverse transcriptase inhibitors	
Doravirine	CYP3A4 and 3A5 substrate
Efavirenz	CYP 2B6, 2A6, 3A4 substrate; CYP3A4 inhibitor, CYP3A4, 2B6, 2C19 inducer
Etravirine	CYP3A4, 2C9, 2C19 substrate; CYP2C9, 2C19 inhibitor, CYP3A4 inducer
Nevirapine	CYP3A4, 2B6 substrate; CYP3A4, 2B6 inducer
Rilpivirine	Concentration decreased with increased gastric pH; CYP3A4 substrate
Protease inhibitors	
Atazanavir, atazanavir/cobicistat	Concentration decreased with increased gastric pH, P-gP substrate and inhibitor (atazanavir alone is also inducer); CYP3A4 substrate; CYP3A4, 2C8 inhibitor; UGT1A1 inhibitor
Atazanavir/ritonavir	Concentration decreased with increased gastric pH; P-gP substrate and inhibitor; CYP3A4, 2D6 substrate; CYP3A4, 2D6, 2C8 inhibitor; CYP1A2, 2B6, 2C8, 2C9, 2C19 inducer; atazanavir inhibits UGT1A1, ritonavir induces UGT1A1
Darunavir/cobicistat	CYP3A4 substrate; CYP3A4, 2D6 inhibitor
Darunavir/ritonavir	CYP3A4 and 2D6 substrate; CYP3A4, 2D6 inhibitor; CYP 1A2, 2B6, 2C8, 2C9, 2C19 inducer; UGT1A1 inducer
Lopinavir/ritonavir	P-gp substrate; CYP3A4, 2D6 substrate; CYP3A4 inhibitor; CYP 1A2, 2B6, 2C8, 2C9, 2C19 inducer; UGT1A1 inducer
CD4 Post-attachment Inhibitors	
Fostemsavir	CYP3A4 substrate, BCRP/ABCG2, and P-glycoprotein/ABCB1 substrate
Chemokine receptor antagonist	
Maraviroc	P-gp substrate; CYP3A4 substrate
Integrase Inhibitors	
Bictegravir	Concentration decreased by polyvalent cations (Ca, Mg, Al, Fe, Zn); P-gp substrate; CYP3A4 substrate; UGT1A1 substrate
Dolutegravir	Concentration decreased by polyvalent cations (Ca, Mg, Al, Fe, Zn); P-gp substrate; CYP3A4 substrate; UGT1A1 substrate
Elvitegravir/cobicistat	Concentration decreased by polyvalent cations (Ca, Mg, Al, Fe, Zn); P-gp inhibitor; CYP3A4 substrate; CYP3A4, 2D6 inhibitor; CYP2C9 inducer; UGT1A1 substrate
Raltegravir	Concentration decreased by polyvalent cations (Ca, Mg, Al, Fe, Zn); UGT1A1 substrate

resistance testing are available, an HIV genotype and an HIV phenotype. Genotyping involves detecting mutations by genetically sequencing the virus, whereas phenotyping determines the ability of the virus to replicate in the presence of varying antiretroviral concentrations. Phenotyping involves exposing a sample of a patient's HIV to antiretroviral drugs and directly measuring the ability of HIV to grow in the presence of these drugs to determine which drugs will have activity. Genotyping is more rapid and less costly than phenotyping but results in a list of mutations that may be more difficult to interpret than phenotyping. An HIV virtual phenotype report may also be obtained when genotypes are ordered.[9] This compares the patient's viral sequence to a database of matched genotypes and drug susceptibilities to estimate the patient's phenotype (the likely susceptibility of the patient's virus to different antiretrovirals). Web-based tools are available to assist with interpretation of resistance mutations (eg, Stanford University's HIV Drug Resistance Database; http://hivdb.stanford.edu/index.html). However, interpretation of genotype and phenotype reports is recommended in conjunction with practitioners with advanced infectious diseases training.

Resistance testing should be obtained when all patients enter into care, in patients with virologic failure on an antiretroviral regimen, or with suboptimal suppression after initiation of ART. Testing is generally preferred for antiretroviral naïve patients. For resistance testing to be useful, the patient should ideally have a plasma HIV RNA of at least 1000 copies/mL (1×10^6 copies/L) (testing can be considered down to a HIV RNA level of 500 copies/mL) and should be currently taking their antiretroviral medications (or be within 4 weeks of discontinuing ART). Generally, this viral concentration is necessary to yield reliable amplification of the virus, and the antiretroviral medications are needed because the dominant viral species reverts to wild-type within 4 to 6 weeks after medications are stopped.

Management of antiretroviral-experienced patients is complex, and expert opinion is advised before selecting therapy. KEY CONCEPT As with antiretroviral-naïve patients, at least two, and preferably three, fully active drugs should be prescribed.[9] Since considerable cross-resistance can occur between medications within an antiretroviral class, using drugs to which the patient has not been exposed may be insufficient. Complete cross-resistance occurs within the first generation of NNRTIs (nevirapine, delavirdine, and efavirenz), whereas the NRTIs and PIs have variable overlapping resistance patterns. For this reason, HIV resistance assays are important tools for choosing effective therapies. The use of antiretrovirals with unique mechanisms of action such as enfuvirtide (fusion inhibitor) or maraviroc (CCR5 antagonist) may be warranted as salvage therapy. If maraviroc is chosen, a tropism assay is a test that should be performed to determine if the patient's virus utilizes the CCR5 co-receptor to enter host cells (as opposed to CXCR4 co-receptors). Resistance testing for enfuvirtide can also be performed.

In heavily treatment-experienced patients with multidrug-resistant HIV infection failing treatment, two newer options that can be considered in combination with other antiretrovirals include ibalizumab (post-attachment inhibitor) or fostemsavir (gp120 attachment inhibitor). Ibalizumab is deferred for last-line therapy due to the need for IV therapy, higher cost, and currently limited data assessing safety and efficacy. Fostemsavir is the latest novel antiretroviral approved in July 2020, and serves an oral option that can be added to a failing regimen. Notably, drug resistance testing is not available for these two agents. If HIV suppression is not achieved with currently approved agents, consideration should be given to enrolling patients in clinical trials or expanded access programs utilizing investigational antiretroviral therapies. In all patients failing therapy with resistance to one or more drugs, expert consultation is needed as well as continued strong adherence support.

The above information details the management of antiretroviral-experienced patients who experience ongoing viral replication and treatment failure. However, treatment-experienced patients who achieve and maintain HIV virologic suppression may be switched to different regimens in an attempt to further optimize their regimen in terms of adverse effect profile, dosing frequency, and pill burden to name a few examples. Options include other three-drug regimens that are within- or between-classes, select two-drug regimens, and more recently, long-acting antiretroviral therapy. The first long-acting complete regimen is Cabenuva (cabotegravir and rilpivirine), a once-monthly injection FDA approved in January 2021. More information about Cabenuva and other strategies utilized for the optimization of ART in the setting of viral suppression can be found in the 2021 DHSS guidelines.

Given the complexity of selecting appropriate cART therapy and the ability of the virus to rapidly develop resistance, the concept of antiretroviral stewardship is important. Antiretroviral Stewardship encompasses practices aimed at improving antiretroviral medication use with the goal of minimizing medication errors related to cART and optimizing HIV treatment outcomes. Such efforts may entail routine review of patients admitted to an institution on antiretrovirals and provider education in order to ensure an appropriate and complete cART regimen is selected (with regards to drug, dose, formulation, administration considerations) and drug–drug interactions are minimized. Antiretroviral stewardship can have a significant impact on cART medication error prevention, with a medication error rate reduction rate of 12% to 35% demonstrated in studies, depending on the type of intervention implemented.[12,13]

Treatment Considerations in Special Populations

▶ *Acute HIV Infection*

Diagnosis of acute HIV infection is difficult, since many patients are asymptomatic or have nonspecific clinical symptoms similar to other common respiratory infections. The fourth generation antigen/antibody test increases the ability to detect acute HIV-1 infection, but no laboratory assay can detect HIV immediately after it is acquired.

Treatment of acute infection can decrease the severity of acute disease and decrease the viral set point; this may decrease progression rates and reduce the rate of viral transmission.[9] Limitations include an increased risk of chronic drug-induced toxicities and the development of viral resistance. Resistance testing should be performed prior to initiation of therapy due to an increase in transmitted resistance in antiretroviral naïve patients.[9]

Patients should be quickly engaged in care after HIV diagnosis and, in general, be initiated on cART as soon as possible. Data from the Ward 86 Rapid ART Program for Individuals with an HIV Diagnosis (RAPID) ART program at the University of California, San Francisco assessed 225 patients referred to immediate ART at diagnosis and showed that viral suppression rates were 92.1% over a median of 1.09 years at last recorded viral load.[14] While early cART can improve the rate of virological suppression, a short delay may be necessary in patients with some opportunistic infections to prevent a paradoxical worsening of a known infection or manifestation of a new infection, known as the immune reconstitution inflammatory syndrome (IRIS). Additionally, there is limited data on initiation of ART in a small subset of PLWHIV who maintain viral loads below detectable levels without initiation of cART, known as elite controllers.

▶ *Adolescent and Young Adult Patients*

Adolescents infected after puberty acquire HIV in similar ways to adults and are thus treated as adults. In this population, dosing of antiretroviral drugs should not be based on age, but on the Tanner stage (which considers external primary and secondary sexual characteristics).[9] Adolescents in early puberty should be dosed according to pediatric guidelines, whereas those in late puberty should be dosed as adults. During growth spurts, adolescents should be monitored closely for drug efficacy and toxicity, since rapid changes in weight can lead to altered drug concentrations. Adherence is of concern in this population due to denial of the disease, misinformation, distrust of healthcare professionals, low self-esteem, and a lack of family and/or social support. Additionally, asymptomatic patients this age find it more difficult to adhere to therapy while feeling well.

▶ *Pediatric Patients*

There are unique considerations in the treatment of HIV-infected children. Specific treatment guidelines exist,[15] but a thorough review is outside the scope of this chapter. Most children acquire HIV infection through perinatal transmission either in utero, intrapartum, or postpartum through breastfeeding, although antiretroviral interventions have dramatically reduced transmission rates.[9] ART research is limited in pediatric patients, as some drugs have no dosing recommendations for this population or are not available in a formulation that can be easily administered to children. Additionally, drug exposures can change dramatically during early childhood development due to altered drug-metabolizing enzyme and drug transporter activities.

▶ *Pregnancy, Women of Reproductive Potential, and Breastfeeding*

The goals of ART for women of reproductive age and pregnant women are the same as for other adult patients. Specific guidelines for pregnant women living with HIV are available.[16] For women trying to conceive, preferred regimens include dolutegravir, raltegravir, atazanavir/ritonavir, or darunavir/ritonavir plus TDF/emtricitabine, TDF/lamivudine, or abacavir/lamivudine. Whereas previous data showed a higher prevalence of neural tube defects in infants born to women receiving dolutegravir, updated data indicates that this difference is minimal and not statistically significant. This data from Botswana showed a difference in prevalence of neural tube defects between pregnant women receiving dolutegravir and those receiving non-dolutegravir based regimens of 0.09% (95% CI, –0.03, 0.30). (reference 17) Although dolutegravir is considered a preferred antiretroviral drug for women of childbearing potential, the risks and benefits should be discussed prior to administration of a dolutegravir-based regimen in this patient population.

If a woman is already virally suppressed on an antiretroviral regimen at the time she becomes pregnant, it is recommended that she remain on that regimen. Exceptions include women on two-drug regimens; such patients should switch regimens or add additional ART agents to these regimens. Other agents to consider switching include cobicistat-boosted elvitegravir, darunavir, or atazanavir due to pharmacokinetic changes in the second and third trimesters of pregnancy. If not already on ART, preferred therapies in pregnancy include atazanavir + ritonavir, darunavir + ritonavir, raltegravir, or dolutegravir all administered with a two-NRTI backbone (abacavir/lamivudine or TDF/emtricitabine or TDF/lamivudine). Alternate regimens include efavirenz or rilpivirine administered with a two-NRTI backbone. A dual nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone that includes one or more NRTIs with high levels of transplacental passage, if possible, is recommended. The goal of therapy is to reduce plasma HIV RNA below detectable levels and prevent MTCT of HIV. Limited data are available on some antiretroviral pharmacokinetics in pregnancy, with close plasma HIV RNA and CD4 monitoring warranted in the third trimester of pregnancy. Standard doses are currently recommended for most antiretroviral drugs, although higher doses of some PIs may be indicated depending on the trimester of pregnancy.

Efavirenz, nevirapine, and many ritonavir- or cobicistat-boosted PIs decrease the concentrations of different estrogens and/or progestins in oral contraceptives, which could lead to treatment failure.[9] For patients prescribed these drugs, barrier forms of contraception are preferred to prevent pregnancy. Atazanavir may be taken with oral contraceptives with extreme caution, as it can increase or decrease the exposure to estrogen and progesterone, depending on whether it is used in combination with ritonavir. Depo-Provera (medroxyprogesterone) is likely the safest alternative, as studies have shown no significant interactions between depot medroxyprogesterone acetate and antiretrovirals.[18] Maraviroc, raltegravir, elvitegravir/cobicistat, dolutegravir, and bictegravir have not shown clinically significant effects when used with oral contraceptives.

After delivery, mothers are strongly recommended not to breastfeed if safe alternatives are available. Due to widespread availability of formula feeding options in the United States, breastfeeding should be avoided.[19] In resource-limited settings, breastfeeding may be encouraged with concomitant use of ART.

▶ *Hepatitis B Coinfection*

Patients living with HIV coinfected with the hepatitis B virus (HBV) have higher concentrations of DNA and hepatitis B early antigen (HBeAg) and higher rates of HBV-associated liver disease than in patients with chronic HBV infection without HIV. Indications to initiate therapy for HBV/HIV coinfected patients are the same as in HIV-negative patients and are based on the HBV DNA level, serum alanine aminotransferase (ALT), and severity of liver disease. One option to treat HBV is nucleoside/tide analogs. Nucleoside/tide analogs that treat HBV but not HIV are adefovir and entecavir. Entecavir, however, exhibits minimal antiviral activity against HIV and should never be administered to coinfected patients who are not concurrently receiving fully suppressive HIV therapy. If given without suppressive antiretrovirals, entecavir can select for M184 resistance, leading to HIV resistance to emtricitabine and lamivudine. Nucleoside/tide analogs that are used to treat HBV and HIV are lamivudine, emtricitabine, and tenofovir. Combinations of TDF + emtricitabine, tenofovir alafenamide + emtricitabine or TDF + lamivudine should comprise the NRTI backbone of a fully suppressive regimen.[20] When changing HIV therapy in a patient with HBV viral suppression, the new regimen should also treat HBV; the lamivudine, emtricitabine, or tenofovir formulation should be continued for treatment of HBV in addition to the new HIV regimen.[9] Abrupt discontinuation of these antiretrovirals may result in significant hepatic injury due to the exacerbation of hepatitis B. Of note, HBV infection should not be treated if a patient is not being treated for HIV. Additionally, two-drug ART regimens are not recommended for person with active HBV infection.

Vaccination against HBV can effectively prevent transmission. If there is no record of vaccination, or immunization history is unknown, patients living with HIV should be vaccinated.

▶ *Hepatitis C Coinfection*

All patients living with HIV should be screened for hepatitis C virus (HCV) infection. Patients coinfected with HCV and HIV have an increased rate of progression to cirrhosis, decompensated liver disease, hepatocellular carcinoma, and death compared with monoinfected HCV alone.[20] All HCV/HIV coinfected patients should be considered for therapy. Comprehensive treatment guidelines for HIV/HCV-coinfected patients are available and reflect the rapidly evolving treatment options for HCV.[9,21] It is important to consider the potential for clinically significant drug–drug interactions when selecting an HCV regimen for a patient living with HIV on ART.

Patient Encounter 2

A 30-year-old Caucasian woman presents to your clinic requesting medication to prevent the transmission of HIV. She has seen commercials for two drugs but cannot remember the difference between them. She has entered with a new relationship with her partner who has disclosed that he is HIV positive. She is interested in PrEP and wants additional information regarding HIV transmission prevention. Her and he partner have not engaged in sexual activities but plan to in the future.

What additional information do you need to know before creating a treatment plan for this patient?

What laboratory tests do you recommend?

What pharmacologic and nonpharmacologic options are available for this patient to protect herself from acquiring HIV?

What monitoring assessments and follow-up would you recommend?

Patient Encounter 3

A 45-year-old woman with HIV and Hepatitis B (virologically suppressed) presents to your clinic for follow-up after initiating Reyataz (atazanavir) + Norvir (ritonavir) + Truvada (emtricitabine/tenofovir disoproxil fumarate) 8 months ago (baseline HIV viral load: 325,000 copies/mL (325 × 10^6 copies/L), CD4+ T cell count = 475 cells/mm^3 (475 × 10^6/L).

At her last appointment 1 month ago, her HIV viral load was < 20 copies/mL and CD4+ T-cell count = 780 cells/mm^3 (780 × 10^6/L). Today, her HIV viral load is 12,000 copies/mL (12 × 10^6 copies/L). Today, she complains of GERD and has been taking omeprazole for the past month. She also complains of noticeable yellowing of her eyes which she states is really bothering her.

Was this patient initiated on a first-line guideline-recommended treatment regimen for HIV?

What factors should be considered when trying to determine causes of virologic failure?

You decide to switch the patient's regimen due to side effects and her inability to take the medication as prescribed.

What additional laboratory tests should be obtained at this visit?

Given the patient's comorbidity, what agents should you try to include in this new regimen?

What are some important general counseling points for this patient?

What monitoring assessments and follow-up would you recommend?

Preexposure Prophylaxis (PrEP)

Multiple large-scale clinical trials in populations at highest risk for acquiring HIV have demonstrated that antiretrovirals, particularly TDF + emtricitabine, in combination with effective risk-reduction services (eg, counseling, access to condoms, and treatment of STI), reduce the rate of HIV transmission. Data from these trials have led to the FDA approval of Truvada (fixed-dose combination of TDF 300 mg and emtricitabine 200 mg), as preexposure prophylaxis (PrEP), to reduce the risk of acquiring HIV-1 in adult men who have sex with men (MSM), heterosexually active men and women, and injection drug users who are at substantial risk of HIV acquisition.[20,22] Patients must be tested for HIV at baseline and minimally every 3 months while taking PrEP. STI testing should occur every 3 to 6 months for patients taking PrEP. Additionally, due to the potential toxicities associated with TDF, renal function must be assessed at baseline and at 6-month intervals in patients taking (Truvada) as PrEP. Patient counseling including stressing the importance of medication adherence should be routinely provided as medication adherence has been linked to PrEP efficacy.[22] In 2019, the FDA approved Tenofovir alafenamide + emtricitabine (Descovy) is for PrEP in at-risk adults and adolescents weighing at least 35 kg, except in individuals at risk from receptive vaginal sex.

OUTCOME EVALUATION

KEY CONCEPT The success of ART is measured by the degree to which the therapy (a) restores and preserves immunologic function, (b) maximally and durably suppresses plasma HIV RNA, (c) improves quality of life, (d) reduces HIV-related morbidity and mortality, and (e) prevents opportunistic infections. **KEY CONCEPT** The major outcome parameters are plasma HIV RNA, CD4 T-lymphocyte absolute count, and percentage. Adequate virologic response in antiretroviral naïve patients is a 1-log decrease in plasma HIV RNA by 2 to 8 weeks after starting medications, followed by concentrations less than 50 copies/mL (50 × 10^3 copies/L) by 12 to 16 weeks based upon the assay available (if plasma HIV RNA < 100,000/mL [100 × 10^6/L] or by 16–24 weeks if plasma HIV RNA > 100,000/mL [100 × 10^6/L]). An immunologic response in antiretroviral naïve patients consists of an increase in CD4 cell count that averages 50 to 150 cells/mm^3 (50 × 10^6–150 × 10^6/L) during the first year of cART (with a faster response in the first 3 months). Virologic failure is defined as the inability to obtain or maintain a plasma HIV RNA less than 200 copies/mL (200 × 103 copies/L), whereas incomplete virologic response is defined as two consecutive plasma HIV RNA greater than 200 copies/mL (200 × 103 copies/L) after 24 weeks of therapy.

Upon initiating or changing ART, plasma HIV RNA should be measured after 2 to 8 weeks and every 4 to 8 weeks until undetectable. Once the viral load is stable (eg, undetectable), plasma HIV RNA is monitored generally every 3 to 6 months. In highly treatment-experienced patients, adequate immunologic response may be only a stable, or slightly increased, CD4$^+$ count and a stable HIV RNA. This may be enough to prevent clinical progression. However, with new agents available for treatment-experienced patients, the goal of treatment should be to reestablish maximal viral suppression to less than 20 to 75 plasma HIV RNA copies/mL (20–75 × 10^3 copies/L), depending on the assay used.[9]

There should be a plan for each patient to assess the effectiveness of ART after initiation. Patients should have follow-up within the first week after initiating a new drug regimen. At each clinic visit, patients should be evaluated for the presence of adverse drug reactions, drug allergies, medication adherence, and potential drug interactions. Antiretrovirals have both class-associated and drug-specific adverse effects (see Tables 87–5 and Table 87–6). If the patient experiences any of the serious, life-threatening effects (Table 87–8), the offending agent should be discontinued promptly, and in most cases, the patient cannot be rechallenged. Potential long-term complications that may reduce the quality of life are listed in Table 87–9. If the patient does not tolerate a medication despite efforts to minimize or eliminate barriers to adherence, consider changing the drug.[9]

KEY CONCEPT Treatment of HIV is lifelong. Unplanned short-term treatment interruptions may be necessary due to illness that precludes administration of oral therapy. If a patient must interrupt therapy due to illness, all drugs of the regimen should be stopped at the same time, regardless of half-life. The strategy of scheduling elective treatment interruptions (where patients stop and start ART based on CD4$^+$ T-cell count criteria) has been evaluated in several clinical trials. Viral rebound occurs quickly after stopping therapy and worsens immune function, causes clinical progression, and may even result in death. More information about treatment interruption can be found in the 2021 DHHS Guidelines.[9]

Table 87–8

Serious Adverse Effects and Management

Adverse Effects	Drug	Signs and Symptoms	Risk Factors	Prevention/Monitoring	Management
Hepatotoxicity	Efavirenz, nevirapine, PIs, most NRTIs, dolutegravir in patients with HBC/HCV coinfection and MVC	**Onset:** NNRTI—60% within first 12 weeks PI—weeks to months NRTI—months to years **Symptoms:** NNRTI—asymptomatic to nonspecific symptoms, such as anorexia, weight loss, or fatigue PI—generally asymptomatic, some with anorexia, weight loss, jaundice NRTI—zidovudine, didanosine, stavudine may cause hepatotoxicity associated with lactic acidosis; lamivudine, emtricitabine, or tenofovir may cause HBV flare when these drugs are withdrawn Dolutegravir: asymptomatic, some with jaundice	HBV or HCV coinfection Alcoholism Concomitant hepatotoxic drugs	Monitor LFTs at least every 3–4 months	Rule out other causes. For symptomatic patients: D/C all antiretrovirals and other potential hepatotoxic agents; after symptoms and LFTs normalize, begin new antiretroviral regimen (without the potential offending agents). For asymptomatic patients: If ALT > 5–10 × ULN, may consider D/C antiretrovirals or continue with close monitoring; after symptoms and LFTs normalize, begin new antiretroviral regimen (without the potential offending agents)
Lactic acidosis/hepatic steatosis ± pancreatitis	NRTIs (esp. stavudine, didanosine, zidovudine)	**Onset:** Months after initiation **Symptoms:** Nonspecific GI (nausea, anorexia, abdominal pain, vomiting, weight loss, fatigue) Laboratory values: ↑ lactate, ↓ arterial pH, ↓ serum bicarbonate, ↑ AST/ALT, ↑ PT, ↑ T.bili, ↓ serum albumin, ↑ amylase/lipase (with pancreatitis)	Stavudine + didanosine Female sex Obesity Pregnancy Didanosine + hydroxyurea or ribavirin ↑ Duration of NRTI use	None unless symptoms present Consider lactate concentrations in patients with ↓ serum bicarbonate or ↑ anion gap	D/C all antiretrovirals; symptomatic support with fluids; some patients require IV bicarbonate, hemodialysis, parenteral nutrition, or mechanical ventilation; once syndrome resolves, consider using NRTIs with ↓ mitochondrial toxicity (abacavir, tenofovir, lamivudine, or emtricitabine); monitor lactate after restarting NRTIs; some clinicians use NRTI-sparing regimens
Stevens–Johnson syndrome/toxic epidermal necrosis	Nevirapine > efavirenz, delavirdine, etravirine; also, amprenavir, abacavir, zidovudine, didanosine, indinavir lopinavir/r, atazanavir, darunavir, rilpivirine, raltegravir	**Onset:** First day–weeks after therapy start **Symptoms:** Skin eruption with mucosal ulcerations; fever, tachycardia, malaise, myalgia, arthralgia; for nevirapine may also have hepatic toxicity	Nevirapine—female, Black, Asian, Hispanic	Nevirapine: use 2-week lead in 200 mg daily, then 200 mg twice a day Avoid corticosteroid use during dose escalation—may increase rash incidence Educate patients to report symptoms as soon as they appear	D/C all antiretrovirals as well as any other possible cause; aggressive symptom support; do not rechallenge patient with offending agent; if caused by nevirapine, avoid NNRTI class, if possible

Hypersensitivity reaction (HSR)	Abacavir	**Onset:** Median = 9 days; 90% within first 6 weeks **Symptoms:** Acute onset of symptoms (most frequent to least): high fever, diffuse skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms	HLA-B*5701, HLA-DR7, HLA-DQ3 Antiretroviral-naïve patients Higher incidence with 600 mg every day compared with twice a day dosing	HLA-B*5701 screening prior to abacavir if (+), label as abacavir allergic in medical chart Educate patients about signs and symptoms of HSR and the need of a prompt report	D/C abacavir and other antiretrovirals; rule out other causes of symptoms, most signs and symptoms resolve 48 hours after abacavir/D/C; do not rechallenge with abacavir after suspected HSR
Bone marrow suppression	Zidovudine	**Onset:** Few weeks–months **Symptoms:** Fatigue, risk of ↑ bacterial infections due to neutropenia; anemia, neutropenia	Advanced HIV High-dose zidovudine Preexisting anemia or neutropenia Concomitant use of bone marrow suppressants	Avoid in patients at high risk for bone marrow suppression; avoid other suppressing agents; monitor CBC with differential at least every 3 months	Switch to another NRTI; D/C concomitant bone marrow suppressant, if possible; for anemia: identify and treat other causes; consider erythropoietin treatment or blood transfusion, if indicated; for neutropenia: Identify and treat other causes; consider filgrastim treatment, if indicated
Nephrotoxicity	Tenofovir disoproxil fumarate. Switching from TDF to TAF is associated with improvement in proteinuria and renal biomarkers	**Onset:** Tenofovir—weeks to months after therapy **Symptoms:** Tenofovir disoproxil fumarate—asymptomatic to symptoms of nephrogenic diabetes insipidus, Fanconi syndrome; ↑ serum creatinine, proteinuria, hypophosphatemia, glycosuria, hypokalemia, nonanion gap metabolic acidosis	History of renal disease Concomitant use of nephrotoxic drugs	Avoid use of other nephrotoxic drugs; adequate hydration if on indinavir; monitor creatinine, urinalysis, serum potassium and phosphorus in patients at risk	D/C offending agent, generally reversible; supportive care; electrolyte replacement as indicated

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood cell count; CPK, creatine phosphokinase; D/C, discontinue; HBV, hepatitis B virus; HCV, hepatitis C virus; LFT, liver function tests; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; PT, prothrombin time; T.bili, total bilirubin; ULN, upper limit of normal.

Table 87–9

Other Adverse Effects and Management

Adverse Effects	Drug	Signs and Symptoms	Risk Factors	Prevention/Monitoring	Management
Potential Long-Term Complications					
Cardiovascular	Potentially all PIs and other antiretrovirals (efavirenz, stavudine—unfavorable lipid effect; abacavir, didanosine—unknown)	**Onset:** months to years after therapy initiation **Symptoms:** premature CVD	Other risk factors for CVD	Consider non–PI-based regimen; lifestyle modification, counseling	Early diagnosis, prevention, and pharmacologic therapy for hyperlipidemia, HTN, insulin-resistance/diabetes mellitus; assess cardiac risk factors; switch to NNRTI- or atazanavir-based regimen; avoid stavudine
Hyperlipidemia	All PIs (except atazanavir); stavudine; efavirenz (to a lesser extent) Tenofovir alafenamide	**Onset:** weeks to months after therapy initiation **Symptoms:** all PIs except atazanavir—↑ LDL and total cholesterol (TC), ↑↓ HDL; lopinavir/ritonavir and ritonavir—disproportionate ↑ TG; stavudine—↑ TG; may also ↑ LDL and TC; efavirenz or nevirapine—↑ HDL, slight ↑ TG Tenofovir alafenamide: ↑ TG, ↑ LDL, ↑ HDL	Underlying hyperlipidemia PI: Tipranavir/r > lopinavir/r and ritonavir > nelfinavir and amprenavir > indinavir and saquinavir > atazanavir NNRTI: < PIs; efavirenz > nevirapine, etravirine, or rilpivirine NRTI: stavudine > zidovudine and tenofovir most common	Use non-PI, non–stavudine-based regimens; use atazanavir-based regimen; monitor fasting lipid profile at baseline, 3–6 months after new regimen, then at least annually	Assess cardiac risk factor; lifestyle modification; switch to antiretrovirals with fewer lipid effects; consider statin therapy
Insulin resistance/ diabetes mellitus	All PIs	**Onset:** weeks to months after therapy initiation **Symptoms:** polyuria, polydipsia, polyphagia, fatigue, weakness; exacerbation of hyperglycemia in patients with underlying diabetes	Underlying hyperglycemia, family history of diabetes mellitus	Use PI-sparing regimens; monitor fasting blood glucose 1–3 months after starting new regimen, then at least every 3–6 months	Diet and exercise; consider switching to an NNRTI-based regimen; if need for pharmacologic therapy, consider metformin, sulfonylurea, "glitazones," or insulin, where indicated
Osteoporosis/ Osteonecrosis	All ARTs, Tenofovir disoproxil fumarate. TDF has been shown to lead to 1%–3% greater bone mineral density loss compared to other NRTIs	**Onset:** insidious **Symptoms:** mild-to-moderate periarticular pain; 85% of cases involve one or both femoral heads	Diabetes Prior steroid use Advanced age Alcohol use Hyperlipidemia	Risk reduction (limit steroid and alcohol use): for asymptomatic cases with < 15% bony head involvement, monitor with MRI every 3–6 months × 1 year, then every 6 months × 1 year, then annually	Conservative: reduce weight-bearing activity on affected joint; reduce risk factors; analgesics as needed; surgical: core decompression ± bone grafting (early disease); total joint arthroplasty (severe disease)
Quality-of-Life Complications					
CNS effects	Efavirenz, Doravirine, all INSTIs	**Onset:** first few doses **Symptoms:** one or more of the following: drowsiness, insomnia, abnormal dreams, dizziness, impaired concentration, depression, hallucination; exacerbation of psychiatric disorders; psychosis; suicidal ideation	Preexisting or unstable psychiatric illness Use of other drugs with CNS effects May be more common in African Americans due to genetic predisposition of ↓ clearance	Take no earlier than 2–3 hours before bedtime; take on an empty stomach; counsel patients to avoid operating machinery during first 2–4 weeks of therapy	Symptoms usually diminish or resolve after 2–4 weeks; may consider discontinuing therapy if symptoms persist and significantly impair daily function or exacerbate psychiatric illness

Fat maldistribution	PIs, thymidine analogs (stavudine more common than zidovudine)	**Onset:** gradually, months after therapy initiation **Symptoms:** lipoatrophy—peripheral fat loss (facial thinning, thinning of extremities and buttocks); lipohypertrophy—increase in abdominal girth, breast size, and dorsocervical fat pad (buffalo hump)	Lipoatrophy—low baseline body mass index	DEXA scan; lipoatrophy: avoid thymidine analogs or switch from zidovudine or stavudine to abacavir or tenofovir	Switching to other agents may slow or stop progression, but may not reverse effects; injectable poly-L-lactic acid for facial lipoatrophy, human growth hormone
GI intolerance	All PIs, zidovudine, Elvitegravir/cobicistat, Ibalizumab	**Onset:** first few doses **Symptoms:** nausea, vomiting, abdominal pain; diarrhea commonly seen with nelfinavir, lopinavir/ritonavir, and didanosine-buffered formulations	All patients	Taking with food may reduce symptoms (not for ibalizumab); may preemptively need antiemetics or antidiarrheals	May spontaneously resolve or become tolerable with time; nausea and vomiting: consider antiemetic prior to dosing; switch to less emetogenic agent; diarrhea: consider antimotility agents, calcium tablets, bulk-forming agents, and/or pancreatic enzymes
Injection site reactions	Enfuvirtide	**Onset:** first new doses **Symptoms:** pain, pruritus, erythema, ecchymosis, warmth, nodules, rarely injection site infection	All patients	Educate regarding use of sterile technique, solution at room temperature, rotation of injection sites, avoidance of sites with little subcutaneous fat or existing reactions	Massaging the area vigorously before and after injection may reduce pain; wear loose clothing around injection-site areas; take warm shower or bath prior to injection; rarely, warm compact or analgesics may be necessary

ART, antiretroviral; CVD, cardiovascular disease; D/C, discontinue; DEXA, dual-energy X-ray absorptiometry; GI, gastrointestinal; HTN, hypertension; INSTI, integrase inhibitor; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; TG, triglyceride.

Patient Care Process: Newly Diagnosed

Collect Information:

- Confirm HIV infection, screen for additional sexually transmitted infections, and assess the risk for opportunistic infections and need for prophylaxis.
- Create a safe and comfortable environment to obtain a thorough medical and medication history (prescription, nonprescription, and natural drug product use). Review and update patient allergies.
- Acquire baseline laboratory data (see Table 87–1) to stage HIV disease and to assist in the selection of cART drug regimens (genotypic resistance testing, HLA-B*5701).

Assess the Information:

- Assess patient's readiness for initiating cART.
- Evaluate comorbid conditions (eg, mental illness, substance abuse) and social issues (economic stability, lack of social support, insurance coverage) that may impair medication adherence.
- Assess the potential for clinically significant drug–drug, drug–food, drug–disease interactions.

Develop a Care Plan:

- Utilize results of genotype in conjunction with patient-specific factors to construct a recommended cART regimen.

Implement the Care Plan:

- Provide patient with basic information regarding HIV infection, progression of HIV/prognosis, treatment options, and support services available.
- Inform patient of the benefits of initiating cART, stressing the importance of 100% medication adherence.
- Educate patient on regimen-specific administration and common adverse drug effects (see Table 87–5). Warn patient of the key signs and symptoms of severe toxicity (i.e., jaundice and abacavir hypersensitivity reaction [HSR]).
- Provide risk reduction counseling on effective strategies to prevent HIV transmission and disclosure to sexual and/or needle-sharing partners.

Follow-up: Monitor and Evaluate:

- Assess response to cART therapy by drawing plasma HIV RNA within 2 to 4 weeks (no later than 8 weeks) after initiation of cART and every 4 to 8 weeks until plasma HIV RNA is suppressed.
- Monitor immune reconstitution by measuring CD4 count 3 months after initiation of cART.
- Evaluate tolerability of regimen by assessing for adverse events and medication adherence.
- Ensure continued coordination of care and management of mental and psychosocial determinants of health

Abbreviations Introduced in This Chapter

AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
cART	Combination antiretroviral therapy
CPK	Creatine phosphokinase
CVD	Cardiovascular disease
CYP	Cytochrome P-450 isoenzyme
D/C	Discontinue
DEXA	Dual-energy X-ray absorptiometry
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GERD	Gastroesophageal reflux disease
Gp	Glycoprotein
HAART	Highly active antiretroviral therapy
HBeAg	Hepatitis B early antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSR	Hypersensitivity reaction
HTN	Hypertension
IAS-USA	International Antiviral Society–USA
INSTI	Integrase strand transfer inhibitor
LDL	Low-density lipoprotein
LFTs	Liver function tests
MSM	Men who have sex with men
MTCT	Mother-to-child transmission
NAT	Nucleic acid test
NNRTI	Nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NtRTI	Nucleotide reverse transcriptase inhibitor
P-gp	P-glycoprotein
PCP	*Pneumocystis jiroveci* (formerly *carinii*) pneumonia
PI	Protease inhibitor
PrEP	Preexposure prophylaxis
PT	Prothrombin time
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
STI	Sexually transmitted disease
STI	Sexually transmitted infection
T.bili	Total bilirubin
TDF	Tenofovir disoproxil fumarate
TG	Triglyceride
ULN	Upper limit of normal

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Cancer Principles and Therapeutics

Lisa M. Holle

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the etiology of cancer.
2. Define the tumor, nodes, metastases (TNM) system of cancer staging.
3. Classify each drug used in the treatment of cancer and compare and contrast the mechanisms of action, uses, and adverse effects.
4. Outline actions for all healthcare professionals to prevent medication errors with cancer treatments.
5. Describe what cancer survivorship means and how this impacts future healthcare needs of an individual.

INTRODUCTION

KEY CONCEPT The word cancer covers a diverse array of tumor types that affect a significant number of Americans and individuals worldwide and are a major cause of mortality. The term cancer actually refers to more than 100 different diseases. What is common to all cancers is that the cancerous cell is uncontrollably growing and has the potential for invading local tissue and spreading to other parts of the body, a process called metastases. Cancer is the second leading cause of death behind heart disease.[1] In 2021, it was projected that nearly 1.9 million Americans will be diagnosed with cancer, and that an estimated 608,570 Americans will die from cancer.[1] Figure 88–1 describes cancers by gender, new cases, and deaths.

Once diagnosed, a cancer patient may encounter many different healthcare professionals. All healthcare professionals must collaborate to ensure safe and appropriate prescribing, preparation, administration, and monitoring of anticancer agents; management of toxicities; resolution of reimbursement issues; and participation in clinical trials. The pharmacist is a pivotal member of the care team because of their medication expertise.[2,3]

As a result of advances in research and technology, available cancer treatments have increased dramatically in the last couple of decades. The fields of radiation therapy, surgery, and drug development have made enormous progress over the years. Therefore, patients are often receiving treatments that are less toxic and with better treatment outcomes than in the past. Supportive care therapies have also improved, and patients now may be at less risk for toxicity and have a better quality of life than patients in the past. Twenty years ago, most patients received chemotherapy in the hospital because of side effects. Today, many more patients are able to receive chemotherapy in outpatient clinics and/or take oral anticancer agents at home.

Cancer Prevention

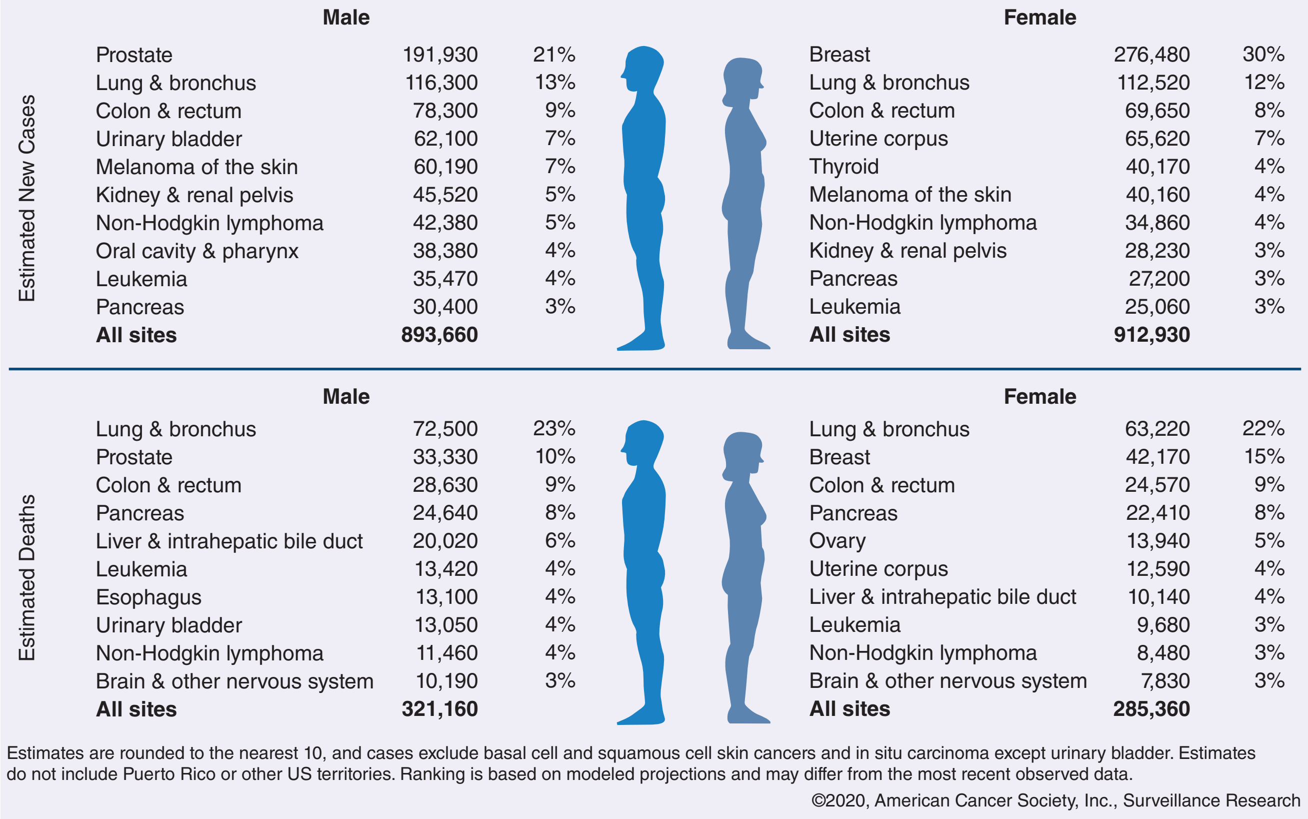
Because most cancers are not curable in advanced stages, cancer prevention is an important and active area of research. Both lifestyle modifications and chemoprevention agents may significantly reduce the risk of developing some cancers. An active area of investigation, The Food and Drug Administration (FDA) has approved vaccines that can help prevent cancer. Available vaccines include those that prevent infection with human papillomavirus (HPV), responsible for many cancers of the cervix, vulva, vagina, and anus and a vaccine that prevents hepatitis B viral infections, which can cause liver cancer. Additionally, orally administered medications, such as the selective estrogen receptor (ER) modulator (SERM) tamoxifen, reduces the risk of breast cancer in premenopausal women. Another SERM, raloxifene and the aromatase inhibitor (AI) exemestane both have shown a reduction in breast cancer in high-risk postmenopausal women. Because these agents will have adverse effects and possible long-term complications (eg, an increased risk of endometrial cancer with the use of tamoxifen), benefits versus risks needs to be weighed when initiating these breast cancer prevention strategies.

Tobacco

Tobacco smoking increases the risk of developing not only lung cancer but also many other types of cancer, including cancer of the bladder, mouth, pharynx, larynx, and esophagus as well as kidney cancer. Smoking cessation is associated with a gradual decrease in the risk of cancer, but more than 5 years is needed before a major decline in risk is detected. In addition, most studies have found that passive smoking (ie, secondhand smoke) also increases a person's risk of developing lung cancer.[4]

Ultraviolet Radiation

Ultraviolet light (sunlight or tanning booths and lamps) exposure may increase the risk of developing melanoma and other skin cancers, especially in individuals who have a positive family history, fair skin, light-colored eyes, high degrees of freckling, and a tendency to burn instead of tan. Practitioners can counsel patients on proper sun protection, including minimizing sun exposure, using sunscreens with a sun protection factor (SPF) of 15 or greater on exposed areas (along with proper reapplication), wearing protective clothing and sunglasses, avoiding tanning beds and sun lamps, and the importance of early detection.



Estimated New Cases

Male			Female		
Prostate	191,930	21%	Breast	276,480	30%
Lung & bronchus	116,300	13%	Lung & bronchus	112,520	12%
Colon & rectum	78,300	9%	Colon & rectum	69,650	8%
Urinary bladder	62,100	7%	Uterine corpus	65,620	7%
Melanoma of the skin	60,190	7%	Thyroid	40,170	4%
Kidney & renal pelvis	45,520	5%	Melanoma of the skin	40,160	4%
Non-Hodgkin lymphoma	42,380	5%	Non-Hodgkin lymphoma	34,860	4%
Oral cavity & pharynx	38,380	4%	Kidney & renal pelvis	28,230	3%
Leukemia	35,470	4%	Pancreas	27,200	3%
Pancreas	30,400	3%	Leukemia	25,060	3%
All sites	**893,660**		**All sites**	**912,930**	

Estimated Deaths

Male			Female		
Lung & bronchus	72,500	23%	Lung & bronchus	63,220	22%
Prostate	33,330	10%	Breast	42,170	15%
Colon & rectum	28,630	9%	Colon & rectum	24,570	9%
Pancreas	24,640	8%	Pancreas	22,410	8%
Liver & intrahepatic bile duct	20,020	6%	Ovary	13,940	5%
Leukemia	13,420	4%	Uterine corpus	12,590	4%
Esophagus	13,100	4%	Liver & intrahepatic bile duct	10,140	4%
Urinary bladder	13,050	4%	Leukemia	9,680	3%
Non-Hodgkin lymphoma	11,460	4%	Non-Hodgkin lymphoma	8,480	3%
Brain & other nervous system	10,190	3%	Brain & other nervous system	7,830	3%
All sites	**321,160**		**All sites**	**285,360**	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

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FIGURE 88–1. Cancer incidences (*top*) and deaths (*bottom*) in the United States for males and females—2020 estimates. (Reproduced, with permission, from American Cancer Society. Cancer Facts and Figures 2020. Atlanta, GA: American Cancer Society, Inc.)

CARCINOGENESIS

The exact cause of cancer remains unknown and is probably very diverse given the vast array of diseases called cancer. It is thought that cancer develops from a single cell in which the normal mechanisms for control of growth and proliferation are altered. Current evidence indicates that there are four stages in the cancer development process. The first step, **initiation**, occurs when a carcinogenic substance encounters a normal cell to produce genetic damage and results in a mutated cell. The environment is altered by carcinogens or other factors to favor the growth of the mutated cell over the normal cell during **promotion**, the second step. The main difference between initiation and promotion is that promotion is a reversible process. Third, **transformation** (or **conversion**) occurs when the mutated cell becomes malignant. Depending on the type of cancer, many years may elapse between the carcinogenic phases and the development of a clinically detectable tumor. Finally, **progression** occurs when cell proliferation takes over and the tumor spreads or develops metastases.

There are substances known to have carcinogenic risks, including chemicals, environmental factors, and viruses. Chemicals in the environment, such as aniline and benzene, are associated with the development of bladder cancer and leukemia, respectively. Environmental factors, such as excessive sun exposure, can result in skin cancer, and smoking is widely known as a cause of lung cancer. Viruses, including HPV, Epstein-Barr virus, and hepatitis B virus, have been linked to cervical cancers, lymphomas, and liver cancers, respectively. Anticancer agents such as the alkylating agents (eg, melphalan), anthracyclines (eg, doxorubicin), epipodophyllotoxins (eg, etoposide), and poly ADP ribose polymerase (PARP) inhibitors (eg, olaparib) can cause secondary malignancies (eg, leukemias) years after therapy has been completed. Additionally, factors such as the patient's age, gender, family history, diet, and chronic irritation or inflammation may be considered to be promoters of carcinogenesis.

Cancer Genetics

Because the human genome has been sequenced and with the great improvements in genetic technology, growing knowledge regarding the genetic changes of cancer exist. Two major classes of genes are involved in carcinogenesis: **oncogenes** and **tumor suppressor genes**. **Proto-oncogenes** are normal genes that, through some genetic alteration caused by carcinogens, change into oncogenes. Proto-oncogenes are present in all normal cells and regulate cell function and replication. Genetic damage of the proto-oncogene may occur through point mutation, chromosomal rearrangement, or an increase in gene function, resulting in the oncogene. The genetic damage may either be inherited from an individual's parents (germline mutations) or by way of carcinogenic agents (eg, smoking). The oncogene produces abnormal or excessive gene product that disrupts normal cell growth and proliferation.[5] As a result, this may cause the cell to have a distinct growth advantage, increasing its likelihood of becoming cancerous. Table 88–1 provides examples of oncogenes by their cellular function and associated cancer.[6]

Table 88–1

Examples of Oncogenes and Tumor Suppressor Genes

Gene	Function	Associated Human Cancer
Oncogenes		
Genes for growth factors or their receptors		
EGFR? ERBB1	Codes for epidermal growth factor (EGFR) receptor	Glioblastoma, breast, head and neck, and colon cancers
HER2/ERBB2	Codes for a growth factor receptor	Breast, salivary gland, prostate, bladder, and ovarian cancers
RET	Codes for a growth factor receptor	Thyroid cancer
Genes for cytoplasmic relays in stimulatory signaling pathways		
KRAS and NRAS	Code for guanine nucleotide-proteins with GTPase activity	Lung, ovarian, colon, pancreatic cancers Neuroblastoma, acute leukemia
Genes for transcription factors that activate growth-promoting genes		
cMYC	Codes for transcription factor	Leukemia and breast, colon, gastric, and lung cancers
NMYC	Codes for transcription factor	Neuroblastoma, small cell lung cancer, and glioblastoma
Genes for cytoplasmic kinases		
BCR-ABL	Codes for a nonreceptor tyrosine kinase	Chronic myelogenous leukemia
ALK	Receptor tyrosine kinase	Lung cancer, lymphomas, neuroblastoma, and ovarian cancer
BRAF	Serine-threonine protein kinase	Colon cancer, lung cancer, melanoma, ovarian, thyroid cancer
KIT (CD117)	Receptor tyrosine kinase	Acute Leukemia, gastrointestinal, stromal tumor, and gastrointestinal stromal tumor
PIK2CA	Lipid kinases	Lung cancer, ovarian cancer
RET	Codes a receptor tyrosine kinase	Lung cancer, thyroid cancer
Genes for other molecules		
BCL2	Codes for a protein that blocks apoptosis	Indolent B-cell lymphomas
BCL1/PRAD1	Codes for cyclin D_1, a cell-cycle clock stimulator	Breast, head, and neck cancers
MDM2	Protein antagonist of p53 tumor suppressor protein	Sarcomas
Tumor-Suppressor Genes		
Genes for proteins in the cytoplasm		
APC	Step in a signaling pathway	Colon and gastric cancer
NF1	Codes for a protein that inhibits the stimulatory Ras protein	Neurofibroma, leukemia, and pheochromocytoma
NF2	Codes for a protein that inhibits the stimulatory Ras protein	Meningioma, ependymoma, and schwannoma
Genes for proteins in the nucleus		
MTS1	Codes for p16 protein, a cyclin-dependent kinase inhibitor	Involved in a wide range of cancers
RB1	Codes for the pRB protein, a master brake of the cell cycle	Retinoblastoma, osteosarcoma, and bladder, small cell lung, prostate, and breast cancers
TP53	Codes for the p53 protein, which can halt cell division and induce apoptosis	Involved in a wide range of cancers
PTEN	Phosphatase and tensin homolog deleted on chromosome ten	Lung cancer, ovarian cancer
Genes for protein whose cellular location is unclear		
BRCA1	DNA repair, transcriptional regulation	Breast and ovarian cancers
BRCA2	DNA repair	Breast cancer
VHL	Regulator of protein stability	Kidney cancer
MSH2, MLH1, PMS1, PMS2, MSH6	DNA mismatch repair enzymes	Hereditary nonpolyposis colorectal cancer

From Cordes LM, Shord SS. Cancer treatment and chemotherapy. In: DiPiro JT, Yee GC, Posey LM, et al. eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020: Table 144–2.

Tumor suppressor genes inhibit inappropriate cellular growth and proliferation. When gene loss or mutation occurs, this results in a loss of control over normal cell growth. The *TP53* gene is one of the most common tumor suppressor genes, and mutations of *TP53* may occur in up to 50% of all malignancies. This gene stops the cell cycle to enable "repair" of the cell. If *TP53* is inactivated, then the cell allows the mutations to occur. Although mutations of the *TP53* gene are found in many tumors, such as breast, colon, and lung cancer, it is also associated with drug resistance of cancer cells. Deoxyribonucleic acid (DNA) repair genes fix errors in DNA that occur because of environmental factors or errors in replication and can be classified as tumor suppressor genes. Mutations in DNA repair genes have been reported in hereditary nonpolyposis colon cancer and in some breast cancer syndromes.

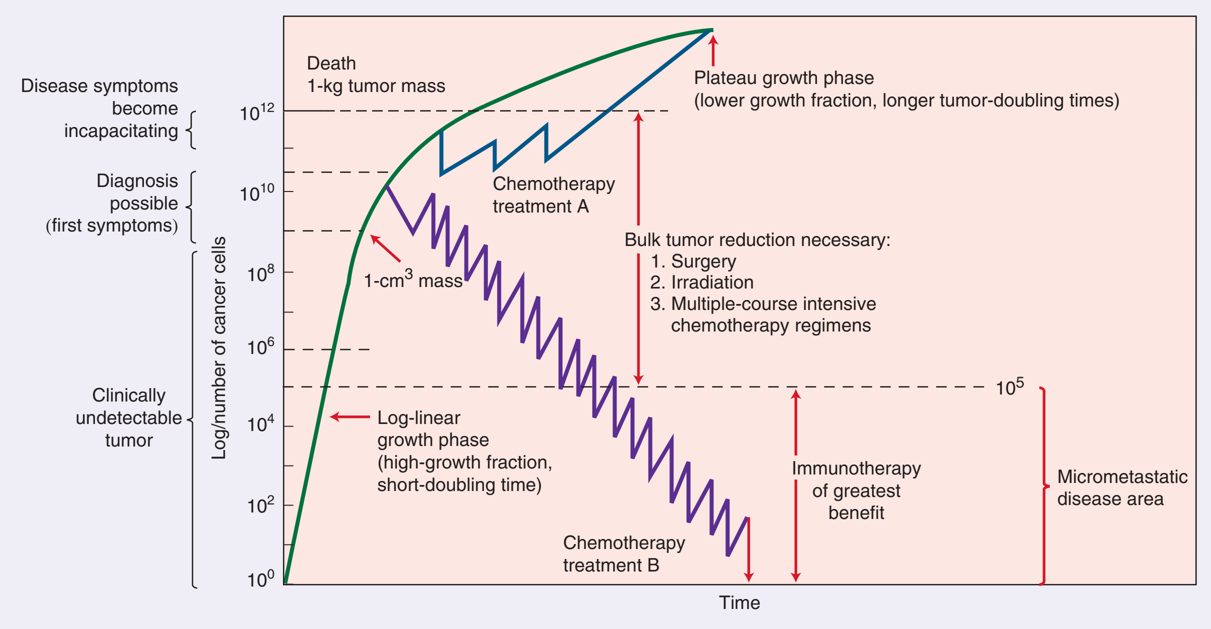

FIGURE 88–2. The Gompertzian growth curve demonstrating symptoms and treatments versus tumor volume.

KEY CONCEPT Numerous cellular changes occur in the genetic material of the cancer cell so that programmed cell death (PD), or apoptosis, does not occur. Proliferation of cancer cells goes unregulated. If mutations persist and cells are not repaired or suppressed, cancer may develop. Apoptosis, or PD, may prevent the mutated cell from becoming cancerous. Loss of *TP53* and overexpression of B-cell lymphoma 2 (*BCL2*) are two examples of changes within the cell that occur to result in enhanced cell survival.

Identification of genes involved in cancer may be conducted for various reasons, including cancer screening to determine if an individual is at an increased risk of cancer, to develop new anticancer agents, to aid in diagnosis, and to predict response and/or the toxicity of the agents used in individual patients.

Principles of Tumor Growth

It takes about 10^9 cancer cells to be clinically detectable by palpation or radiography. Figure 88–2 demonstrates the classic Gompertzian kinetics tumor growth cycle. From the diagram, one can see that malignant cell growth occurs many times before a mass may be detected. The number of malignant cells may decrease drastically because of surgery or in decreasing steps by each administration of chemotherapy. One dosing round, or cycle, of chemotherapy does not eliminate all malignant cells; therefore, repeated cycles of chemotherapy are administered to eliminate tumor cell burden. The cell kill hypothesis states that a fixed percentage of tumor cells will be killed with each cycle of chemotherapy. According to this hypothesis, the number of tumor cells will never reach zero. This theory assumes that all cancers are equally responsive and that anticancer drug resistance and metastases do not occur, which is not the case.[7]

Metastases

A metastasis is a growth of the same cancer cell found at some distance from the primary tumor site.[8] The metastasis may be large, or it may be just a few cells that may be detected through polymerase chain reaction (PCR); however, the presence of metastasis at diagnosis usually is associated with a poorer prognosis than a patient with no known metastatic disease. As the technology to detect malignant cells evolves, the dilemma exists on how to treat patients based on current guidelines that were not based on cellular detection technology.

Cancers spread usually by two pathways: hematogenous (through the bloodstream) or through the lymphatics (drainage through adjacent lymph nodes). The malignant cells that split from the primary tumor find a suitable environment for growth. It is believed that malignant cells secrete mediators that stimulate the formation of blood vessels for growth and oxygen, the process of angiogenesis. Common metastatic sites for solid tumors include the brain, bone, lung, and liver.

PATHOPHYSIOLOGY

Tumor Origin

Tumors may arise from any of four basic tissue types: epithelial, connective (ie, muscle, bone, and cartilage), lymphoid, or nerve tissue. The suffix *-oma* is added to the name of the cell type if the tumor cells are benign. A *lipoma* is a benign growth that resembles fat tissue.

Precancerous cells have cellular changes that are abnormal but not yet malignant and may be described as *hyperplastic* or *dysplastic*. Hyperplasia occurs when a stimulus is introduced and reverses when the stimulus is removed. Dysplasia is an abnormal change in the size, shape, or organization of cells or tissues.

Malignant cells are divided into categories based on the cells of origin. Carcinomas arise from epithelial cells, whereas sarcomas arise from muscle or connective tissue. Adenocarcinomas arise from glandular tissue. *Carcinoma* in situ refers to cells limited to epithelial origin that have not yet invaded the basement membrane. Malignancies of the bone marrow or lymphoid tissue, such as leukemias or lymphomas, are named differently.

Tumor Characteristics

Tumors are either benign or malignant. Benign tumors often are encapsulated, localized, and indolent; they seldom metastasize; and they rarely recur once removed. Histologically, the cells resemble the cells from which they developed. Malignant tumors are invasive and spread to other locations even if the primary tumor is removed. The cells no longer perform their usual functions, and their cellular architecture changes. This loss of structure and function is called anaplasia. Despite improvements in screening procedures, many patients have metastatic disease at the time of diagnosis. Usually, once distant metastases have occurred, the cancer is considered incurable.[9]

Patient Encounter 1, Part 1

The patient is a 71-year-old previously healthy man who has had symptoms of fatigue, bright red blood when urinating for 2 weeks and back pain. He has self-treated with over-the-counter (OTC) pain products without relief. Today, he presents to his primary care provider for evaluation. His complete blood count (CBC) reveals a hemoglobin level of 12.6 g/dL and his PSA level is 22.4 ng/dL. He is referred to an urologist for further evaluation.

After a prostate gland biopsy and subsequent computed tomography (CT) and bone scans, a diagnosis of metastatic prostate cancer is made and treatment is planned to start as soon as possible.

What signs and symptoms does this patient have that are consistent with a cancer presentation?

What is your desired outcome when treating this patient?

DIAGNOSIS OF CANCER

Cancer can present as a number of different signs and symptoms. Unfortunately, many people fear a diagnosis of cancer and may not seek medical attention at the first warning signs when the disease is at its most treatable stage. After the initial visit with the clinician, a variety of tests will be performed, which are somewhat dependent on the initial differential diagnoses. Appropriate laboratory tests, radiologic scans, and tissue samples are necessary. The sample of tissue may be obtained by a biopsy, fine-needle aspiration, or exfoliative cytology. No treatment of cancer should be initiated without a pathologic diagnosis of cancer. During the pathologic workup, genetic analysis may be done. Depending on the type of cancer, the genetic analysis can provide the additional information on prognosis of the malignancy and whether certain therapies may be appropriate.

Once the pathology of cancer is established, staging of the disease is done before treatment is initiated. **KEY CONCEPT** The basis of cancer staging is tumor size, extent of lymph node involvement, and the presence or absence of metastases, also referred to as the tumor, nodes, metastases (TNM) system (Table 88–2),[10] and is usually referred to as stages I, II, III, or IV. Not all cancers can be staged according to this system, but many of the solid tumors are. Staging cancer is an important for determing prognosis and guiding treatment decisions.

Some cancers produce substances (eg, proteins) that are detected by a blood test and may be useful in following response to therapy or detecting a recurrence; these are referred to as tumor markers. An example of a clinically used tumor marker is the prostate-specific antigen (PSA). The PSA serum level is used to monitor response to treatment. Unfortunately, some tumor markers are nonspecific and may be elevated from nonmalignant causes. In the case of PSA, nonmalignant causes such as prostatitis, trauma, surgery, ejaculation, some medications, benign prostatic hypertrophy, or riding on an exercise bicycle can all cause increased PSA levels, which needs to be considered when using tumor markers to assess cancer presence of response.[9]

Clinical Presentation and Diagnosis: Cancer Chemotherapy and Treatment

Signs and Symptoms

The seven warning signs of cancer are:

- Change in bowel or bladder habits
- A sore that does not heal
- Unusual bleeding or discharge
- Thickening or lump in breast or elsewhere
- Indigestion or difficulty in swallowing
- Obvious change in a wart or mole
- Nagging cough or hoarseness

The eight warning signs of cancer in children are:

- Continued, unexplained weight loss
- Headaches with vomiting in the morning
- Increased swelling or persistent pain in bones or joints
- Lump or mass in abdomen, neck, or elsewhere
- Development of a whitish appearance in the pupil of the eye
- Recurrent fevers not caused by infections
- Excessive bruising or bleeding
- Noticeable paleness or prolonged tiredness

Diagnostic Procedures

- Laboratory tests: CBC, lactate dehydrogenase (LDH), renal function, and liver function tests
- Radiologic scans: X-rays, CT scans, magnetic resonance imaging (MRI), positron emission tomography (PET)
- Biopsy of tissue or bone marrow with pathologic evaluation
- Cytogenetics
- Tumor markers

Staging determination of the primary tumor size, extent of lymph node involvement, and the presence or absence of metastases, referred to as the TNM system (see Table 88–2). Most solid tumors are staged according to the TNM classification system. The size of the primary tumor, extent of nodal involvement, and the presence of metastases are used to determine the stage. Metastases are cancer cells that have spread to sites distant from the primary tumor site and have started to grow. The most frequently occurring sites of metastases of solid tumors are the brain, bone, liver, and lungs.

Table 88–2

Tumor (T), Node (N), Metastasis (M) Staging for Non–Small Cell Lung Cancer

Primary Tumor		Description
Tx		Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0		No evidence of primary tumor
Tis		Carcinoma in situ
T_1	T_{1a} (mi)	Tumor under 3 cm in greatest dimension, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus
		Minimally invasive adenocarcinoma
	T_{1a}	Superficial spreading tumor in central airways (spreading tumor of any size but confined to the tracheal or bronchial wall) and tumor ≤ 1 cm in greatest dimension
	T_{1b}	Tumor > 1 cm but ≤ 2 cm in greatest dimension
	T_{1c}	Tumor > 2 cm but ≤ 3 cm in greatest dimension
T_2		Tumor > 3 cm but ≤ 5 cm, or tumor with any of the following features: • Involves main bronchus regardless of distance from the carina but without involvement of the carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
	T_{2a}	Tumor > 3 cm but ≤ 4 cm in greatest dimension
	T_{2b}	Tumor > 4 cm but ≤ 5 cm in greatest dimension
T_3		Tumor > 5 cm but ≤ 7 cm in greatest dimension of associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: • chest wall (including the parietal pleura and superior sulcus) • phrenic nerve • parietal pericardium
T_4		Tumor > 7 cm in greatest dimension or associated with separate tumor nodules(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures • diaphragm • mediastinum • heart • great vessels • trachea • recurrent laryngeal nerve • esophagus • vertebral body • carina
Regional lymph nodes (N)		
N_x		Regional lymph nodes cannot be assessed.
N_0		No regional lymph node metastases
N_1		Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N_2		Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N_3		Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant metastasis (M)		
M_0		No distant metastasis
M_1		Distant metastasis
	M_{1a}	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion
	M_{1b}	Single extrathoracic metastasis
	M_{1c}	Multiple extrathoracic metastasis in one or more organs

Stage	T	N	M	5-Year Survival (%)
Stage 0	T_{is}	N_0	M_0	
Stage Ia	T_{1a}	N_0	M_0	92
Stage Ib	T_{2a}	N_0	M_0	68
Stage IIa	T_{2b}	N_0	M_0	60
Stage IIb	T_1, T_2	N_1	M_0	53
	T_3	N_0	M_0	
Stage IIIa	T_1, T_2	N_2	M_0	36
	T_3, T_4	N_1	M_0	
	T_4	N_0	M_0	
Stage IIIb	T_1, T_2	N_3	M_0	26
	T_3, T_4	N_2	M_0	
Stage IIIc	T_3, T_4	N_3	M_0	13
Stage IVa	Any T	Any N	M_{1a} or M_{1b}	10
Stage IVb	Any T	Any N	M_{1c}	0

From Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The eighth edition lung cancer stage classification. Chest. 2017;151(1):193–203.

TREATMENT

Desired Outcome

Surgery may be able to remove all macroscopic disease; however, microscopic cells may still be present near the surgical site or may have traveled to other parts of the body. When malignant cells have traveled to other parts of the body and become established there and are able to grow in this new environment, they are called metastatic cancer cells. Thus, for chemotherapy-sensitive diseases, systemic therapies may be administered after surgery to destroy these microscopic malignant cells; this is called **adjuvant chemotherapy**. The goals of adjuvant chemotherapy are to decrease cancer recurrence by eliminating microscopic malignant cells and to prolong survival. Chemotherapy may also be given before surgical resection of the tumor; this is referred to as **neoadjuvant chemotherapy**. Chemotherapy given before surgery should decrease the tumor burden to be removed (which may result in a shorter surgical procedure or less physical disfigurement to the patient) and make the surgery easier to perform because the tumor has shrunk away from vital organs or vessels. Neoadjuvant chemotherapy also gives the clinician an idea of the responsiveness of the tumor to that particular chemotherapy.

Chemotherapy may be given to cure cancers, or it may be given to help control the symptoms of an incurable cancer (also known as palliation). **Palliative care**, however, is used throughout therapy to prevent or treat, as early as possible, the symptoms and side effects of the disease and treatment psychological, social, and spiritual problems. It consists of pharmacologic and nonpharmacologic treatments to improve quality of life and is most effective when initiated at the time of other treatments.[11]

Response

The responses to chemotherapy for solid tumors are described as **complete response (CR)**, **partial response (PR)**, **stable disease (SD)**, or **disease progression**. A cure in oncology implies that the cancer is completely gone, and the patient will have the same life expectancy as a patient without cancer. The response evaluation criteria in solid tumors (RECIST) was developed in 2000 and revised in 2009 and is considered to be the standard criteria to evaluate a response to therapy (Table 88–3).[12] The term **overall objective response rate** refers to all patients with a PR or a CR.

Cancer cells may be **sensitive** to certain chemotherapy agents, but with repeated exposure, the cells may become **resistant** to treatment. The resistant cells then may grow and multiply. In some cancers, a number of genetic mutations, including epidermal growth factor receptor *(EGFR)*, reticular activating system (*RAS*), and *BRAF*, may be used to predict which patients will be sensitive to certain chemotherapy that targets these mutations. These mutations will be discussed in depth in the following cancer-specific chapters.

Nonpharmacologic Therapy

The three primary treatment modalities of cancer are surgery, radiation, and pharmacologic therapy. Surgery is useful to gain tissue for diagnosis of cancer and for treatment, especially those cancers with limited disease. Radiation plays a key role not only in the treatment and possible cure of cancer but also in palliative therapy. Together, surgery and radiation therapy may provide local control of symptoms of the disease. However, when cancer is widespread, surgery may play little or no role, but radiation therapy localized to specific areas may palliate symptoms.

Table 88–3

RECIST 1.1 Criteria: Target Lesion Evaluation

Term	Description
Complete response (CR)	Disappearance of all targeted lesions. All pathological lymph nodes must have decreased to < 10 mm in short axis
Partial response (PR)	At least a 30% decrease in the sum of the longest diameter (SLD) of target lesions from baseline
Progressive disease	SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest) The SLD must also demonstrate an absolute increase of at least 5 mm. (Two lesions increasing from 2 to 3 mm, for example, do not qualify)
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease

Adapted from Eisenhauer E, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–247.

Pharmacologic Therapy

Chemotherapy of cancer started in the early 1940s when nitrogen mustard was first administered to patients with lymphoma. Since then, numerous agents have been developed for the treatment of different cancers.

Dosing of Chemotherapy

Chemotherapeutic agents typically have a very narrow therapeutic index. If too much is administered, the patient may suffer from severe or even fatal toxicities. If too little is given, the desired effect on cancer cells may not be achieved. Many chemotherapy agents have significant organ toxicities that preclude using steadily increasing doses to treat the cancer. The doses of chemotherapy must be given at a frequency that allows the patient to recover from the toxicity of the chemotherapy; each period of chemotherapy dosing is referred to as a cycle. Each cycle of chemotherapy may have the same dosages; the dosages may be modified based on toxicity; or a chemotherapy regimen may alternate from one set of drugs given during the first, third, and fifth cycles to another set of different drugs given during the second, fourth, and sixth cycles. **Dose density** of chemotherapy refers to shortening of the period between cycles of chemotherapy. This can accomplish two things: first, the tumor has less time between cycles of chemotherapy to grow, and second, patients receive the total number of required cycles in a shorter time period. Administration of dose-dense chemotherapy regimens often requires the use of colony-stimulating factors (eg, filgrastim or granulocyte–colony stimulating factor [G-CSF], pegfilgrastim) to be administered. These agents shorten the duration and severity of neutropenia. The chemotherapy regimens that are dose dense tend to be adjuvant regimens, and the goal of therapy is cure. When a chemotherapy regimen is used as *palliation* (to control symptoms), the dosages of chemotherapy may be decreased

Table 88–4

Performance Status Scales

Description: Karnofsky Scale	Karnofsky Scale (%)	Zubrod Scale (ECOG)	Description: ECOG Scale
No complaints; no evidence of disease	100	0	Fully active, able to carry on all predisease activity
Able to carry on normal activity; minor signs or symptoms of disease	90		
Normal activity with effort; some signs or symptoms of disease	80	1	Restricted in strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
Cares for self; unable to carry on normal activity or to do active work	70		
Requires occasional assistance but is able to care for most personal needs	60	2	Out of bed > 50% of time; ambulatory and capable of self-care but unable to carry out any work activities
Requires considerable assistance and frequent medical care	50		
Disabled; requires special care and assistance	40	3	In bed > 50% of time; capable of only limited self-care
Severely disabled; hospitalization indicated, although death not imminent	30		
Very sick; hospitalization necessary; requires active supportive treatment	20	4	Bedridden; cannot carry out any self-care; completely disabled
Moribund; fatal processes progressing rapidly	10		
Dead	0	5	Deceased

ECOG, Eastern Cooperative Oncology Group.

based on toxicity or the interval between cycles may be lengthened to maintain quality of life.

Patient and tumor biology also affect how cancer therapy is dosed. Patients with a uridine diphosphate–glucuronosyltransferase 1A1 enzyme (UGT1A1*28) deficiency can have life-threatening diarrhea and complications from irinotecan related to a decreased ability to metabolize the parent drug. The patient may have a blood test before irinotecan therapy to determine if this genetic mutation is present. In the case of some monoclonal antibodies and targeted agents, flow cytometry results reveal whether the tumor has the receptor where the drug will bind and exert the pharmacologic effect.[13] The therapeutic uses of oncology drugs with valid genomic biomarkers, called targeted therapies, will be discussed briefly in this chapter and in more detail in the following chapters.

Another consideration of chemotherapy administration is the patient. Factors that affect chemotherapy selection and dosing are age, concurrent disease states, and performance status. Performance status can be assessed either with the Eastern Cooperative Oncology Group (ECOG) Scale or the Karnofsky Scale (Table 88–4). Performance status is a very important prognostic factor for many types of cancer. If a patient has renal dysfunction and the chemotherapy is eliminated primarily by the kidney, dosing adjustments will need to be made. If a patient has had a myocardial infarction recently or preexisting heart disease, the clinician will weigh the risks of anthracycline therapy against the benefit of the treatment of the cancer.

Another important consideration for treatment of cancers is insurance coverage for off-label use. Off-label use is when a medication is used to treat a cancer that is not an FDA-approved indication. Because of rapid advancements in oncology, it is estimated that up to 75% of chemotherapy agents are prescribed "off-label." Drugs used according to FDA-approved indications are usually paid for by insurance. If sufficient supportive literature exists and the use is supported by one of the Medicare-approved compendia (eg, AHFS-DI, Clinical Pharmacology, Micromedex DrugDex, and National Comprehensive Cancer Network [NCCN] Compendium), an insurer should cover the cost of the anticancer treatment that does not have an FDA indication.

During the time of chemotherapy administration, patients will likely experience various toxicities. The National Cancer Institute (NCI) has provided a standardized system for evaluating and grading the toxicity from chemotherapy to provide uniform grading of toxicity and evaluation of new agents and regimens (Table 88–5).[14]

Combination Chemotherapy

The underlying principles of using combination therapy are to use (a) agents with different pharmacologic actions, (b) agents with different organ toxicities, (c) agents that are active against the tumor and ideally synergistic when used together, and (d) agents that do not result in significant drug interactions (although these can be studied carefully and the interactions addressed). When two or more agents are used together, the risk of development of resistance may be lessened, but toxicity may be increased.

KEY CONCEPT Traditional chemotherapy agents have some similar side effects, usually manifested on the most rapidly proliferating cells of the body. However, there are unique toxicities of various pharmacologic categories of antineoplastic agents. Anthracyclines (eg, doxorubicin) have the potential to cause cardiac toxicity, which is related to the cumulative dose. Microtubule-targeting agents (eg, vincristine) are associated with various forms of neurotoxicity. Alkylating agents (eg, melphalan) are associated with secondary malignancies.

Currently, anticancer agents are categorized by their mechanism of action. As depicted in Figure 88–3, different agents work in different parts of the cell.[15]

Table 88–5

Selected National Cancer Institute Common Toxicity Criteria

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
General	Mild	Moderate	Severe	Life-threatening	–
Neutropenia	Lowest baseline: 1500/mm^3 (1.5 × 10^9/L)	< 1500–1000/mm^3 (1.5–1 × 10^9/L)	< 1000–500/mm^3 (1–0.5 × 10^9/L)	< 500/mm^3 (0.5 × 10^9/L)	
Thrombocytopenia	Lowest baseline: 75,000/mm^3 (75 × 10^9/L)	< 75,000–50,000/mm^3 (75–50 × 10^9/L)	< 50,000–25,000/mm^3 (50–25 × 10^9/L)	< 25,000 mm^3 (25 × 10^9/L)	–
Diarrhea	Increase of less than four stools per day over baseline or mild increase in ostomy output compared to baseline	Increase of four to six stools per day over baseline; moderate increase in ostomy output compared with baseline; limiting ADLs	Increase of greater than or equal to seven stools per day over baseline; hospitalization; severe increase in ostomy output compared with baseline; limiting self-care ADL	Life-threatening consequences (eg, hemodynamic collapse); urgent intervention indicated	Death
Esophagitis	Asymptomatic clinical or diagnostic only; intervention not indicated	Symptomatic altered eating or swallowing; oral supplements indicated	Severely altered eating or swallowing; tube feedings, or TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration, or malnutrition	Inadequate oral caloric or fluid intake; tube feedings, TPN or hospitalization indicated > 24 hours	–	–
Vomiting	Intervention not indicated	Outpatient intravenous hydration; medical intervention indicated	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences	Death

ADL, activity of daily living; IV, intravenous; TPN, total parenteral nutrition.

National Cancer Institute, Division of Cancer Treatment and Diagnosis | CTEP. Common Terminology Criteria for Adverse Events (CTCAE). Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf (accessed October 14, 2020).

Table 88–6 lists the currently FDA-approved anticancer drugs by drug class and name. The next section will describe the most commonly used anticancer agents or those with unique mechanisms of action.

Antimetabolites: Pyrimidine Analogues

▶ *5-Fluorouracil and Capecitabine*

5-Fluorouracil (5-FU) is a fluorinated analogue of the pyrimidine uracil. Once administered, this prodrug is metabolized by dihydropyrimidine dehydrogenase (DPD). 5-Fluorouracil ultimately is metabolized to fluorodeoxyuridine monophosphate (FdUMP), which interferes with the function of thymidylate synthase (TS), a requirement of thymidine synthesis. The triphosphate metabolite of 5-fluorouracil is incorporated into ribonucleic acid (RNA) to produce the second cytotoxic effect. Inhibition of TS occurs with the continuous infusion regimens, whereas the triphosphate form is associated with bolus administration. Capecitabine is an orally active prodrug of 5-fluorouracil and is enzymatically converted to 5-fluorouracil, sharing the same mechanism of action. Patients with a low activity of DPD appear to be at risk for life-threatening toxicities. Folates, such as leucovorin, increase the stability of FdUMP–TS inhibition and enhance the drug activity in certain cancers. These agents have clinical activity in several solid tumors and are frequently used to treat both breast and colon cancer. The most common toxicities include myelosuppression when administered by intravenous (IV) bolus and palmar–plantar erythrodysesthesia, and diarrhea, when administered as continuous IV infusion or orally. Palmar–plantar erythrodysesthesia, also called hand–foot syndrome (HFS), refers to redness, itching, and blistering of the palms of the hands and soles of the feet. Patients should be counseled to notify the prescriber when this adverse effect occurs. Significant increases in international normalization ratio (INR) and prothrombin time may occur within several days when capecitabine is initiated in patients concomitantly receiving warfarin. The INR

Patient Encounter 1, Part 2

The decision to treat the patient with a systemic hormonal and chemotherapy regimen is made. He will be receiving the standard regimen of leuprolide 22.5 mg intramuscularly every 12 weeks indefinitely and docetaxel 75 mg/m^2/day (intravenous) IV infusion over 60 minutes on day 1 every 21 days × six cycles.

Before initiating this chemotherapy regimen in the patient, what patient-specific issues need to be addressed?

What adverse effects will the patient likely experience with these two drugs?

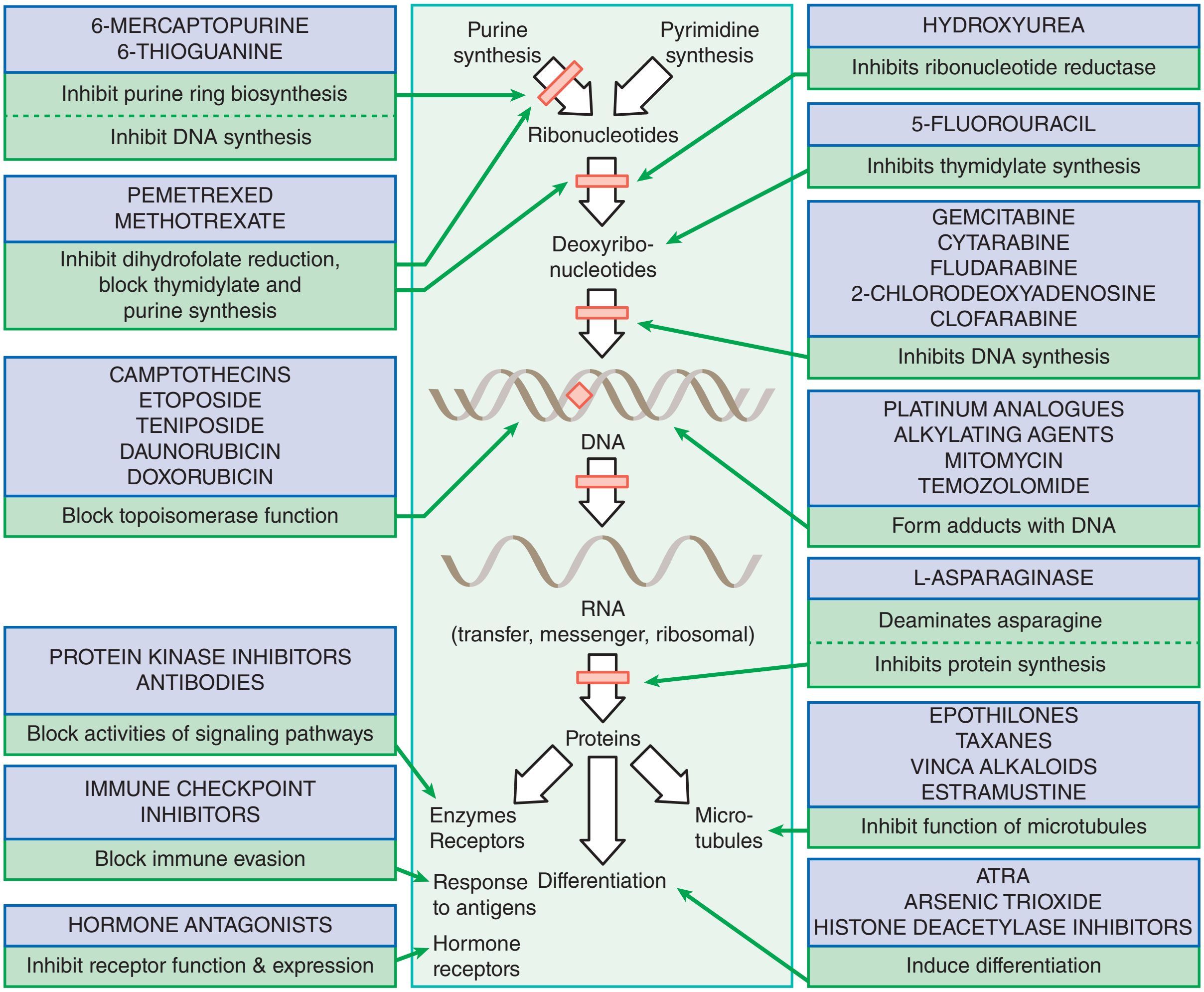
6-MERCAPTOPURINE
6-THIOGUANINE
Inhibit purine ring biosynthesis
Inhibit DNA synthesis
PEMETREXED
METHOTREXATE
Inhibit dihydrofolate reduction, block thymidylate and purine synthesis
CAMPTOTHECINS
ETOPOSIDE
TENIPOSIDE
DAUNORUBICIN
DOXORUBICIN
Block topoisomerase function
PROTEIN KINASE INHIBITORS
ANTIBODIES
Block activities of signaling pathways
IMMUNE CHECKPOINT INHIBITORS
Block immune evasion
HORMONE ANTAGONISTS
Inhibit receptor function & expression
Purine synthesis
Pyrimidine synthesis
Ribonucleotides
Deoxyribo-nucleotides
DNA
RNA
(transfer, messenger, ribosomal)
Proteins
Enzymes
Receptors
Micro-tubules
Response to antigens
Differentiation
Hormone receptors
HYDROXYUREA
Inhibits ribonucleotide reductase
5-FLUOROURACIL
Inhibits thymidylate synthesis
GEMCITABINE
CYTARABINE
FLUDARABINE
2-CHLORODEOXYADENOSINE
CLOFARABINE
Inhibits DNA synthesis
PLATINUM ANALOGUES
ALKYLATING AGENTS
MITOMYCIN
TEMOZOLOMIDE
Form adducts with DNA
L-ASPARAGINASE
Deaminates asparagine
Inhibits protein synthesis
EPOTHILONES
TAXANES
VINCA ALKALOIDS
ESTRAMUSTINE
Inhibit function of microtubules
ATRA
ARSENIC TRIOXIDE
HISTONE DEACETYLASE INHIBITORS
Induce differentiation

FIGURE 88–3. The mechanisms of action of commonly used antineoplastic agents. (Reproduced with permission from Wellstein A. General Principles of Chemotherapy. In: Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's The Pharmacologic Basis of Therapeutics, 13th ed. New York, NY: McGraw-Hill; 2017.)

should be monitored closely or the patient may be switched to a low-molecular-weight heparin. Other drug interactions can also occur. Patients should be instructed to take capecitabine within 30 minutes after a meal to increase absorption of the drug.

▶ *Cytarabine*

Cytarabine is a structural analogue of cytosine and is phosphorylated intracellularly to the active triphosphate form, which inhibits DNA polymerase. The triphosphate form also may be incorporated into DNA to result in chain termination to prevent DNA elongation. The drug may be administered as a low-dose continuous infusion, high-dose intermittent infusion, and into the subdural space via intrathecal or intraventricular administration. A liposomal formulation is also available for less frequent administration into the central nervous system (CNS). Cytarabine is eliminated by the kidneys with a renal clearance of 90 mL/min (1.5 mL/s). Cytarabine has shown efficacy in the treatment of acute leukemias and some lymphomas. The toxicities of cytarabine in high doses include myelosuppression; cerebellar syndrome (ie, nystagmus, dysarthria, and ataxia); and chemical conjunctivitis, an eye irritation that requires prophylaxis with steroid eye drops. The risk of neurotoxicity is increased with high doses (more than 1 g/m^2), advanced age, and renal dysfunction. If cerebellar toxicity does occur, the drug needs to be discontinued immediately, and decisions regarding further therapy need to be carefully considered.[16]

▶ *Gemcitabine*

Gemcitabine is a deoxycytidine analogue that is structurally related to cytarabine. Gemcitabine inhibits DNA polymerase activity and ribonucleotide reductase to result in DNA chain elongation. Gemcitabine has activity in several solid tumors and some lymphomas. The toxicities include myelosuppression; flu-like syndrome with fevers during the first 24 hours after administration; rash that appears 48 to 72 hours after administration; and hemolytic uremic syndrome, a rare but life-threatening adverse effect. Patients should be counseled to use acetaminophen to treat the fevers during the first 24 hours; however, fevers occurring 7 to 10 days after gemcitabine are likely to be febrile neutropenia and need prompt treatment with broad-spectrum antibiotics.

▶ *Azacitidine and Decitabine*

Azacitidine and decitabine are nucleoside analogues approved for the treatment of patients with myelodysplastic syndrome (MDS), a hematopoietic disorder that can transform into acute myeloid leukemia (AML). Both of these agents cause cytotoxicity by directly incorporating in the DNA and inhibiting DNA methyltransferase, which causes hypomethylation of DNA.

Table 88–6

Anticancer Drugs

Drug Class	Drug Name
Alkylating agents	
Alkyl sulfonate	Busulfan
Nitrogen mustards	Bendamustine
	Chlorambucil
	Cyclophosphamide
	Ifosfamide
	Melphalan
	Mechlorethamine
Nitrosoureas	Carmustine
	Lomustine
Nonclassical	Lurbinectedin
	Mitomycin C
	Thiotepa
	Trabectedin
Platinum complexes	Carboplatin
	Cisplatin
	Oxaliplatin
Triazenes and hydrazine	Dacarbazine
	Procarbazine
	Temozolomide
Anthracene derivatives	Daunorubicin
	Doxorubicin
	Epirubicin
	Idarubicin
	Mitoxantrone
Antitumor antibiotics	Bleomycin
Antimetabolites	
Cytidine deaminase inhibitor	Cedazuridine
Folate Antagonists	Methotrexate
Purine analogs	Pemetrexed
	Pralatrexate
	Cladribine
	Clofarabine
	Fludarabine
	6-Mercaptopurine
	Pentostatin
	Thioguanine
Pyrimidine analogs	Azacitidine
	Capecitabine
	Cytarabine
	Decitabine
	5-Fluorouracil
	Gemcitabine
	Nelarabine
	Trifluridine/(tipiracil)[a]
Histone deacetylase (HDAC) inhibitors	Belinostat
	Panobinostat
	Romidepsin
	Tazemetostat
	Vorinostat
Hormonal therapies	
Antiandrogens	Bicalutamide
	Flutamide
	Nilutamide
Androgen receptor antagonist	Apalutamide
	Darolutamide
	Enzalutamide
Antiestrogens	Raloxifene
	Tamoxifen
Aromatase inhibitors	Anastrozole
	Exemestane
	Letrozole
CYP17 inhibitor	Abiraterone acetate
Luteinizing hormone–releasing hormone agonist	Goserelin
	Leuprolide
Luteinizing hormone–releasing hormone antagonist	Degarelix
Immunomodulatory agents	Lenalidomide
	Pomalidomide
	Thalidomide
Immunotherapy	
Cell-based immunotherapy	Sipuleucel-T
CAR T cell	Tisagenlecleucel
	Axicabtagene ciloleucel
	Brexucabtagene autoleucel
Checkpoint inhibitors	Atezolizumab
	Avelumab
	Cemiplimab
	Durvalumab
	Ipilimumab
	Nivolumab
	Pembrolizumab
Miscellaneous immune therapies	Interferons
	Aldesleukin
Microtubule-targeting agents	
Taxanes	Cabazitaxel
	Docetaxel
	Paclitaxel
Vinca alkaloids	Vinblastine
	Vincristine
	Vinorelbine
Other	Eribulin
	Estramustine
	Ixabepilone
Miscellaneous agents	Asparaginase
	Arsenic trioxide
	Bexarotene
	Calaspargase pegol
	Hydroxyurea
	Liposome encapsulated doxorubicin-cytarabine
	Omacetaxine mepesuccinate
	Pegaspargase
	Tagraxofusp
	Tretinoin
	Ziv-aflibercept
Monoclonal antibodies	Alemtuzumab
	Bevacizumab
	Blinatumomab
	Cetuximab
	Daratumumab
	Dinutuximab
	Elotuzumab
	Emapalumab
	Isatuximab
	Mogamulizumab
	Obinutuzumab
	Ofatumumab
	Olaratumab
	Necitumumab
	Panitumumab
	Pertuzumab
	Ramucirumab
	Rituximab
	Tafasitamab
	Trastuzumab

(Continued)

Table 88–6

Anticancer Drugs (*Continued*)

Drug Class	Drug Name
	Trastuzumab and hyaluronidase
Antibody–drug conjugate	Ado-trastuzumab emtansine
	Brentuximab vedotin
	Belantamab mafodotin
	Fam-trastuzumab deruxtecan
	Inotuzumab ozogamicin
	Gemtuzumab ozogamicin
	Moxetumomab pasudotox
	Polatuzumab vedotin
	Sacituzumab govitecan
Antibody–radioimmunotherapy conjugate	Ibritumomab tiuxetan
Topoisomerase inhibitors	
Camptothecin derivatives	Irinotecan
	Topotecan
Epipodophyllotoxins	Etoposide
Tyrosine kinase inhibitors	
Anaplastic lymphoma kinase (ALK)	Alectinib
	Brigatinib
	Ceritinib
	Crizotinib
	Lorlatinib
B-cell lymphoma 2 (Bcl-2)	Venetoclax
BCR-ABL	Bosutinib
	Dasatinib
	Imatinib
	Nilotinib
	Ponatinib
BRAF	Cobimetinib
	Dabrafenib
	Encorafenib
	Vemurafenib
Bruton's tyrosine kinase (BTK)	Acalabrutinib
	Ibrutinib
	Zanubrutinib
Cyclin-dependent kinase (CDK)	Abemaciclib
	Palbociclib
	Ribociclib
Epidermal growth factor receptor (EGFR)	Afatinib
	Dacomitinib
	Erlotinib
	Gefitinib
	Osimertinib
EGFR/HER2	Vandetanib
	Lapatinib
	Neratinib
	Tucatinib
Hedgehog pathway inhibitors	Glasdegib
	Sonidegib
	Vismodegib
Fibroblast growth factor receptor (FGFR)	Erdafitinib
	Pemigatinib
Isocitrate dehydrogenase 2 (IDH2)	Enasidenib
	Ivosidenib
Janus-associated kinase (JAK)	Fedratinib
	Ruxolitinib
	Binimetinib
	Capmatinib
Mitogen-activated extracellular kinase (MEK)	Cobimetinib
	Selumetinib
	Trametinib
Multikinase	Axitinib
	Brigatinib
	Cabozantinib
	Gilteritinib
	Lenvatinib
	Midostaurin
	Pazopanib
	Pexidartinib
	Regorafenib
	Ripretinib
	Sorafenib
	Sunitinib
	Vandetanib
Mammalian target of rapamycin (mTOR)	Everolimus
	Temsirolimus
Neurotrophic tyrosine receptor kinase (NTRK)	Entrectinib
	Larotrectinib
Phosphoinositide 3-kinase (PI3K)	Alpelisib
	Copanlisib
	Duvelisib
	Idelalisib
Platelet-derived growth factor receptor (PDGFR)	Avapritinib
	Pralsetinib
Poly ADP ribose polymerase (PARP)	Niraparib
	Olaparib
	Rucaparib
Proteasome inhibitors	Bortezomib
	Carfilzomib
	Ixazomib
RET tyrosine kinase (RET)	Selpercatinib
Selective inhibitor of nuclear export antagonist	Selinexor

[a] Tipiracil is a thymidine phosphorylase inhibitor used to increase bioavailability of trifluridine.

Hypomethylation of DNA appears to normalize the function of the genes that control cell differentiation and proliferation to promote normal cell maturation. Major side effects reported are myelosuppression and infections. Most recently an oral formulation of azacitidine was approved by the FDA.[17,18] Additionally, a combination product of an oral formulation of decitabine, along with the cytidine deaminase inhibitor cedazuridine, was approved for use in MDS. Cedazuridine prevents the breakdown of decitabine, thereby increasing its bioavailability and efficacy. Adverse events of these oral hypomethylating agents are similar to their IV counterparts.

Antimetabolites: Purine Analogues

▶ *Mercaptopurine*

6-Mercaptopurine (6-MP) is an oral purine analogue that is converted to ribonucleotides that inhibit purine synthesis. Mercaptopurine is converted into thiopurine nucleotides, which are catabolized by thiopurine *S*-methyltransferase (TPMT). TPMT is subject to genetic polymorphisms and may cause severe myelosuppression; therefore, TPMT status may be assessed before therapy to reduce drug-induced morbidity and the costs of hospitalizations for neutropenic events. 6-MP is used in the treatment of acute lymphocytic leukemia (ALL) and chronic myeloid leukemia (CML). Significant side effects include myelosuppression, mild nausea, skin rash, cholestasis, and rarely, veno-occlusive disease. Mercaptopurine is metabolized by xanthine oxidase, an enzyme that is inhibited by allopurinol. This represents a major drug–drug interaction. To avoid toxicities of mercaptopurine when these drugs are used concomitantly, the dose of mercaptopurine must be reduced by 66% to 75%.

▶ *Fludarabine*

Fludarabine is an analogue of the purine adenine. It interferes with DNA polymerase to cause chain termination and inhibits transcription by its incorporation into RNA. Fludarabine is dephosphorylated rapidly and converted to 2-fluoro-Ara-AMP (2-FLAA), which enters the cells and is phosphorylated to 2-fluoro-Ara-ATP, which is cytotoxic. Fludarabine is used in the treatment of chronic lymphocytic leukemia (CLL), some lymphomas, and refractory AML. Significant and prolonged myelosuppression may occur, along with immunosuppression, so patients are susceptible to opportunistic infections. Prophylactic antibiotics and antivirals are recommended until cluster of differentiation (CD) 4 counts return to normal. Mild nausea and vomiting and diarrhea have been observed. Rarely, interstitial pneumonitis has occurred.

Antimetabolites: Folate Antagonists

Folates carry one-carbon groups in transfer reactions required for purine and thymidylic acid synthesis. Dihydrofolate reductase is the enzyme responsible for supplying reduced folates intracellularly for thymidylate and purine synthesis.

▶ *Methotrexate*

Methotrexate inhibits dihydrofolate reductase of both malignant and nonmalignant cells. When high doses of methotrexate are given, the "rescue drug" leucovorin, a reduced folate, is administered to bypass the methotrexate inhibition of dihydrofolate reductase of normal cells and is usually initiated 24 hours after methotrexate administration. This is done to prevent potentially fatal myelosuppression and mucositis. For safety purposes, the term folinic acid, another term used for leucovorin, should not be used because of the potential for a medication error in which folic acid might be given instead. Methotrexate concentrations should be monitored to determine when to stop leucovorin administration. Generally, leucovorin administration may be stopped when methotrexate concentrations decrease to 5×10^{-8} M, although this may vary by the chemotherapy regimen. Higher doses of methotrexate may place an individual at risk for methotrexate to crystallize in the acidic environment of the urine, often resulting in acute renal failure and decreased methotrexate clearance. Administration of IV hydration with sodium bicarbonate to maintain urinary pH greater than or equal to 7 is necessary to prevent methotrexate-induced renal dysfunction. Methotrexate is eliminated by tubular secretion; therefore, concomitant drugs (eg, probenecid, salicylates, penicillin G, and ketoprofen) that may inhibit or compete for tubular secretion should be avoided. Methotrexate doses must be adjusted for renal dysfunction and close monitoring of methotrexate concentrations is advised. In patients with toxic levels of methotrexate (> 1 μmol/L) because of impaired renal function, the antidote glucarpidase can be administered. However, efficacy can be compromised so it is not used in patients with normal or slightly elevated levels. Side effects of methotrexate include myelosuppression, nausea and vomiting, and mucositis. Methotrexate may also be administered via the intrathecal route or via an Ommaya reservoir in very low doses as small as 12 mg, so it is crucial for the clinician to know the correct dose by the correct route in order to avoid substantial toxicity. The methotrexate used for intrathecal and intraventricular injection must be preservative-free to prevent CNS toxicity.

▶ *Pemetrexed*

Pemetrexed inhibits four pathways in thymidine and purine synthesis. Pemetrexed has shown activity in the treatment of mesothelioma and non–small cell lung cancer (NSCLC). Side effects include myelosuppression, rash, diarrhea, and nausea and vomiting. Patients should receive folic acid and cyanocobalamin to reduce bone marrow toxicity and diarrhea. Doses of folic acid of at least 400 mcg/day starting 7 days before treatment and continuing throughout therapy, as well as for 21 days after the last pemetrexed dose, have been used.[18] Cyanocobalamin 1000 mcg is given intramuscularly the week before pemetrexed and then every three cycles thereafter. Dexamethasone 4 mg twice daily the day before, the day of, and the day after pemetrexed administration helps to decrease the incidence and severity of rash.

Microtubule-Targeting Agents

▶ *Vinca Alkaloids (Vincristine, Vinblastine, and Vinorelbine)*

The vinca alkaloids (vincristine, vinblastine, and vinorelbine) are derived from the periwinkle (vinca) plant and cause cytotoxicity by binding to tubulin, disrupting the normal balance between polymerization and depolymerization of microtubules, and inhibiting the assembly of microtubules, which interferes with the formation of the mitotic spindle. As a result, cells are arrested during the metaphase of mitosis. The vinca alkaloids are used in several malignancies, primarily hematologic. Even though these agents have similar structures, the incidence and severity of toxicities vary. The dose-limiting toxicity of vincristine is neurotoxicity, which can consist of depressed tendon reflexes, paresthesias of the fingers and toes, toxicity to the cranial nerves, or autonomic neuropathy (constipation or ileus, abdominal pain, and/or orthostatic hypotension). In contrast, the dose-limiting toxicity associated with vinorelbine and vinblastine is myelosuppression. All of the vinca alkaloids are vesicants and can cause tissue damage; therefore, extravasation needs to be prevented. Biliary excretion accounts for a significant portion of elimination of vincristine and its metabolites, so doses need to be adjusted for obstructive liver disease.

Vincristine, vinblastine, and vinorelbine have similar sounding names, which is a potential cause of medication errors. As with all chemotherapy prescribing, dispensing, and administration, the clinician must be very careful with sound-alike, look-alike medications. Unfortunately, vincristine has been involved in numerous cases of fatal chemotherapy errors, including inadvertent intrathecal administration. When administered intrathecally, widespread tissue damage and potentially deaths can occur. An example of a strategy that health systems can use to decrease the likelihood of an error such as this is for the pharmacy to only dispense vincristine in a mini-bag for IV administration. Many clinicians cap IV vincristine doses at 2 mg to prevent severe neuropathic side effects; however, if the intent of chemotherapy is curative, the vincristine dose may be dosed above the 2-mg cap.[19]

▶ Taxanes (Cabazitaxel, Docetaxel, Nanoparticle Albumin-Bound Paclitaxel, and Paclitaxel)

Taxane plant alkaloids are similar to the vinca alkaloids, exhibiting cytotoxicity during the M phase of the cell cycle by binding to tubulin. Unlike the vinca alkaloids, however, the taxanes do not interfere with tubulin assembly. Rather, the taxanes promote microtubule assembly and inhibit microtubule disassembly. Once the microtubules are polymerized, the taxanes stabilize against depolymerization.

Hepatic metabolism and biliary excretion account for the majority of paclitaxel's elimination. Paclitaxel has demonstrated activity in several solid tumors. The diluent for paclitaxel, Cremophor EL, is composed of ethanol and castor oil. Infusions must be prepared and administered in non–polyvinyl chloride–containing bags and tubing, and solutions must be filtered. Patients receive dexamethasone, diphenhydramine, and an histamine $(H)_2$ blocker to prevent hypersensitivity reactions caused by Cremophor EL. Patients also may have asymptomatic bradycardia during the infusion. Approximately 3 to 5 days after administration, patients may complain of myalgias and arthralgias that may last several days. Myelosuppression, flushing, neuropathy, ileus, and total-body alopecia are other common side effects. Because paclitaxel is a substrate for cytochrome P450 (CYP)-3A4, patients receiving phenytoin (a strong CYP3A4 inducer) had lower steady-state concentration of paclitaxel than patients not receiving phenytoin and this combination should be avoided. In addition, paclitaxel clearance is decreased by 33% when it was administered after cisplatin, so for regimens containing both agents, paclitaxel is administered before cisplatin.

A nanoparticle albumin-bound nab-paclitaxel product is also available for the treatment of metastatic breast cancer resistant to conventional chemotherapy. The nab-paclitaxel formulation uses nanotechnology to combine human albumin with paclitaxel allowing for the delivery of an insoluble drug in the form of nanoparticles. This unique formulation allows for an increased bioavailability and higher intracellular concentrations of the drug. It does not have the serious hypersensitivity reactions encountered with paclitaxel solubilized in Cremophor EL, so premedication with H_1 and H_2 blockers and steroids is not necessary. Also, a significantly lower incidence of severe neutropenia occurs with nab-paclitaxel. The dose is infused over 30 minutes and does not require a special IV bag, tubing, or filter. The dosing of this product is also different from that of the original paclitaxel and the formulation needs to be clearly indicated when prescribed. The pharmacokinetics of the albumin-bound paclitaxel displays a higher clearance and larger volume of distribution than paclitaxel. The drug is eliminated primarily via fecal excretion. Bone marrow suppression, neuropathy, ileus, arthralgias, and myalgias still occur.

Docetaxel has activity in the treatment of several solid tumors. Dexamethasone, 8 mg twice daily for 3 days starting the day before treatment, is used to prevent the fluid-retention syndrome associated with docetaxel and possible hypersensitivity reactions. The fluid-retention syndrome is characterized by edema and weight gain that is unresponsive to diuretic therapy and is associated with cumulative doses greater than 800 mg/m². Myelosuppression, alopecia, and neuropathy are other side effects associated with docetaxel treatment.

Cabazitaxel is a newer taxane used in combination with prednisone for the treatment of metastatic hormone-refractory prostate cancer. Cabazitaxel has shown to have similar adverse effects as paclitaxel and docetaxel. Premedication with an antihistamine, corticosteroid, and H_2 antagonist to prevent hypersensitivity reactions is required.

▶ Eribulin

Eribulin mesylate is a nontaxane microtubule dynamics inhibitor. It is a synthetic analogue of halichondrin B, which is a product isolated from the sea sponge *Halichondria okadai*. While taxanes inhibit cell division by stabilizing microtubules, eribulin arrests the cell cycle through inhibition of the growth phase of microtubules without interfering with microtubule shortening. The cytotoxicity results from its effects via a tubulin-based antimitotic mechanism, resulting in G_2/M cell cycle arrest and mitotic blockage. Apoptotic cell death results from prolonged mitotic blockage. Eribulin mesylate is an IV medication that is specifically indicated for the treatment of patients with metastatic breast cancer and liposarcoma. The most common adverse effects reported are neutropenic fever, anemia, asthenia or fatigue, alopecia, peripheral neuropathy, nausea, and constipation. Eribulin has been reported to cause significant neutropenia and QTc interval prolongation. It has vesicant properties. Dosages should be adjusted in renal and hepatic impairment.

▶ Ixabepilone

Ixabepilone, an epothilone analogue, binds to β-tubulin subunits on microtubules, which results in suppression of microtubule dynamics. Ixabepilone is primarily eliminated by the liver by oxidation through the CYP3A4 system. Ixabepilone, in combination with capecitabine or alone if resistant to capecitabine, is indicated for the treatment of metastatic or locally advanced breast cancer. Studies have shown a possible synergy when used in combination with capecitabine. Side effects include hypersensitivity reactions, myelosuppression, and peripheral neuropathy. To minimize the occurrence of hypersensitivity reactions, patients must receive both H_1 and H_2 antagonists before therapy. If a reaction still occurs, corticosteroids should be added to the premedications.

Topoisomerase Inhibitors

Topoisomerase is responsible for relieving the pressure on the DNA structure during unwinding by producing strand breaks. Topoisomerase I produces single-strand breaks, whereas topoisomerase II produces double-strand breaks.

▶ Epipodophyllotoxins (Etoposide)

Etoposide is a semisynthetic podophyllotoxin derivative that inhibits topoisomerase II, causing multiple DNA double-strand breaks. Etoposide has shown activity in the treatment of several types of lymphoma, testicular and lung cancer, retinoblastoma, and carcinoma of unknown primary. Oral bioavailability is approximately 50%, so oral dosages are approximately two times those of IV doses. It should be slowly administered to prevent hypotension. Side effects include mucositis, myelosuppression, alopecia, phlebitis, hypersensitivity reactions, and secondary leukemias. Hypersensitivity reactions are caused by the solubilizing agents, polysorbate 80 and may be life-threatening.

▶ Camptothecin Derivatives (Irinotecan and Topotecan)

Irinotecan and topotecan, both camptothecins, inhibit the topoisomerase I enzyme to interfere with DNA synthesis through the active metabolite SN-38. Topoisomerase I enzymes stabilize DNA single-strand breaks and inhibit strand resealing. Irinotecan has shown activity in the treatment of cancers of the colon, rectum, cervix, and lung. Irinotecan-induced diarrhea is a serious complication and may be life-threatening. One form of diarrhea (early) can occur during or immediately after the infusion. This is a result of a cholinergic process in which the patient may experience facial flushing, diaphoresis, and abdominal cramping. IV atropine should be administered to treat diarrhea that occurs any time during the first 24 hours of administration. Another form of diarrhea (late) can occur several days after administration and can result in severe dehydration. This adverse effect should be treated immediately with loperamide at a dosage of 2 mg every 2 hours or 4 mg every 4 hours until diarrhea has stopped for 12 hours. Other side effects include myelosuppression, fatigue, and alopecia. Individuals homozygous for *UGT1A1*28* have an increased risk of febrile neutropenia and diarrhea and should be considered for an empiric dose reduction of one level; heterozygotes should receive closer monitoring, including more frequent CBCs to detect myelosuppression.

Topotecan has shown clinical activity in the treatment of ovarian and lung cancer, MDS, and AML. The IV infusion may be scheduled daily for 5 days or once weekly. Side effects include myelosuppression, mucositis, and diarrhea. Diarrhea is less common than with irinotecan.

Anthracene Derivatives

▶ *Daunorubicin, Doxorubicin, Idarubicin, and Epirubicin*

Anthracyclines (daunorubicin, doxorubicin, idarubicin, and epirubicin) are also referred to as antitumor antibiotics or topoisomerase inhibitors when considering their mechanism of action. All of the anthracyclines contain a four-membered anthracene ring, a chromophore, with an attached sugar portion. This chromophore results in red-orange urine after administration, which is an important counseling point for patients. Free radicals formed from the anthracyclines combine with oxygen to form superoxide, which can make hydrogen peroxide. These agents are able to insert between base pairs of DNA to cause structural changes in DNA. However, the primary mechanism of cytotoxicity appears to be the inhibition of topoisomerase II. These drugs are widely used in a variety of cancers.

Oxygen-free-radical formation is a cause of cardiac damage and extravasation injury, which is common with these drugs. The anthracyclines can cause cardiac toxicity as manifested by a congestive heart failure or cardiomyopathy symptomatology, alopecia, nausea or vomiting, mucositis, myelosuppression, and urinary discoloration. These drugs are vesicants.

To reduce the risk of cardiotoxicity associated with doxorubicin, the maximum lifetime cumulative dose is 550 mg/m^2; similarly, the other anthracyclines have maximum lifetime cumulative doses. Ventricular ejection fractions should be measured before therapy and periodically if therapy is continued. Therapy should be halted if there is a 10% to 20% decrease from baseline in ejection fraction. Patients at increased risk of cardiotoxicity include patients reaching the upper limit of cumulative lifetime dose; those taking concomitant or previous cardiotoxic drugs, concurrent paclitaxel, or bolus administration; patients with preexisting cardiac disease or mediastinal radiation; and the very young and elderly. Cardioprotectants (eg, dexrazoxane) have been used to decrease risk in some cases. Clinical guidelines for cardioprotective agents' use are available.[20]

Liposomal doxorubicin is an **irritant**, not a vesicant, and is dosed differently from doxorubicin and formulation must be clearly specified when prescribing. Liposomal doxorubicin may also be less cardiotoxic than doxorubicin. Liposomal doxorubicin has significant activity in the treatment of breast and ovarian cancer along with multiple myeloma (MM) and Kaposi sarcoma. Side effects include mucositis, myelosuppression, alopecia, and palmar–plantar erythrodysesthesia.

Liposomal daunorubicin is also available but only in a combination product with liposomal cytarabine used in the treatment of AML. This product uses a synergistic ratio of daunorubicin to cytarabine (1:5) in a liposomal formulation to enhance exposure within the bone marrow. The dosing of this drug is different than traditional daunorubicin and cytarabine.

▶ *Mitoxantrone*

Mitoxantrone is a royal blue–colored anthracenedione that inhibits DNA topoisomerase II. Mitoxantrone has clinical activity in the treatment of acute leukemias, breast and prostate cancer, and non-Hodgkin lymphomas with myelosuppression, mucositis, nausea and vomiting, and cardiac toxicity its major adverse effect. The total cumulative dose limit is 160 mg/m^2 for patients who have not received prior anthracycline or mediastinal radiation. Patients with prior doxorubicin or daunorubicin therapy should not receive a cumulative dose greater than 120 mg/m^2 of mitoxantrone. Patients should be counseled that their urine will turn a blue-green color.

Alkylating Agents

Although still widely used for many malignancies, the alkylating agents are the oldest class of anticancer drugs. The agents cause cytotoxicity via transfer of their alkyl groups to nucleophilic groups of proteins and nucleic acids. The major site of alkylation within DNA is the N7 position of guanine, although alkylation does occur to a lesser degree at other bases. These interactions can either occur on a single strand of DNA (monofunctional agents) or on both strands of DNA through a cross-link (bifunctional agents), which leads to strand breaks. The major toxicities of the alkylating agents are myelosuppression, alopecia, nausea or vomiting, sterility or infertility, and secondary malignancies.

▶ *Nitrogen Mustards (Cyclophosphamide and Ifosfamide)*

Cyclophosphamide and ifosfamide are bifunctional alkylating agents with similar adverse effects and activity and are used in a variety of solid and hematologic cancers. Both are prodrugs, requiring activation by mixed hepatic oxidase enzymes to phosphoramide and ifosfamide mustard. During the activation process, additional byproducts (acrolein and chloroacetaldehyde) are formed. Acrolein has no cytotoxic activity but is responsible for the hemorrhagic cystitis associated with ifosfamide and high-dose cyclophosphamide. Acrolein produces cystitis by directly binding to the bladder wall. Prophylaxis is necessary with aggressive hydration, administration of 2-mercaptoethane sulfonate sodium (mesna, which binds to and inactivates acrolein in the bladder), frequent voiding, and monitoring in patients receiving ifosfamide and high-dose cyclophosphamide. Patients should be counseled to drink plenty of fluids; void frequently; and report any hematuria, irritation, or flank pain. Dosing regimens of mesna range from an equal milligram dose to the ifosfamide mixed in the same IV bag to 20% of the dose administered before ifosfamide and 20% of the dose repeated at 4 and 8 hours after the ifosfamide dose.

Chloroacetaldehyde, a metabolite of ifosfamide, can result in encephalopathy, especially in patients with renal dysfunction or advanced age. This adverse effect can occur within 48 to 72 hours of administration and is usually reversible.

▶ Busulfan

Busulfan is an alkylating agent that forms DNA–DNA and DNA–protein cross-links to inhibit DNA replication. Oral busulfan is well absorbed, has a terminal half-life of 2 to 2.5 hours, and is eliminated primarily by hepatic metabolism. It is also available in an IV formulation, which is commonly used for high doses, to reduce pill burden. Busulfan has significant clinical activity in the treatment of AML and CML and has been used as a conditioning regimen before hematopoietic stem cell transplantation (HSCT). Side effects include bone marrow suppression; hyperpigmentation of skin creases; and rarely, pulmonary fibrosis. High doses used for HSCT preparatory regimens can cause severe nausea and vomiting, tonic–clonic seizures, and sinusoidal obstruction syndrome and require anticonvulsant prophylaxis. A discussion of busulfan adaptive dosing can be found in Chapter 98.

▶ Nitrosoureas (Carmustine and Lomustine)

Carmustine (BCNU) and lomustine (CCNU) are lipophilic nitrosureas that can cross the blood–brain barrier. Carmustine may be administered IV or as a biodegradable wafer formulation that is implanted during surgical resection of brain tumors. Lomustine is available in an oral formulation. Carmustine has shown clinical activity in the treatment of lymphoma, MM, and brain tumors. Lomustine has shown clinical activity in the treatment of non-Hodgkin lymphoma and brain tumors. Side effects include myelosuppression, severe nausea and vomiting, and pulmonary fibrosis with long-term therapy.

▶ Nonclassic Alkylating Agents (Dacarbazine and Temozolomide)

Although the exact mechanism of action remains unclear, dacarbazine and temozolomide appear to inhibit DNA, RNA, and protein synthesis. Dacarbazine is used to treat melanoma, Hodgkin lymphoma, and soft tissue sarcomas. Side effects include myelosuppression, severe nausea and vomiting, and a flu-like syndrome that starts about 7 days after treatment and lasts 1 to 3 weeks.

Temozolomide is a well-absorbed orally active agent that also crosses the blood–brain barrier. Temozolomide is converted via pH-dependent hydrolysis to the active metabolite 5-(3-methyltriazeno)-imidazole-4-carboxamide. Temozolomide may be used in the treatment of melanoma, refractory anaplastic astrocytoma, and glioblastoma multiforme. Nausea may be minimized by administering the drug at bedtime. Because patients receiving temozolomide may have confusion secondary to their brain tumors and dosing can consist of multiple capsule sizes, care must be taken by all providers to simplify regimens to prevent chemotherapy overdose.[21]

▶ Procarbazine

Although the exact mechanism of action of procarbazine is unknown, it does inhibit DNA, RNA, and protein synthesis. Procarbazine is used most often in the treatment of lymphoma. Myelosuppression is the major side effect. Nausea, vomiting, and a flu-like syndrome occur initially with therapy. Patients must be counseled to avoid tyramine-rich foods because procarbazine is a monoamine oxidase inhibitor. Patients should be provided a list of foods and beverages to avoid a hypertensive crisis. A disulfiram-like reaction can occur with the ingestion of alcohol.

Heavy Metal Compounds

Platinum drugs form reactive platinum complexes that bind to cells, so the pharmacokinetics of the individual drug may be of the platinum, both free and bound, rather than of the parent drug.

▶ Cisplatin

Cisplatin forms inter- and intrastrand DNA cross-links to inhibit DNA synthesis. Cisplatin has clinical activity in the treatment of numerous tumor types and remains front-line therapy for lung and ovarian cancers. Cisplatin is highly emetogenic, even when low doses are given daily for 5 days, and causes delayed nausea and vomiting as well; patients require aggressive antiemetic regimens for both delayed and acute emesis. Significant nephrotoxicity and electrolyte abnormalities can occur if inadequate hydration occurs. Ototoxicity, which manifests as a high-frequency hearing loss, and a glove-and-stocking neuropathy may limit therapy.

▶ Carboplatin

Carboplatin has the same mechanism of action as cisplatin; however, its side effects are similar but less intense than those of cisplatin. Many chemotherapy regimens dose carboplatin based on an area under the curve (AUC), also called the Calvert equation. According to the Calvert equation for adults, the dose in milligrams of carboplatin = (creatinine clearance [CrCl] + 25) × AUC desired, where CrCl is expressed in mL/min.[22] Carboplatin has shown clinical activity in the treatment of several solid tumors and lymphoma. Thrombocytopenia, nausea and vomiting, and hypersensitivity reactions are common adverse effects.

▶ Oxaliplatin

Oxaliplatin is commonly used to treat colorectal cancer. Its adverse effect profile is similar to cisplatin with hypersensitivity reactions and moderate nausea and vomiting commonly observed.[23] In addition, oxaliplatin can cause cold-induced neuropathy. Patients should be counseled to avoid cold beverages, to use gloves to remove items from the freezer, and to wear protective clothing in cold climates for the first week after treatment. A glove-and-stocking neuropathy also occurs with long-term administration.

Miscellaneous Agents

▶ Bleomycin

Bleomycin is a mixture of peptides with drug activity expressed in units, where 1 U equals to 1 mg. Bleomycin causes DNA strand breakage. Bleomycin has activity in testicular cancer and malignant effusions, squamous cell carcinomas of the skin, and Kaposi sarcoma. Hypersensitivity reactions and fever may occur, so premedication with acetaminophen may be required. The most serious side effect of bleomycin is pulmonary toxicity that presents as a pneumonitis with a dry cough, dyspnea, rales, and infiltrates. Pulmonary function studies show decreased carbon monoxide diffusing capacity and restrictive ventilatory changes. “Bleomycin lung” is associated with cumulative dosing greater than 400 U and occurs rarely with a total dose of 150 U and is potentiated by thoracic radiation and by hyperoxia. Additional side effects include fever with or without chills, mild-to-moderate alopecia, and nausea and vomiting.

Bleomycin is also used to manage malignant plural effusions at doses of 15 to 60 U through installation into the affected area. The drainage tube of the effusion is clamped off for some period of time after administration of bleomycin and then the amount of drainage is monitored to determine efficacy of the treatment.[23]

▶ Hydroxyurea

Hydroxyurea is an oral drug that inhibits ribonucleotide reductase, which converts ribonucleotides into the deoxyribonucleotides used in DNA synthesis and repair. Hydroxyurea has activity in CML, polycythemia vera, sickle cell disease, and thrombocytosis. The major side effects are myelosuppression, nausea and vomiting, diarrhea, and constipation. Rash, mucositis, and renal tubular dysfunction occur rarely.

▶ L-Asparaginase

L-Asparaginase is an enzyme that may be produced by *Escherichia coli*. Asparaginase hydrolyzes the reaction of asparagine to aspartic acid and ammonia to deplete lymphoid cells of asparagine, which inhibits protein synthesis. L-Asparaginase has activity in ALL and childhood AML. Severe allergic reactions may occur when the interval between doses is 7 days or greater, so while a skin test result may be negative, patients should be observed closely after asparaginase administration. If the patient suffers an allergic reaction to L-asparaginase, alternatively formulated agents, such as pegaspargase or calaspargase pegol, may be given. These drugs include L-asparaginase modified through a linkage with polyethylene glycol or monomethoxypolyethylene glycol, respectively, which extends the half-life and allows for lower doses and less-frequent administration. Cost and limited availability limit their use in the front line setting.

▶ Tretinoin

Tretinoin, also referred to as all-*trans*-retinoic acid (ATRA), is used to treat acute promyelocytic leukemia (APL). ATRA is a retinoic acid that is not cytotoxic but promotes the maturation of early promyelocytic cells that have the charatersitic t(15;17) translocation. A severe side effect of ATRA is retinoic acid syndrome, which may occur anytime during treatment and consists of fever, respiratory distress, and hypotension. Chest radiographs are consistent with a pneumonia-like process and it is important to differentiate pneumonia from APL syndrome, as the treatment for retinoic acid syndrome is dexamethasone 10 mg IV every 12 hours, which may be detrimental to administer to a neutropenic patient with pneumonia.

▶ Immunomodulatory Agents (Thalidomide, Lenalidomide, and Pomalidomide)

Thalidomide was initially approved in Europe on October 1, 1957, as a sedative–hypnotic. Some children born to women who had taken thalidomide were born with severe limb deformities (phocomelia) which led to its removal from the market. Thalidomide was subsequently identified an angiogenesis inhibitor, with clinical activity in the treatment of MM. Patients receiving thalidomide are enrolled in the Risk Evaluation and Mitigation Strategies (REMS) program and counseled on the risks of phocomelia should they become pregnant. Common adverse effects include somnolence, constipation, peripheral neuropathy, and deep vein thrombosis (DVT). Recommendations for DVT prophylaxis for all thalidomides is based upon a risk-assessment model whereby prophylaxis with low-molecular-weight heparin or dose-adjusted warfarin is recommended for high-risk patients and aspirin for low-risk patients.[24]

Lenalidomide is approved for the treatment of MDS when the 5q deletion is present and MM. Because lenalidomide is an analogue of thalidomide, all of the same precautions must be taken to prevent phocomelia. However, lenalidomide has fewer adverse effects than thalidomide. Dosing adjustments are necessary for renal dysfunction. Other side effects are neutropenia, thrombocytopenia, DVT, and pulmonary embolus.

Pomalidomide is also used in treatment of refractory or progressive MM and Kaposi's sarcoma. Similar precautions to prevent phocomelia are also required. Adverse effects include myelosuppression and infections. The use of the immunomodulatory agents in the treatment of MM is discussed thoroughly in Chapter 96.

▶ Omacetaxine Mepesuccinate

Omacetaxine mepesuccinate is an alkaloid from *Cephalotaxus harringtonia*. The agent reversibly inhibits protein synthesis, causing cell death in both malignant and nonmalignant cells. It is a subcutaneous (SC) injection and is indicated for the treatment of CML patients (including those patients with the T315I mutation) showing resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKIs). The most common nonhematological adverse effects are gastrointestinal (GI) disruption, fatigue, and hyperglycemia. Rare but serious adverse reactions include febrile neutropenia, infections, and cerebral hemorrhage.

▶ Histone Deacetylase (HDAC) Inhibitors (Belinostat, Panobinostat, Romidepsin, Tazemetostat, and Vorinostat)

Histone deacetylase (HDAC) inhibitors agents catalyze the removal of acetyl groups from acetylated lysine residues in histones, resulting in the modulation of gene expression. Belinostat, romidepsin, and vorinostat are used for the treatment of cutaneous T-cell lymphoma; panobinostat for MM; and tazemetostat for epithelioid sarcoma and follicular lymphoma. Panobinostat, tazemetostat, and vorinostat are orally available agents, and belinostat and romidepsin are only available in an IV formulation. These drugs are metabolized by CYP3A4 and have potential drug interactions strong CYP3A inducers and inhibitors. Side effects include fatigue, myelosuppression, and GI toxicities. Tazemetostat and vorinostat are associated with hypercholesterolemia, hypertriglyceridemia, and hyperglycemia. Despite anemia, thrombocytopenia, and neutropenia, patients receiving vorinostat have developed pulmonary embolism and DVT while on therapy. Panobinostat carries a boxed warning for severe diarrhea (occurring in 25% of patients) and cardiac events, severe arrhythmia and electrocardiogram changes that can be exacerbated by electrolyte abnormalities. Tazemetostat has a risk of a developing a second primary hematologic malignancy.

Immunotherapy

▶ Chimeric Antigen Receptor (CAR) T-Cell Therapies (Axicabtagene ciloleucel, Brexucabtagene autoleucel, Tisagenlecleucel)

One of the newer immunotherapy classes is the chimeric antigen receptor (CAR) T-cell therapies that are autologous T-cell immunotherapies comprising T cells that are genetically modified using a vector to encode an anti-CD19 CAR. Axicabtagene ciloleucel, brexucabtagene autoleucel and tisagenlecleucel are prepared from the patient's own peripheral mononuclear cells, which are obtained through a leukapheresis procedure.[18] The cells are sent to a laboratory whereby they are enriched with the lentiviral vector containing anti-CD19 CAR transgene. The transduced T cells are then expanded and formulated into a suspension that is cryopreserved. Once passing a sterility test, it is shipped back in a patient-specific infusion bag to the institution for administration. Axicabtagene ciloleucel is approved for large B-cell lymphoma; brexucabtagene autoleucel is approved for mantle cell lymphoma; and tisagenlecleucel is approved for us in ALL and diffuse large B-cell lymphoma. The most common side effect is a cytokine-release syndrome (CRS), which can be fatal. CRS occurs when the cytokines are released by activated T cells, producing a systemic inflammatory response. Patients may initially present with a low-grade fever, fatigue, and anorexia which can quickly progress to high fever, hypoxia, and organ failure. Immediate identification and treatment is necessary to prevent death. Another potentially serious side effect is neurotoxicity which often manifests within 4 to 10 days and can be mild such as headache and dizziness but can progress to delirium, aphasia, seizures, and encephalopathy. NCCN has guidelines on monitoring and treating CRS, neurologic symptoms, and other CAR T-cell therapy toxicities.[25] Other side effects include decreased appetite, headache, nausea/vomiting, infections, and diarrhea.

Monoclonal Antibodies

The cell surface contains molecules, which are referred to as *CD*. The antibodies are produced against a specific antigen. When administered, usually by an IV injection, the antibody binds to the antigen, which may trigger the immune system to result in cell death through complement-mediated cellular toxicity, or the antigen–antibody cell complex may be internalized to the cancer cell, which results in cell death. Monoclonal antibodies may also carry radioactivity, sometimes referred to as *hot antibodies*, and are referred to as *radioimmunotherapy*, so the radioactivity is delivered to the cancer cell. Antibodies that contain no radioactivity are referred to as *cold antibodies*.

All monoclonal antibodies end in the suffix *-mab*. The syllable before *-mab* indicates the source of the monoclonal antibody (Table 88–7).[26] When administering an antibody for the first time, one should consider the source. The less humanized an antibody, the greater the chance for the patient to have an allergic-type reaction to the antibody. The more humanized the antibody, the lower the risk of a reaction. The severity of the reactions may range from fever and chills to life-threatening allergic reactions. Premedication with acetaminophen and diphenhydramine is common before the first dose of any antibody. If a severe reaction occurs, the infusion should be stopped and the patient treated with antihistamines, corticosteroids, or other supportive measures.

Table 88–7

Syllable Source Indicators for Monoclonal Antibodies[a]

U	Human
O	Mouse
Xi	Chimeric: A cross between humanized and animal source
Axo	Rat/mouse hybrid
Xizu	Combination of humanized and chimeric chains

[a]These letters appear before mab, which stands for monoclonal antibody.

Data from American Medical Association. Monoclonal Antibodies. Available from: https://www.antibodysociety.org/wordpress/wp-content/uploads/2017/07/INN-2017-Reference-20.pdf (accessed October 10, 2020).

Many monoclonal antibodies now have biosimilar products approved in the United States for cancer treatment. A biosimilar is a type of biological product that is highly similar to the originator product and is expected to have no meaningful clinical difference. They are thought to be interchangeable from the innovator product. New biologics approved by the FDA now have a four-letter suffix to differentiate innovator and biosimilar products.

▶ Alemtuzumab

Alemtuzumab is an antibody to the CD52 receptor present on B and T lymphocytes. Alemtuzumab has shown clinical activity in the treatment of CLL. Severe and prolonged (6 months) immunosuppression may result, which necessitates *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis and antifungal and antiviral prophylaxis to prevent opportunistic infections. Infusion-related reactions typically occur with the first dose and can be severe. Premedication with antihistamines and acetaminophen is recommended. SC administration will also alleviate the severity of infusion reactions.

▶ Bevacizumab

Bevacizumab is a humanized monoclonal antibody that binds to vascular endothelial growth factor (VEGF), which prevents it from binding to its receptors, ultimately resulting in inhibition of angiogenesis. Bevacizumab has shown clinical activity in the treatment of breast, colorectal, glioblastoma, gynecologic, head and neck, kidney, and lung cancer. Patients treated with bevacizumab products may develop hypertension requiring chronic medication during therapy. Impaired wound healing, thromboembolic events, proteinuria, bleeding, and bowel perforation are serious side effects that occur with this drug.

▶ Blinatumomab

Blinatumomab is a bispecific CD19-directed CD3 T-cell therapy. It activates T cells by connecting the CD3 antigen in the receptor complex with the CD19 surface antigen on both benign and malignant B cells, activating inflammatory cytokine release and T-cell proliferation resulting in apoptosis of CD19+ cells. It is effective in patients with Philadelphia negative B-cell precursor ALL. Common side effects include pyrexia, neutropenia, infections, and infusion-related reactions. Patients should receive dexamethasone before infusion and when restarting an infusion if interrupted for more than 4 hours. Rare but serious side effects include CRS and neurologic toxicity, such as paresthesia, confusion, dizziness, and tremor. Thus, patients are typically hospitalized for the first cycle and first 2 days of the second cycle. Medication errors can occur when preparing and administering blinatumomab because preparation instructions are more complicated than most other IV drugs. Doses are based on weight, dose, and duration of infusion. Additionally, specific instructions for use of an IV solution stabilizer are provided rather than mixing with the drug for reconstitution and the volume for infusion.

▶ Cetuximab, Necitumumab, and Panitumumab

Cetuximab is a chimeric antibody that binds to the EGFR to block its stimulation. Panitumumab binds to the EGFR to prevent receptor autophosphorylation and activation of receptor-associated kinases, which results in inhibition of cell growth and induction of apoptosis. Necitumumab is an anti-EGFR recombinant human monoclonal antibody. Cetuximab has shown clinical activity in the treatment of colorectal and head and neck cancers, necitumumab in non–small cell lung cancer, and panitumumab in colorectal cancers. Tumors that have *RAS* mutations do not respond to treatment with cetuximab or panitumumab; therefore, tumors should be tested for *RAS* mutations before initiating therapy. An acne-like rash may appear on the face and upper torso 1 to 3 weeks after the start of therapy. Preventive therapies with topical corticosteroids with moisturizer, sunscreen, and oral doxycycline are recommended. Other side effects include hypersensitivity reactions, fever, nausea and vomiting, and interstitial lung disease. Electrolyte disturbances, such as hypomagnesemia and hypocalcemia, can occur; these are more common with necitumumab and panitumumab.

▶ *Daratumumab and Isatuximab*

Daratumumab and isatuximab are monoclonal antibodies to the CD38 receptor, highly expressed on myeloma cells and weakly on other hematopoietic stem cells. They are used in patients with MM. Infusion-related reactions are common so patients must be pretreated with acetaminophen, an antihistamine, and IV methylprednisolone. Additionally, with daratumumab, an oral corticosteroid is administered for each of the 2 days following infusion to prevent delayed reactions. Also, these drugs also interact with cross matching and red blood cell antibody screening, by causing a positive indirect Coombs test that can persist for 6 months after discontinuation of therapy. Thus, patients should be typed and screened before therapy, and blood banks should be informed when a patient has received either of these drugs.

▶ *Elotuzumab*

Elotuzumab is a humanized recombinant monoclonal antibody that specifically targets signaling lymphocytic activation molecule family member 7 protein. It works by directly activating natural killer cells to mediate the killing of myeloma cells through antibody-dependent cellular cytotoxicity (ADCC). Premedications to prevent infusion-related reactions should include dexamethasone, H_1 blocker, H_2 blocker, and acetaminophen. The most common side effects are fatigue, diarrhea, pyrexia, constipation, and cough.

▶ *Obinutuzumab, Ofatumumab, and Rituximab*

Obinutuzumab, ofatumumab, and rituximab are monoclonal antibodies to the CD20 receptor expressed on the surface of B lymphocytes; the presence of the antibody is determined during flow cytometry of the tumor cells. Cell death results from ADCC. All of these drugs have shown clinical activity in the treatment of B-cell lymphomas that are CD20 positive. Side effects include infusion-related reactions, hypotension, fevers, chills, rash, headache, and mild nausea and vomiting. Premedication with acetaminophen and an antihistamine is recommended for rituximab to minimize the first-dose infusion reaction. Acetaminophen, an antihistamine, and a glucocorticoid are administered prior to obinutuzumab and ofatumumab. In patients with extensive disease, prevention of tumor lysis syndrome is also recommended. Serious adverse events, including fatal infections, progressive multifocal leukoencephalopathy, and reactivation of hepatitis B, have been reported. Thus, all patients should be tested for hepatitis B and treated before therapy commences.

▶ *Pertuzumab, Trastuzumab, and Trastuzumab/Hyaluronidase*

Pertuzumab and trastuzumab-based products are humanized monoclonal antibodies directed against human epidermal receptor 2 (HER-2). When compared to trastuzumab products, pertuzumab recognizes different extracellular epitopes, binds uniquely, which causes structural changes and, therefore, interrupts receptor dimerization. These differences were thought to be able to provide greater inhibition of HER-2 when compared to trastuzumab, but this has not been proven to be the case. Cancer tissue must be tested for the presence of HER-2 because patients who do not express HER-2 do not respond to trastuzumab. Trastuzumab hyaluronidase is trastuzumab combined with an enzyme hyaluronidase-oysk that allows the drug to be delivered subcutaneously, reducing potential for infusion-related reactions and shorter administration. Trastuzumab-products and pertuzumab are used for certain patients with HER-2 positive breast cancers; trastuzumab (but not all products) can also be used in other solid tumors that are HER-2 positive (eg, gastric cancer). Trastuzumab products are not interchangeable and may have different dose, schedules, and indications.

Severe congestive heart failure may occur with concurrent HER-2 monoclonal antibody and anthracycline administration. Cardiac toxicity may be seen when the drug is administered months after anthracycline administration, so patients must be counseled on the signs and symptoms of heart failure. A common side effect associated with trastuzumab is a first-dose infusion-related reaction which includes chills. The patient may be given acetaminophen and diphenhydramine and/or the infusion may be slowed. Other side effects that are rare include hypersensitivity reactions, abnormal liver function tests, and pulmonary reactions.[32] Pertuzumab has similar adverse effects as trastuzumab. When used in combination with trastuzumab, it does not appear to increase the incidence of cardiac toxicity. A more detailed discussion of the use of trastuzumab products and pertuzumab in breast cancer can be found in Chapter 89.

Antibody Conjugates

Antibody conjugates contain both an antibody and either a drug or radioisotope. In many cases, the antibody is used as a drug vehicle to deliver an anticancer agent either an antineoplastic agent or the radioisotope. In some cases, a linking agent is also used to link the antibody and anticancer drug. Antibody–drug conjugates are often referred to as ADCs.

▶ *Ado-Trastuzumab Emtansine (Trastuzumab Emtansine) and Fam-Trastuzumab Deruxtecan*

Ado-trastuzumab emtansine combines trastuzumab and the anticancer agent emtansine (a maytansine derivative). Fam-trastuzumab deruxtecan is composed of fam-trastuzumab (which has same basic structure of trastuzumab), a topoisomerase I inhibitor exatecan derivative (DXd), and a compound that links the drugs, deruxtecan. The most common serious adverse effect with ado-trastuzumab emtansine was thrombocytopenia. The platelet nadir usually occurs about 7 days after treatment and recovers within a week. Other side effects are similar to trastuzumab products. See more detail in Chapter 89.

▶ *Belantamab Mafodotin*

Belantamab mafodotin is composed of the monoclonal antibody belantamab directed against B-cell maturation antigen (BMCA) and the conjugate mafodotin, an auristatin analogue and microtubule inhibitor monomethyl auristatin phenylalanine (MMAF) that has antineoplastic activity. It is used in MM. It has boxed warning regarding corneal epithelium changes including severe vision loss and corneal ulcer. Ophthalmologic exams are, therefore, required at baseline and throughout therapy. Additionally infusion-related reactions and fatigue may occur.

▶ Brentuximab Vedotin

Brentuximab vedotin is a CD30-directed antibody, a microtubule disrupting agent called monomethyl auristatin E (MMAE), and a protease-cleavable linker that covalently attaches MMAE to the antibody. It is reported that the cytotoxic activity is a result of the binding of the ADC to CD30-expressing cells followed by internalization of the ADC–CD30 complex, and then proteolytic cleavage and release of MMAE into the cell. Binding of MMAE to tubulin disrupts the microtubule network, resulting in cell cycle arrest and apoptosis. This IV agent is indicated for some Hodgkin lymphoma and non-Hodgkin lymphoma patients. In vitro data suggests that MMAE is a substrate and an inhibitor of CYP3A4/5; therefore, patients need to be monitored for drug–drug interactions. The most common adverse effects are neutropenia, peripheral neuropathy, fatigue, nausea and vomiting, diarrhea, anemia, thrombocytopenia, and upper respiratory infection.

▶ Ibritumomab Tiuxetan

Ibritumomab tiuxetan, a "*hot antibody*," is linked to yttrium and binds to the CD20 receptor of B lymphocytes. Hematologic toxicity may occur several weeks after administration and may take weeks to resolve.

▶ Polatuzumab Vedotin

Polatuzumab vedotin is an ADC directed against CD79B via a proteas-cleavable peptide linker to MMAE, an auristatin derivative and potent microtubule inhibitor. This drug is used for diffuse large B-cell lymphoma and is associated with myelosuppression, peripheral neuropathy, serious infections, and infusion-related reactions. Thus, an antihistamine and antipyretic are used for premedications and patients should receive prophylaxis for herpes virus and PJP.

▶ Sacituzumab Govitecan

Sacituzumab govitecan is an antibody against tumor-associated calcium signal transducer 2 linked to an irinotecan metabolite, SN-38. This drug is indicated for metastatic triple-negative breast cancer. It is has boxed warnings for neutropenia and severe diarrhea. It is associated with nausea, anorexia, fatigue, and infusion-related reactions. Prior to each dose, premedicate with antipyretics and H_1/H_2 antagonists; corticosteroids may be administered if an infusion-related reaction occurred with a prior dose that required premedications. Patients with UGT1A1*28 deficiency are at an increased risk of neutropenia and other adverse events.

Checkpoint Inhibitors

The immune system is in a continual state of balance between tolerating "normal" tissue and attacking foreign substances. Immunological tolerance is regulated by immune cells, suppressive cytokines, and immune checkpoint pathways.[27] Immune checkpoints become involved following immune activation, creating an inhibitory feedback loop to reduce involvement of normal tissues. Inhibitors of the immune checkpoints act by inhibiting key regulatory steps, promoting activation and proliferation of T cells to induce tumor infiltration and regression. Tumor responses to checkpoint inhibitors differ from those observed with other anticancer therapies. Responses can be seen long after the start of treatment, and pseudoprogression can be seen immediately after starting therapy which, instead of representing a tumor progression, can represent inflammation only within the tumor area. Checkpoint inhibitors are now approved for use not only in many solid tumors but also in some hematologic tumors and can be administered alone or in combination with each other, chemotherapy and targeted therapies.

Adverse effects of checkpoint inhibitors are related to their effect on the immune system, whereby they attack normal cells as well. This can result in severe and fatal immune-mediated adverse reactions, including enterocolitis, hepatitis, toxic epidermal necrolysis, neuropathy, pneumonitis, and endocrine abnormalities. Thus a physical examination and review of systems is important to quickly identify and treat toxicity. Complete blood counts (CBCs) with differentials, comprehensive metabolic panel, and liver function tests should be performed at baseline and cortisol and thyroid function tests periodically. Patients should be monitored for symptoms of inflammatory responses (eg, diarrhea as early sign of colitis, shortness of breath as early sign of pneumonitis). These symptoms can occur during treatment or weeks to months after discontinuation of the drug. If any of these reactions occur, treatment should be initiated with systemic corticosteroids, which are tapered once symptoms improve, and the drug should be held until symptoms resolve. Severe toxicities require permanent discontinuation. Unlike other anticancer agents, dose reductions are not used as a toxicity management strategy with checkpoint inhibitors. Typically, these side effects can be more severe with the cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) inhibitor than PD-1 or PD-ligand (PD-L)-1 inhibitors. NCCN publishes guidelines for management of immunotherapy toxicities and more details can be found in the Supportive Care (Chapter 99).[25]

▶ Ipilimumab

Ipilimumab is a recombinant, human monoclonal antibody that binds to the CTLA-4, which is a molecule on T cells that causes a suppression of the immune response. CTLA-4 is a negative regulator of T-cell activation. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands. This blockage has been reported to enhance T-cell activation and proliferation. The antitumor effects appear to be T-cell–mediated immune responses and are the highest with this drug of all the available checkpoint inhibitors.

▶ Cemiplimab, Nivolumab, and Pembrolizumab

Cemiplimab, nivolumab, and pembrolizumab are human monoclonal antibodies that block the interaction of the binding to PD-1 and its ligands, PD-L1 and PD-L2. Cemiplimab is approved for patients with cutaneous squamous cell carcinoma. Both nivolumab and pembrolizumab are active in many solid and some hematologic tumors. Pembrolizumab is also the first monoclonal antibody to be approved as a tumor agnostic therapy. That is, it is approved for patients with any cancer that have high microsatellite instability or high mutational tumor burden. Side effects are much less common with PD-1 inhibitors compared with the CTLA-4 inhibitor ipilimumab.

▶ Atezolizumab, Avelumab, and Durvalumab

Atezolizumab, avelumab, and durvalumab are recombinant, human monoclonal antibodies that bind PD-L1 and block interaction with the PD-1 receptors. These drugs are active in many solid tumors. Side effects are much less common with PD-L1 inhibitors compared with the CTLA-4 inhibitor ipilimumab.

Tyrosine Kinase Inhibitors (TKI)

More than 100 different types of tyrosine kinases are present in the body. TKIs have been developed to block either several or a specific tyrosine kinase (see Table 88–6). They are used to treat solid tumors, leukemias, and lymphomas and can be used as alone or in combination with IV chemotherapy, surgery, and/or radiation. Some are continuously administered until disease progression occurs or intolerance develops whereas others are given cyclically (eg, 2 weeks on, 1 week off; then repeat). Side effects often limit use if uncontrolled and typically are different than those observed from traditional chemotherapy or immunotherapy. Drug interactions are common as many of these drugs are metabolized through the CYP450 and P-glycoprotein systems and can have decreased concentrations in the presence of antacids, H_2 blockers, and/or proton pump inhibitors.

▸ *Anaplastic Lymphoma Kinase (ALK) Inhibitors (Alectinib, Brigatinib, Ceritinib, Crizotinib, and Lorlatinib)*

These small molecules primarily inhibit anaplastic lymphoma kinase (ALK) and often will inhibit others such as mesenchymal epithelial transition growth factor *c-MET, (*crizotinib), Ret proto-oncogene (RET), (alectinib); or insulin-like growth factor 1 receptor, insulin receptor, and ROS proto-oncogene 1 (ROS1), (brigatinib and lorlatinib). These orally available agents are approved for the treatment of NSCLC, that is ALK positive (about 2%–7% of NSCLC patients) as detected by an FDA-approved test. Adverse effects include mild GI symptoms and elevated liver function tests. Visual changes, pulmonary disease, and QTc prolongation can also occur as well as creatine kinase elevations specifically with alectinib. Lorlatinib is associated with CNS effects such as changes in cognitive function, mood, sleep, and seizures.

▸ *B-cell Lymphoma 2 (Bcl-2) Inhibitor (Venetoclax)*

Venetoclax selectively inhibits the anti-apoptotic protein Bcl-2, which is over-expressed in CLL and AML, thus restoring the apoptotic process. This drug can work quickly and put patients at risk for tumor lysis syndrome. Thus, the dose is escalated slowly with tumor lysis monitoring and prophylaxis required. A reduced renal function increases the risk of tumor lysis syndrome. Myelosuppression, nausea, and diarrhea can occur.

▸ *BCR-ABL TKIs (Bosutinib, Dasatinib, Imatinib, Nilotinib, and Ponatinib)*

Imatinib was the first FDA-approved TKI. Imatinib inhibits phosphorylation during cell proliferation. The drug was designed to block the breakpoint cluster region tyrosine kinase (BCR-ABL) produced by the Philadelphia chromosome associated with CML and ALL. Imatinib also has shown activity against GI stromal tumors (GIST) that are positive for c-kit (CD117). Imatinib is usually well tolerated, but common adverse effects include myelosuppression, rash, GI upset, edema, fatigue, arthralgias, myalgias, and headaches. A cumulative cardiotoxicity is a serious but rare adverse effect; therefore, it is recommended to closely monitor patients with preexisting cardiac conditions.

Advanced generation BCR-ABL TKIs are more potent than imatinib and can overcome most BCR-ABL mutations that lead to imatinib resistance. Bosutinib, dasatinib, and nilotinib are second-generation BCR-ABL TKIs and are used frontline in the treatment of CML and in CML with resistance or intolerance to imatinib. Side effects of dasatinib and nilotinib are similar to imatinib and include myelosuppression, nausea and vomiting, headache, fluid retention, and hypocalcemia. Pleural effusions have been reported with dasatinib and imatinib but not with nilotinib. QTc prolongation can occur with dasatinib and nilotinib. Abnormalities in indirect bilirubin have been reported with nilotinib and is more common in patients with (TA)7/(TA)7 genotype (*UGT1A1*28*).[28] Bosutinib appears to have a milder side effect profile than other TKIs, with GI disturbances and rash being most common.

Ponatinib is a third-generation multikinase inhibitor and the only advanced generation TKI that overcomes the *T315I* mutation. The serious adverse effects thrombosis, hepatotoxicity (rare), and death (rare) are included as boxed warnings. Less serious adverse effects include abdominal pain, dry skin, and rash.

▸ *BRAF Inhibitors (Dabrafenib, Encorafenib, and Vemurafenib)*

Dabrafenib, encorafenib, and vemurafenib are inhibitors of *BRAF* kinases. They most often are used to treat melanoma and also some colon cancers that have *BRAF V600E* mutations. Common adverse effects of BRAF inhibitors include arthralgias, alopecia, GI symptoms, and fatigue. Other adverse effects of vemurafenib include rash, keratoacanthoma or squamous cell cancer, and photosensitivity. Adverse effects associated with dabrafenib include headache, palmar–plantar erythrodysesthesia syndrome, elevated liver enzymes, pyrexia, and papilloma. Encorafenib is associated with electrolyte disturbances, including hyperglycemia and increased serum creatinine.

▸ *Bruton's Tyrosine Kinase (BTK) Inhibitors (Acalabrutinib, Ibrutinib, and Zanubrutinib)*

Bruton's tyrosine kinase (BTK) is an integral component of the B-cell receptor. Constitutive activation of B-cell receptor signaling allows the survival of malignant B cells. BTK inhibitors decrease malignant B-cell proliferation and survival and are used in CLL and some types of non-Hodgkin lymphomas. A noninfectious, transient lymphocytosis should be expected and can last for weeks but does not signify disease progression. Myelosuppression and mild GI toxicities are the most common adverse effects. Infection risk is high; hepatitis B reactivation can occur, thus testing at baseline for hepatitis B is recommended. Secondary cancers, primarily skin malignancies, have also been reported. BTK inhibitors can increase the risk of bleeding, particularly in patients receiving antiplatelet or anticoagulant medications. Additionally, cardiac toxicity, including new-onset atrial fibrillation, hypertension, and ventricular tachyarrhythmias can, occur but are more frequent with ibrutinib. Acalabrutinib is associated with headaches that are typically resolved after 1 to 2 months of therapy and can be managed with acetaminophen and caffeine. Zanubrutinib is associated with rashes.

▸ *Cyclin-Dependent Kinase (CDK) Inhibitors (Abemaciclib, Palbociclib, and Ribociclib)*

Abemaciclib, palbociclib, and ribociclib all inhibit cyclin-dependent kinases (CDKs) 4 and 6, which prevent phosphorylation and subsequent inactivation of the retinoblastoma tumor suppressor protein, ultimately causing cell cycle arrest and inhibiting cancer cell proliferation. Each of the available CDK4/6 inhibitors is used in the treatment of postmenopausal women with hormone receptor positive but HER-2 negative breast cancer. Palbociclib and ribociclib are administered daily for 21 days, followed by 7 days off, whereas abemaciclib is administered daily. Common side effects include neutropenia, GI toxicities, and hair loss. Rarely, abemaciclib is associated with venous thromboembolism, ribociclib with QTc prolongation, and both with hepatotoxicity.

▶ EGFR Pathway Inhibitors (Afatinib, Dacomitinib, Erlotinib, Gefitinib, Lapatinib, Neratinib, Osimertinib, and Tucatinib)

Patients with NSCLC in which the tumors have mutations in exon 19 and/or 21 in the EGFR pathway will likely respond to EGFR TKIs such as afatinib, dacomitinib, and erlotinib. Those with EGFR *T790M* mutations will likely respond to osimertinib. These agents are believed to inhibit the intracellular phosphorylation of the EGFR. Food increases bioavailability to almost 100% but is variable; experts recommend administering erlotinib on an empty stomach. Smoking increases the clearance of erlotinib by 24%, which may result in treatment failure and different doses are used for smokers versus nonsmokers.[29] Side effects of EGFR inhibitors include acneiform rash, diarrhea, dry skin, fatigue, anorexia, pruritus, conjunctivitis, and rarely interstitial lung disease. Diarrhea and rash are highest among afatinib and dacomitinib.

Lapatinib, neratinib, and tucatinib inhibit the intracellular kinase domains of both EGFR and HER-2 and have been shown to retain activity against breast cancer cells that have become resistant to trastuzumab. These are indicated for the treatment of patients with breast cancer whose tumors overexpress HER-2. Common side effects include diarrhea, nausea/vomiting, fatigue, and HFS.

▶ Fibroblast Growth Factor Receptor (FGFR) (Erdafitinib and Pemigatinib)

Fibroblast growth factor receptor (FGFR) inhibitors bind to and inhibit FGFR, which may be overexpressed on certain tumor cells. Erdafitinib is indicated for urothelial carcinoma patients with FGFR-2 or -3 genetic alterations; whereas pemigatinib is indicated for those with cholangiocarcinoma and an FGFR-2 fusion or other gene rearrangement. FGFR inhibitors can cause hyperphosphatemia, stomatitis, fatigue, dry mouth/skin, alopecia, onycholysis, liver function enzyme elevations and rarely ocular disorders such as serous retinopathy/retinal pigment epithelial detachment.

▶ Hedgehog Inhibitors (Glasdegib, Sonidegib, and Vismodegib)

The Hedgehog pathway is a signaling pathway that regulates self-renewal and differentiation of cells. It is abnormally activated in basal cell carcinoma, medulloblastoma, and leukemia. These inhibitors bind to smoothened (SMO), a transmembrane protein, and prevents downstream signaling and activation of the Hedgehog pathway thus preventing tumor growth. Glasdegib is indicated for AML treatment and sonidegib and vismodegib are indicated for basal cell carcinoma. Because the Hedgehog pathway is essential for embryogenesis, these drugs have boxed warnings for severe birth defects and embryo–fetal death and have strict recommendations for contraception for both males and females and pregnancy tests within 7 days of starting therapy. Patients are also advised to not donate blood during and for 30 days to 24 months following the last dose, depending on the drug. The most common adverse effects of sonidegib and vismodegib include muscle spasms, alopecia, dysgeusia, weight loss, fatigue, and GI toxicities. Glasdegib is also associated with myelosuppression, GI toxicities, edema, and dyspnea and may cause QTc prolongation. Sonidegib can increase serum creatine kinase levels, leading to severe musculoskeletal events.

▶ Isocitrate Dehydrogenase (IDH) Inhibitors (Enasidenib and Ivosidenib)

Isocitrate dehydrogenase (IDH) enzymes are part of the citric acid cycle, which is responsible for cellular respiration. In cancer, IDH1 and IDH2 are recurrently mutated and produce 2-hydroxglutarate that alters DNA methylate and leads to the inhibition of cellular differentiation. Enasidenib is a potent selective inhibitor of mutant IDH2 and ivosidenib is a selective reversible inhibitor of mutant IDH1 and are used for IDH-mutated AML. The most common adverse events include hyperbilirubinemia without concurrent transaminase elevation. Enasidenib is associated with nausea and vomiting and requires a prophylactic antiemetic and can cause leukocytosis and tumor lysis syndrome. Ivosidenib is associated with fatigue, noninfectious leukocytosis, arthralgia, diarrhea, and QTc prolongation.

▶ Mitogen-Activated Extracellular Kinases (MEK) Inhibitors (Binimetinib, Cobimetinib, Selumetinib, and Trametinib)

Binimetinib, cobimetinib, and trametinib are reversible inhibitor of mitogen-activated extracellular kinases (MEK)-1 and MEK-2 and are active against *BRAF V600*-mutated forms of BRAF kinases in melanoma cells. They most often are used in combination with BRAF inhibitors for malignant melanoma. Rash, diarrhea, fatigue, acneiform dermatitis, and peripheral and lymph edema are commonly reported. Cardiomyopathy (defined as heart failure) and bleeding have also been reported. Selumetinib is approved for a pediatric with neurofibromatosis type 1. Most common adverse effects are nausea, vomiting, diarrhea, rash, dry skin, and fatigue.

▶ Mammalian Target of Rapamycin (mTOR) Inhibitors: Temsirolimus and Everolimus

The mammalian target of rapamycin (mTOR) is a downstream mediator in the phosphatidylinositol 3-kinase/Akt signaling pathway that controls translation of proteins that regulate not only cell growth and proliferation but also angiogenesis and cell survival. The mTOR is an intracellular component that stimulates protein synthesis by phosphorylating translation regulators and contributes to protein degradation and angiogenesis.

Temsirolimus is approved for the treatment of advanced kidney cancer. Temsirolimus and its metabolite sirolimus are substrates of the CYP3A4/5 isoenzyme system. The primary side effects of temsirolimus include mucositis, diarrhea, maculopapular rash, nausea, leucopenia, thrombocytopenia, and hyperglycemia. Noninfectious pneumonitis can occur and must be identified immediately for best outcomes.

Everolimus is an oral inhibitor of mTOR that is approved for the treatment of patients with advanced kidney cancer, breast cancer, and neuroendocrine tumors. Drug interactions and adverse reactions are similar to those of temsirolimus.

▶ Multikinase Inhibitors (Axitinib, Cabozantinib, Sorafenib, Sunitinib, and Pazopanib)

Multikinase inhibitors inhibit multiple tyrosine kinases and are used for many different cancers. A full list of available multikinase inhibitors is found in Table 88–6. Some of the more common ones are described here. Sorafenib is a multikinase inhibitor that inhibits both intracellular and extracellular kinases and is used in the treatment of hepatic, kidney, and thyroid cancers. The primary side effects of sorafenib include rash, diarrhea, pruritus, and elevations in serum lipase. Hand–foot skin reaction (HFSR) can also occur with those drugs that affect the VEGF receptor. HFSR differs than HFS in that it initially develops as erythema and soreness, progressing to blisters, and eventually hyperkeratosis.

Cabozantinib and pazopanib both primarily inhibit VEGF receptor-1 (VEGFR)-1, VEGFR-2, VEGFR-3, and several other tyrosine kinases. Cabozantinib is available in two dosage forms: tablets and capsules. The tablet formulation is used for patients with advanced kidney cancer, whereas the capsules are a larger dose for patients with medullary thyroid cancer. Pazopanib is used to treat advanced kidney cancer and sarcomas. Common side effects of these drugs are diarrhea, nausea, anorexia, HFSR syndrome, hypertension, and fatigue. Pazopanib also is associated with hair color changes. Serious toxicities that have been observed are fatal hepatotoxicity, prolonged QTc intervals and torsade's de pointes, hemorrhagic events, arterial thrombotic events, GI perforation, and proteinuria.

Regorafenib is another small molecule inhibitor of multiple membrane-bound and intracellular kinases used in the treatment of metastatic colorectal cancer and GI stromal tumor. The proposed mechanism of action is through inhibition of VEGFR involved in angiogenesis. GI effects, hypertension, mucositis, infection, rash, and fever are commonly occurring adverse effects. Hepatotoxicity is listed as a black-box warning; therefore, hepatic function should be monitored closely. It is an orally administered agent given for the first 21 days per 28-day cycle and should be taken with a low-fat breakfast (30 g or less).

▶ *Neurotrophic Tyrosine Receptor Kinase (NTRK) (Entrectinib and Larotrectinib)*

Neurotrophic tyrosine receptor kinase (NTRK) inhibitors are the first oral anticancer agents approved pan-tumor, meaning they are used to treat a specific genetic mutation rather than a tumor type. Both entrectinib and larotrectinib are used adults and pediatric patients with solid tumors that have a NTRK gene fusion without a known acquired resistance. Entrectinib is also approved for *ROS*1-positive NSCLC. The most common adverse reactions include fatigue, nausea/vomiting, diarrhea, constipation, and dizziness. Elevations in transaminases may occur. Rarely, entrectinib is associated with reductions in left ventricular ejection fraction (LVEF), QTc prolongation, vision disorders, hyperuricemia, and skeletal fractures.

▶ *Phosphoinositide 3-Kinase (PI3-K) Inhibitors (Alpelisib, Copanlisib, Duvelisib, and Idelalisib)*

Phosphoinositide 3-kinase (PI3-K), an essential lipid kinase, is the target of inhibition for alpelisib, copanlisib, duvelisib, and idelalisib. Alpelisib is indicated for breast cancer patients with a PI3KCA mutation and the other drugs are used in the treatment of follicular lymphoma and CLL. Adverse effects associated with copanlisib are hyperglycemia, hematologic abnormalities, fatigue, diarrhea, and hypertension. Duvelisib is associated with hepatotoxicity, diarrhea, cutaneous reactions, and myelosuppression. Idelalisib causes GI disturbances, rash, hematological side effects, fatigue, and musculoskeletal pain. Idelalisib caries boxed warnings for hepatotoxicity, colitis, pneumonitis, infections, and intestinal perforation. Because the PI3-K pathway regulates the immune system, PI3K inhibitors result in immunosuppression, placing patients receiving these medications at risk for immunocompromising infections such as PJP and cytomegalovirus; thus close monitoring and consideration of prophylactic antibacterials and antivirals is warranted.

▶ *Poly ADP Ribose Polymerase (PARP) Inhibitors (Niraparib, Olaparib, and Rucaparib)*

PARP enzymes are involved in normal cellular function, including DNA transcription and repair. PARP inhibitors prevent DNA repair, allow apoptosis to occur and inhibit tumor growth. Niraparib is used to treat ovarian, fallopian tube, or peritoneal cancer; olaparib is used to treat some breast, ovarian, pancreatic, and prostate cancers, and rucaparib is used to treat some ovarian and prostate cancers. Common side effects include myelosuppressive side effects, GI toxicities, fatigue, upper respiratory tract infections, and arthralgias and myalgias. Rarely, patients can develop MDS or AML and pneumonitis. Niraparib also causes hypertension and patients must undergo heart rate (HR) and blood pressure (BP) monitoring monthly for the first year.

▶ *Proteasome Inhibitors (Bortezomib, Carfilzomib, and Ixazomib)*

The proteasome is an enzyme complex that exists in all cells and plays an important role in degrading proteins that control the cell cycle. When the proteasome is inhibited, the numerous pathways that are necessary for the growth and survival of cancer cells are disrupted. Bortezomib specifically inhibits the 26S proteasome, which is a large protein complex that degrades ubiquitinated proteins. This pathway plays an essential role in regulating the intracellular concentration of specific proteins, causing the cells to maintain homeostasis. Inhibition of the 26S proteasome prevents this from occuring, ultimately causing a disruption in the homeostasis and cell death. Both carfilzomib and ixazomib inhibit 20S proteasome, which is the proteolytic core with the 26S proteasome.

Bortezomib is approved for the treatment of MM and mantle cell lymphoma. It is administered either as an IV or SC injection. The most commonly reported adverse effects are asthenia, GI disturbances (nausea, diarrhea, decreased appetite, constipation, vomiting), thrombocytopenia, peripheral neuropathy, anemia, headache, insomnia, and edema. Peripheral neuropathy is much lower with the SC injection. Prophylactic anticoagulation is not routinely required. Reactivation of varicella zoster infection is also common with bortezomib, and antiviral prophylaxis with acyclovir should be considered.

Carfilzomib and ixazomib are second-generation proteasome inhibitors. Carfilzomib is administered by IV, whereas ixazomib is a capsule that should be taken on an empty stomach. Both of these drugs used in the treatment of refractory cases of MM and have similar but fewer side effects compared with bortezomib.

▶ *RET Inhibitors (Pralsetinib and Selpercatinib)*

RET inhibitors inhibit wild-type RET and oncogenic RET fusions and mutations that are found in 1%–2% of NSCLCs and some thyroid cancers. These drugs are commonly associated with elevations in transaminases, myelosuppression, fatigue, and hypertension. Impairment of wound healing and hemorrhage can occur. Optimization of hypertension is recommended before initiation. Less commonly selpercatinib can cause QTc prolongation and hypersensitivity. Pralsetinib can cause interstitial lung disease.

▶ *Selective Inhibitor of Nuclear Export Antagonist (Selinexor)*

Selinexor is an orally available, small molecular inhibitor of chromosome region maintenance 1 protein, also known as exportin 1 (XOP1). Essentially, selinexor inhibits tumor suppressor proteins, growth regulators, and mRNA of oncogenic proteins, resulting in accumulation of these cell cycle arrest and cancer apoptosis. It is used in non-Hodgkin lymphoma and MM. Common adverse events include myelosuppression, GI toxicity including nausea and vomiting that requires prophylactic antiemetics, hyponatremia, dizziness, and mental status changes.

Hormonal Therapies

Hormonal or endocrine therapies have activity in the treatment of cancers whose growth is affected by gonadal hormonal control. Hormonal treatments either block or decrease the production of endogenous hormones. These agents are covered extensively in Chapters 89 and 92, in the breast and prostate cancer chapters.

▶ Antiandrogens (Bicalutamide, Flutamide, and Nilutamide)

The antiandrogens block androgen receptors (ARs) and inhibit the action of testosterone and dihydrotestosterone in prostate cancer cells. Side effects common to these agents are hot flashes, gynecomastia, and decreased libido. Flutamide tends to be associated with more diarrhea and requires three times daily administration, whereas bicalutamide is dosed once daily. Nilutamide may cause interstitial pneumonia and is associated with the visual disturbance of delayed adaptation to darkness.

▶ Pure AR Antagonists (Apalutamide, Darolutamide, and Enzalutamide)

Pure antagonists competitively inhibit androgen binding to ARs and AR nuclear translocation and coactivator recruitment of the ligand-receptor complex. All three are indicated for non-metastatic castrate-resistant prostate cancer; both apalutamide and enzalutamide are indicated for the treatment of metastatic hormone sensitive prostate cancer; and enzalutamide is also approved for metastatic castration-resistant prostate cancer. The most common side effect of these therapies is fatigue and hypertension, but overall are they well tolerated. Apalutamide is also associated with rash and hypothyroidism.

▶ Luteinizing Hormone–Releasing Hormone Agonists (Goserelin and Leuprolide)

Initially, luteinizing hormone–releasing hormone (LHRH) agonists increase levels of luteinizing hormone and follicle-stimulating hormone, but testosterone and estrogen levels are decreased because of continuous negative-feedback inhibition. Major side effects are testicular atrophy, decreased libido, gynecomastia, and hot flashes. Goserelin is injected as a pellet under the skin; therefore, SC injection of lidocaine around the injection site before administration helps to decrease the pain associated with administration. Numerous dosage forms are available for leuprolide with varying strengths and dosing intervals. Antiandrogens may be administered during initial therapy to decrease symptoms of tumor flare (eg, bone pain and urinary tract obstruction).

▶ Gonadotropin-Releasing Hormone Antagonist (Degarelix)

Degarelix is a gonadotropin-releasing hormone (GnRH) receptor antagonist that reversibly binds to the pituitary GnRH receptors, thereby reducing the release of gonadotropins and consequently testosterone. Degarelix is indicated for the treatment of advanced prostate cancer. Adverse effects include hot flashes, injection site reactions, and an increase in liver enzymes. An advantage of degarelix over LHRH agonists is the lack of the tumor flare.[30]

▶ Abiraterone

Abiraterone is an orally available androgen biosynthesis inhibitor that inhibits 17α-hydroxylase/C17,20-lyase (CYP17), which is expressed in testicular, adrenal, and prostatic tumor tissues. Abiraterone is indicated in combination with prednisone for the treatment of metastatic prostate cancer. Two formulations are available: abiraterone acetate and micronized abiraterone. Both the dose and the administration are different between formulations. The conventional formulation of abiraterone is taken on an empty stomach; however, the micronized formulation can be taken without respect to food. Adverse effects include hypokalemia, edema, muscle discomfort, fatigue, hot flashes, nocturia, urinary frequency, and hypertension.

▶ Aromatase Inhibitors (AIs) (Anastrozole, Exemestane, Letrozole)

Three AIs are currently available: anastrozole, letrozole, and exemestane. All three agents work by inhibiting aromatase, which prevents the conversion of androstenedione to estrone and testosterone to estradiol in adipose tissue, which is the primary source of estrogens in post menopausal women. All three agents are used to treat breast cancer in postmenopausal women and are considered interchangeable in terms of activity. When compared to tamoxifen, there are less endometrial and uterine cancers, vaginal bleeding, and thrombosis with AI therapy. Common adverse effects associated with the AI therapy include hot flashes and arthralgias. Serious adverse effects include osteoporosis, skeletal-related events, and atherosclerotic cardiovascular disease. More information on the pharmacology and clinical use of AI therapy can be found in Chapter 89.

▶ Antiestrogens (Fulvestrant, Raloxifene, and Tamoxifen)

Antiestrogens bind to ERs and block the effect of estrogen on tissue. Two classes of antiestrogens exist: SERMs (tamoxifen, raloxifene) and selective estrogen-receptor downregulators (SERDs, fulvestrant). SERDs were developed in an effort to eliminate the unwanted estrogenic side effects from the SERMs. Tamoxifen is used for the treatment of ER positive premenopausal or postmenopausal metastatic hormone receptor–positive breast cancer, as adjuvant and primary treatment of breast cancer, and in the prevention of breast cancer in high-risk women. The agent has a beneficial effect on bone density and the lipid profile. Unwanted side effects include hot flashes, fluid retention, and mood swings. Thrombosis, endometrial and uterine cancer, corneal changes, and cataracts are harmful adverse effects that occur more frequently with this agent. Although uncommon, there is a disease/tumor flare that can occur during the initiation of therapy in metastatic breast cancer patients with bone metastases. Because tamoxifen is a substrate of CYP3A4, decreased tamoxifen levels have occurred with use of St. John's wort and rifampin. Tamoxifen is also a substrate for CYP450 2D6 and evidence suggests that those who are *CYP2D6*4/*4* may have a poorer response and more toxicity with tamoxifen.[31] Routine pharmacogenomics screening of these patients is not currently recommended. Significant drug interactions exist and drug–drug interactions affecting this enzyme should be avoided if possible.

Raloxifene is another SERM and is used for the treatment of osteoporosis in postmenopausal women and is the

Patient Encounter 1, Part 3

The patient has progressed following therapy with initial treatment with docetaxel and subsequently was found to have a BRCA1 mutation. He now will be receiving a new prescription for olaparib 300 mg orally, twice daily.

What education and training should be provided to the patient to ensure his understanding of safe handling procedures as well as thorough knowledge of proper administration?

How should the patient be instructed to take this medication, in regards to meals or the time of day?

chemopreventive agent of choice for the prevention of breast cancer in high-risk women. When compared head to head with tamoxifen for breast cancer prevention, it was demonstrated to have equal efficacy with less toxicity. Raloxifene was not studied in premenopausal women; therefore, tamoxifen is still the preventative agent of choice in these women. Hot flashes, arthralgias, and peripheral edema occur frequently with raloxifene, but thrombosis and endometrial cancer is less common than with tamoxifen.

Fulvestrant is used as second-line treatment in hormone receptor–positive metastatic breast cancer, postmenopausal women with disease progression following antiestrogen therapy. Fulvestrant is given as a monthly intramuscular injection, which might be a deterrent to some patients.

ADMINISTRATION ISSUES

Extravasation

Extravasation, or the leakage of an anticancer outside the blood vessel into the surrounding tissue is a concern for a number of anticancer agents. Antineoplastic agents that cause severe tissue damage when they escape from the vasculature are called vesicants. The tissue damage may be severe, with tissue sloughing and loss of mobility, depending on the area of extravasation. Patients need to be educated to alert clinic staff immediately if there is any pain on administration. If extravasation of a vesicant occurs, the injection should be stopped and any fluid aspirated out of the injection site. The prevention, risk factors, signs and symptoms, causative agents, and treatment will be discussed thoroughly in Chapter 99.

Hypersensitivity Reactions

Hypersensitivity reactions to cancer treatments are problematic because of cross-reactivity between agents and the desire to continue active therapies against the cancer.[32] For documented immediate hypersensitivity reactions to a particular agent, further administration of the agent may be achieved through extensive premedication with H_1 and H_2 antihistamines and corticosteroids and through the use of desensitization protocols which include escalating doses of the offending agent given at doses of one-hundredth, one-tenth, and the balance of the dose (so the total dose administered is equivalent to the normally prescribed dose) administered over a much longer period of time. These treatments must be given in an environment where resuscitation is readily available in case of medical emergency.

Secondary Malignancies

Chemotherapy and radiation therapy treatments may cause cancers later in life; these are referred to as secondary malignancies. The most common types of secondary malignancies are MDS and AML. The antineoplastic agents most commonly associated with secondary malignancies are alkylating agents, etoposide, topoisomerase inhibitors, and anthracyclines. Although the risk for secondary cancers is extremely low, it must outweigh the risk of survival produced by treatment of the primary malignancy. Because secondary malignancies may not occur for several years after treatment, patients with relatively short-term survival expectancy related to their current cancer should consider the more immediate benefits of chemotherapy. Radiation therapy may also cause secondary malignancies decades after treatment. The most common example of radiation therapy–induced secondary malignancy is breast cancer, which rarely occurs after mantle field radiation therapy for Hodgkin disease.

CHEMOTHERAPY SAFETY

One of the first Institute of Medicine (IOM) reports, the health arm of the National Academy of Sciences, starts out with a patient who died from an overdose of chemotherapy; the patient did not have an immediately life-threatening cancer, so her death was hastened by a medication error. Chemotherapy agents may cause harm to patients, healthcare professionals, and the environment if not handled correctly.

KEY CONCEPT Because of the risk of severe toxicities associated with many of the chemotherapy agents, safety precautions must be in place to prevent chemotherapy errors or accidental chemotherapy exposures of healthcare professionals or patients. The American Society of Clinical Oncology (ASCO), Hematology/Oncology Pharmacy Association, Oncology Nursing Society, and the American Society of Health-System Pharmacists have information to assist in the safe handling of chemotherapy agents.[19,33,34] National, state, and local regulations regarding the safe disposal of chemotherapy agents and the equipment used to administer them need to be followed to protect the environment.

KEY CONCEPT Each organization should have chemotherapy safety checks built into the prescribing, preparation, and administration of chemotherapy.[19,33] Dosing based on patient-specific information should be included on every order for chemotherapy, whether it is oral or parenteral. Many chemotherapy regimens are referred to by acronyms (eg, AC, which is doxorubicin and cyclophosphamide); these should not be allowed as the only reference to drugs in the prescribing of chemotherapy. Also, abbreviations for the names of chemotherapy agents should be avoided because one abbreviation may stand for two different drug entities. For drugs such as doxorubicin and liposomal doxorubicin, the names should be written out fully, and in this case, the addition of the brand name may help to prevent a mistake.

The measured height and weight, along with the body surface area (BSA), if applicable, should be readily available, along with the dosage in milligrams per meter squared or kilogram, so that the dosage may be checked. If a chemotherapy regimen is a continuous infusion of 800 mg/m^2/day for 4 days, an added safety feature would be to include the total dosage of 3200 mg in order to prevent any ambiguity. In cases where the clinician wants to decrease the dosage based on a laboratory value or side effect, it is recommended that the clinician include that information with the order so the clinical team caring for the patients understands the correct dosage for that patient. Chemotherapy dosages should be checked for route and dose to determine that the dosages prescribed are correct and do not exceed dosing guidelines. Appropriate laboratory values should be checked

Patient Encounter 2

A 68-year-old woman is receiving nivolumab 1 mg/kg and ipilimumab 3 mg/kg as treatment for intermediate-risk metastatic renal cell carcinoma. While receiving treatment, her aspartate aminotransferase (AST) has risen from 16 to 156 IU/L and alanine aminotransferase (ALT) has risen from 42 to 175 IU/L.

What is the likely diagnosis?

What is the most appropriate treatment?

What measures should be taken by patients while receiving checkpoint inhibitors?

prior to administration so the dose can be adjusted for organ dysfunction or toxicity if needed. See examples in Table 88–8. Additionally, drug interactions should be scrutinized closely and whether the patient has the appropriate indication (eg, presence of EGFR mutation for use of erlotinib).[18] Healthcare professionals administering chemotherapy should check the dosage calculation for the patient's weight or BSA along with the five Rs of administering medication (ie, right patient, right medication, right dose, and right route, at the right time). If there is any question about the safe dosage or safe administration of a chemotherapy agent, the chemotherapy should not be administered until the question is resolved.

In addition, a controversy related to chemotherapy dosing is whether actual or ideal body weight should be used for calculating

Table 88–8

Examples of Dose Modifications in Patients With Hepatic and/or Renal Dysfunction

Agent	Organ Dysfunction	Dose Modification
Bleomycin	*Baseline and during therapy*	
	CrCl > 50 mL/min	No dosage adjustment
	CrCl = 40–50 mL/min	70% of normal dose
	CrCl = 30–40 mL/min	60% of normal dose
	CrCl = 20–30 mL/min	55% of normal dose
	CrCl = 10–20 mL/min	45% of normal dose
	CrCl = 5–10 mL/min	40% of normal dose
	Hepatic dysfunction	No dosage adjustments required
Capecitabine	*Baseline*	
	CrCl > 51 mL/min	Initial: no dosage adjustment
	CrCl = 30–50 mL/min	Initial: 75% of normal dose
	CrCl < 30 mL/min	Contraindicated
	Mild-moderate hepatic impairment	No initial dosage adjustment
	Severe hepatic impairment	Not studied
	During therapy	
	SCr > ULN to 1.5 ULN	No dosage adjustment
	SCr > 1.5–3 × baseline to > 1.5–3 × ULN	No dosage adjustment at first instance
	SCr > 3 × baseline to > 3–6 × ULN	75% dosage adjustment at first instance
	SCr > 6 × ULN	Discontinue therapy
	Total bilirubin > 3–10 × ULN if baseline was normal or > 3–10 × baseline if baseline as abnormal	Interrupt therapy until total bilirubin ≤ 3 × ULN; dosage adjustment is based on dosing guidelines for toxicity
Crizotinib	*Baseline and during therapy*	
	CrCl = 30–89 mL/min	No dosage adjustment
	CrCl < 30 mL/min	Decrease dose to 250 mg once daily
	Baseline	No dosage adjustment
	Mild hepatic impairment	
	Moderate hepatic impairment (total bilirubin > 1.5–≤ 3 × ULN and any AST elevation)	Decrease dose to 200 mg twice daily
	Severe hepatic impairment (total bilirubin > 3 × ULN and any AST elevation)	Decrease dose to 250 mg once daily
	During therapy	
	ALT or AST > 5 × ULN with total bilirubin ≤ 1.5 × ULN	Withhold therapy until recovery until baseline or ≤ 3 × ULN, then resume at reduced dose
	ALT or AST > 3 × ULN with total bilirubin ≥ 1.5 × ULN	Discontinue therapy
Idarubicin	*Baseline and during therapy*	
	CrCl > 50 mL/min	No dosage adjustment
	CrCl = 10–50 mL/min	75% of normal dose
	CrCl < 10 mL/min	50% of normal dose
	Bilirubin 2.6–5 mg/dL	50% of normal dose
	Bilirubin > 5 mg/dL	Do not use
Pembrolizumab	*Baseline*	
	Renal dysfunction	No dosage adjustment
	Mild hepatic impairment	No dosage adjustment
	Moderate-severe hepatic impairment	Has not been studied
	During therapy	
	SCr 1.5–2 × above baseline or increase of ≥ 0.3 mg/dL	Consider holding therapy
	SCr 2–3 × above baseline	Withhold therapy and start prednisone 0.5–1 mg/kg/day
	SCr > 3 × above baseline or > 4 mg/dL	Permanently discontinue and start prednisone 1–2 mg/kg/day
	ALT or AST > 3–5 × ULN with total bilirubin ≥ 1.5–3 × ULN[a]	Withhold therapy and start prednisone 0.5–1 mg/kg/day; resume after taper complete and toxicity resolved
	ALT or AST > 5 × ULN with total bilirubin ≥ 3 × ULN[a]	Permanently discontinue and start prednisone 1–2 mg/kg/day

[a] In patients without hepatocellular or renal cell carcinoma; recommendations are different for these cancers.

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CrCl, creatinine clearance; SCr, serum creatinine; ULN, upper limit of normal.

chemotherapy doses for obese individuals. ASCO guidelines currently recommend the use of actual body weight.[35]

ORAL ANTICANCER AGENTS

KEY CONCEPT Over the past decade, self-administration of oral anticancer agents has increased. Although oral anticancer agents have many potential advantages, including convenience and quality of life for patients, oral administration increases the risk of medication errors and the potential for drug and/or food interactions well as accidental exposure to other individuals. Healthcare professionals have an important role in ensuring safe handling of oral anticancer agents, and should be properly trained and perform competently within guidelines for the storage, handling, and disposal of oral agents. The healthcare professionals are also expected to provide proper training and education on safe handling and proper administration (see Table 88–9) to the patient and caregivers.[33,34,36]

Table 88–9

Oral Anticancer Therapy Administration With Respect to Food

	With Food	Empty Stomach	With or Without Food
6-Mercaptopurine			X[a]
Abemaciclib			X
Abiraterone		X	
Acalabrutinib			X
Afatinib		X	
Alectinib	X		
Alpelisib	X		
Anastrozole			X
Apalutamide			X
Avapritinib		X	
Axitinib			X
Azacitidine			X
Bexarotene	X		
Bicalutamide			X
Binimetinib			X
Brigatinib			X
Bosutinib	X		
Busulfan			X
Cabozantinib		X	
Capecitabine	X		
Capmatinib			X
Ceritinib		X	
Chlorambucil			X
Crizotinib			X
Cyclophosphamide			X
Cobimetinib			X
Dabrafenib		X	
Dacomitinib			X
Darolutamide	X		
Dasatinib			X
Decitabine/Cedazuridine		X	
Duvelisib			X
Enasidenib			X
Encorafenib			X
Entrectinib			X
Enzalutamide			X
Erdafitinib			X
Erlotinib		X	
Estramustine		X	
Etoposide		X	
Everolimus			X
Exemestane	X		
Fedratinib			X
Flutamide			X
Gefitinib			X
Glasdegib			X
Gilteritinib			X
Hydroxyurea			X
Ibrutinib			X
Idelalisib			X
Imatinib	X		
Ivosidenib			X (avoid high-fat meal)

(Continued)

Table 88–9

Oral Anticancer Therapy Administration With Respect to Food (*Continued*)

	With Food	Empty Stomach	With or Without Food
Ixazomib		X	
Lapatinib		X	
Larotrectinib			X
Lenalidomide			X
Lenvatinib			X
Letrozole			X
Lomustine		X	
Lorlatinib			X
Melphalan		X	
Methotrexate			X
Midostaurin	X		
Neratinib	X		
Nilotinib		X	
Nilutamide			X
Niraparib			X
Olaparib			X
Osimertinib			X
Palbociclib	X		
Panobinostat			X
Pazopanib		X	
Pemigatinib		X	
Pexidartinib			X
Pomalidomide			X
Ponatinib			X
Pralsetinib		X	
Procarbazine			X (avoid tyramine-containing foods)
Regorafenib	X (low fat meal)		
Ribociclib			X
Ripretinib			X
Rucaparib			X
Ruxolitinib			X
Selinexor			X
Selpercatinib			X
Selumetinib		X	
Sonidegib		X	
Sorafenib		X	
Sunitinib			X
Talazoparib			X
Tamoxifen			X
Tazemetostat			X
Temozolomide			X (must be consistent)
Thalidomide		X	
Thioguanine			X
Toremifene			X
Trametinib		X	
Tretinoin	X		
Trifluridine/Tipiracil	X		
Tucatinib			X
Vandetanib			X
Vemurafenib			X
Venetoclax	X		
Vismodegib			X
Vorinostat	X		
Zanubrutinib			X

[a] Preferably on an empty stomach; but most importantly consistently with or without food.

CANCER SURVIVORSHIP

KEY CONCEPT As early detection of cancers and effective therapies have improved over the last several years, the number of cancer survivors has increased. A cancer survivor by definition, according to the National Coalition for Cancer Survivorship, starts at the point of diagnosis. It is estimated that two out of every three people with cancer live at least 5 years after diagnosis. In 2005, the IOM released a report, "From Cancer Patient to Cancer Survivor: Lost in Transition," which emphasized a lack of definitive guidance and proposed increased efforts were needed to raise awareness regarding the care of cancer survivors.[37] In addition to facing a risk of a cancer recurrence, secondary malignancy, and an increased risk of developing other health conditions, cancer survivors often face physical, emotional, financial,

Patient Care Process

Collect Information:

- Patient characteristics (eg, age, race, sex, patient preferences)
- Patient history (lifestyle factors—alcohol use, tobacco use, diet, physical activity)
- Patient medical and family history (eg, ECOG performance status, concurrent disease states)
- Clinical presentation signs and symptoms (eg, changes in bowel habits, unusual bleeding, weight loss, recurrent fevers)
- Current medications (prescription, over the counter, and complimentary alternative, medical marijuana)
- Objective data
- BP, heart rate, height, weight, and BSA
  - Labs (eg, serum electrolytes, renal function, liver chemistries, complete blood count, coagulation studies, tumor markers)
  - Other diagnostic test (eg, left ventricular ejection fraction)
  - Physical examination data (eg, hepatomegaly, lymphadenopathy)
  - Cancer staging
  - Tumor genomics (eg, *BRAF, HER-2, PIK3CA, RAS*)

Assess the Information:

- Risk factors for treatment-related toxicities (eg, *UGT1A1*28* genotype, poor nutritional intake, uncontrolled BP or hypertension, baseline peripheral neuropathy)
- Type of and response to prior treatments
- Potential for disease responsiveness to specific agents and risk factors for disease recurrence
- Patient characteristics (eg, social history/situation, insurance coverage, pregnancy) and treatment preferences
- Potential problems with medication adherence to oral treatment regimens
- Goals of treatment
- Need for drug dose reductions or supportive care

Develop a Care Plan*:

- Drug therapy regimen including specific anticancer agent(s), dose (calculated correctly for patient characteristics and disease), route, frequency, and duration
- Supportive care plan (eg, antiemetics, prophylactic antidiarrheals, infusion reaction prophylaxis)
- Monitoring parameters including efficacy (eg, cancer imaging studies-chest, abdominal, and/or pelvic CT scans and radiographs, tumor markers if previously elevated, symptoms of recurrence), safety (medication-specific adverse effects, including major dose-limiting toxicities), and timeframe
- Patient education (eg, goals of treatment; expected and potential serious toxicities; drug therapy; monitoring and management plan; safe administration, storage, and disposal)

Implement the Care Plan*:

- Provide patient education regarding all elements of treatment plan
- Survivorship care plan (eg, primary prevention of other diseases, such as infections, and other cancers, support systems for maintaining healthy lifestyle choices and BMI)

Follow-up: Monitor and Evaluate:

- Determine disease response to treatment and occurrence of disease progression or recurrence (cancer imaging studies, tumor markers previously elevated)
- Presence of adverse effects
- Patient adherence to treatment plan using multiple sources of information (eg, patient self-report, medication administration records or refill data)
- Patient's satisfaction with treatment, including understanding of adherence

*Collaborate with patient, caregivers, and other healthcare professionals

and social challenges as a result of the cancer diagnosis and treatment. The American Cancer Society (ACS), Centers for Disease Control, ASCO, and the NCCN all have guidelines that describe strategies to meet the needs of these individuals who experience the long-term effects of cancer and its treatment.[38-40]

OUTCOME EVALUATION

Once a pathologic diagnosis of cancer is made, the patient may be evaluated by a radiation oncologist, a surgical oncologist, and a medical oncologist. Options for treatment are presented that may include surgery, radiation, pharmacologic therapy, or some combination of these modalities. The goals of treatment vary by the cancer and the stage of disease. For example, the patient who has metastatic kidney cancer could be presented with several options. They may have a possible cure with high-dose aldesleukin or receive palliative therapy with pazopanib or sunitinib, or the patient may decline any therapy because of fears of significant toxicity that would decrease quality of life. In this case, if the patient's performance status is poor, such as an ECOG performance status 3, then the patient would not be a candidate for aldesleukin therapy because of significant toxicity or even death from treatment. The patient with the poor performance status will receive palliative therapy to control symptoms of the disease to improve the quality of life at the end of life. For the patient with a poor performance status and extensive metastatic disease, no treatment of the cancer may be appropriate, and the patient may be enrolled in a hospice program or provided comfort care.

Abbreviations Introduced in This Chapter

2-FLAA	2-Fluoro-Ara-AMP
5-FU	5-Fluorouracil
6-MP	6-Mercaptopurine
ACS	American Cancer Society
ADC	Antibody–drug conjugate
ADCC	Antibody-dependent cellular cytotoxicity

AI	Aromatase inhibitor
ALK	Anaplastic lymphoma kinase gene
ALL	Acute lymphocytic leukemia
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
APL	Acute promyelocytic leukemia
AR	Androgen receptor
ASCO	American Society of Clinical Oncology
ATRA	All-*trans*-retinoic acid
AST	Aspartate aminotransferase
AUC	Area under the curve
BSA	Body surface area
Bcl-2	B-cell lymphoma 2
BCNU	Carmustine
BP	Blood pressure
BTK	Bruton's tyrosine kinase
c-MET	Mesenchymal epithelial transition growth factor
CAR	Chimeric antigen receptor
CBC	Complete blood count
CCNU	Lomustine
CD	Cluster of differentiation
CDK	Cyclin-dependent kinase
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CNS	Central nervous system
CrCl	Creatinine clearance
CRS	Cytokine-release syndrome
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocytic-associated antigen 4
CYP	Cytochrome P450
CYP17	17α-hydroxylase/C17,20-lyase
DNA	Deoxyribonucleic acid
DPD	Dihydropyrimidine dehydrogenase
DVT	Deep vein thrombosis
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
FDA	Food and Drug Administration
FdUMP	Fluorodeoxyuridine monophosphate
FGFR	Fibroblast growth factor receptor
G-CSF	Granulocyte–colony stimulating factor
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumor
GnRH	Gonadotropin-releasing hormone
H	Histamine
HDAC	Histone deacetylase
HER-2	Human epidermal receptor-2
HFS	Hand–foot syndrome
HFSR	Hand–foot–skin reaction
HPV	Human papillomavirus
HR	Heart rate
HSCT	Hematopoietic stem cell transplantation
IDH	Isocitrate dehydrogenase
IOM	Institute of Medicine
INR	International normalization ratio
IV	Intravenous
LDH	Lactate dehydrogenase
LHRH	Luteinizing hormone–releasing hormone
MDS	Myelodysplastic syndrome
MEK	Mitogen-activated extracellular kinases
MM	Multiple myeloma
MMAE	Monomethyl auristatin E
MMAF	Monomethyl auristatin phenylalanine
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NSCLC	Non–small cell lung cancer
NTRK	Neurotrophic tyrosine receptor kinase
OTC	Over-the-counter
PARP	Poly ADP ribose polymerase
PCR	Polymerase chain reaction
PD	Programmed cell death
PD-L	Programmed cell death ligand
PET	Positron emission tomography
PI3-K	Phosphoinositide 3-kinase
PSA	Prostate-specific antigen
RAS	Reticular activing system
RECIST	Response evaluation criteria in solid tumors
REMS	Risk Evaluation and Mitigation Strategies
RNA	Ribonucleic acid
SC	Subcutaneous
SERDs	Selective estrogen-receptor downregulators
SERMs	Selective estrogen receptor modulator
SMO	Smoothened
SPF	Sun protection factor
TKI	Tyrosine kinase inhibitor
TNM	Tumor, nodes, metastases
TPMT	Thiopurine *S*-methyltransferase
TS	Thymidylate synthase
UGT1A1*28	Uridine diphosphate–glucuronosyltransferase 1A1 enzyme
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
XOP1	Exportin 1

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89 Breast Cancer

Gerald M. Higa

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Detail epidemiological and clinical disparities of the disease.
2. Analyze risk factors associated with, and strategies that can modify the risk of, developing breast cancer.
3. Summarize the surrogate definitions of the intrinsic breast cancer subtypes.
4. Recognize signs and symptoms related to early and late stages of the disease.
5. Distinguish between good and poor prognostic factors.
6. Determine treatment goals for early-stage, locally advanced, and metastatic breast cancers.
7. State the rationale for inclusion of adjuvant and neoadjuvant therapies.
8. Describe the relevance of hormone, HER2, and PD-1 receptors.
9. Discuss the benefits and risks associated with various therapies.

INTRODUCTION

The growing prevalence of breast cancer in the United States is related to early detection, improved therapies resulting in longer survival and and the relatively high incidence rate. Breast cancer prevalence is increasing in the United States related to early detection, improved therapies resulting in longer survival and the increasing incidence rate. The increased incidence appears to be driven almost exclusively by new breast cancer diagnoses in non-White women.

EPIDEMIOLOGY AND ETIOLOGY

Breast cancer is the most common type of cancer, and second only to lung cancer as a cause of cancer death, in American women. In 2021, female breast cancer will account for 99% of the projected 284,000 new cases, the median age at diagnosis will be 62 years, and and approximately 43,600 deaths will be attributable to the disease.[1] KEY CONCEPT Even though breast cancer occurs more frequently in non-Hispanic White (nHw) women than any other ethnic group, the mortality rate is highest among African Americans.

Tumor size of most breast cancers at diagnosis is usually small (less than 2 cm), and localized disease predominates in all racial and ethnic groups. However, non-Hispanic Black women have the highest rates of triple-negative breast cancers (TNBCs) and proportionally more cases of advanced disease compared with nHw women. Reduced access to proper medical care, including breast cancer screening programs, as well as certain biological factors, may contribute to late diagnoses.

KEY CONCEPT The etiology of breast cancer remains largely unknown though a number of factors have been associated with the risk of developing the disease. Evidence also strongly suggests that breast cancer biology involves complex interactions between sex hormones, genetic factors, environment, and lifestyle. The intrinsic and extrinsic components associated with the disease are discussed further.

Patient Encounter, Part 1

The topic of a recent meeting of the Sierra Club, a women-only group, was breast cancer. A number of women expressed that they knew some people who have or had the disease, many of who were labeled "survivors." Nearly all of the women in the club expressed that being diagnosed with breast cancer was one of their greatest fears.

Discuss relevant breast cancer risk factors.

Intrinsic Components

Aside from gender, the variable most strongly associated with breast cancer risk is age. One of the most frequently quoted breast cancer statistics is the probability that one in eight females will develop the disease sometime in their lifetime. However, a more instructive way of explaining the age-related risk is shown in Table 89–1**.** Although the probability of developing breast cancer increases with age, in more than half, the risk occurs after 60 years of age.

Both personal and family history can influence the risk of developing breast cancer. For example, a woman who has a history of breast cancer has a fivefold increase in the risk of developing contralateral breast cancer. Prior histories of cancers involving the uterus and ovary also appear to be associated with an increased risk of developing breast cancer. Even though family history is often linked to disease risk, the percentage of familial breast cancer is quite low (ie, ~10%). KEY CONCEPT The following key elements describe family history-associated breast cancer risk factors:

- A first-degree relative (ie, mother or sister) with breast cancer is associated with a threefold increase in risk.
- Multiple first-degree relatives with breast cancer have not been consistently shown to be associated with risk greater than one first-degree relative.

Table 89–1

Risk of Developing Breast Cancer: SEER Areas, Women, All Races, 2012–2014

Age Interval (Years)	10-Year Probability
30–40	0.5% or 1 in 220
40–50	1.5% or 1 in 68
50–60	2.3% or 1 in 43
60–70	3.4% or 1 in 29
70–80	3.9% or 1 in 25
From birth to death	12.4% or 1 in 8

SEER, Surveillance, Epidemiology and End Results.

Probability derived by Devcan 6.7.0, June 2017 (http://surveillance.cancer.gov/devcan).

- A second-degree relative with breast cancer is associated with a 1.5-fold increase in risk.
- Family members on the paternal side contribute to risk similar to the maternal side.

KEY CONCEPT The endocrine factor most closely linked to breast cancer is estrogen. The risk is partially related to the duration of exposure to the hormone. Hence, early menarche and late menopause, nulliparity, and certain hormone replacement therapy (HRT) appear to contribute to breast cancer risk. Use of HRT in postmenopausal women is infrequent and generally contraindicated for women with a history of breast cancer based on the Women's Health Initiative (WHI) hormone therapy trial, which demonstrated an increased risk of breast cancer in those receiving HRT.[2]

KEY CONCEPT In the early 1990s, the *BRCA1* gene was found to be mutated in a large percentage of hereditary breast and ovarian cancer patients. A second breast cancer gene, called *BRCA2*, has also been identified. Functional aberrations of *BRCA1* and *BRCA2* result in the loss of key inhibitory activities of both proteins. Compelling evidence of their critical importance is the observation that women who carry germline mutations of *BRCA1* or *BRCA2* have a lifetime risk of breast cancer between 65% and 90%; the 10-year risk of contralateral breast cancer is approximately 25% to 30%. Women with strong family histories of breast cancer are candidates for *BRCA1* and *BRCA2* mutation analysis.

Extrinsic Components

Experimental and epidemiologic evidence suggest a link between breast cancer and being overweight after menopause, especially with body fat distributed around the abdominal region. This risk factor may be related, in part, to peripheral conversion of androgens to estrogens in adipose tissue. In addition, obesity is associated with reduced overall survival in women with hormone receptor–positive breast cancer.[3] Data also indicate a modest relationship between alcohol consumption and breast cancer. And although epidemiological data have been inconsistent, biological evidence suggests smoking is associated with a small, though significant, increase in the risk of developing breast cancer, especially with early initiation (ie, less than 17 years of age) of tobacco use.

Radiation is also associated with an increased risk of breast cancer. Although the risk appears to be dosage-related, the minimal level of exposure is not well defined. Even therapeutic doses of radiation administered in the management of patients with postpartum mastitis, tuberculosis, and certain hematologic malignancies appear to increase breast cancer risk. Notably, this risk appears to be confined to exposure before 40 years of age, which suggests that a "window of initiation" for breast cancer occurs relatively early. On the other hand, it is currently accepted that exposure to radiation doses utilized in diagnostic X-rays, including screening mammography, are not of clinical concern.

KEY CONCEPT The majority of women diagnosed with breast cancer do not have any of the identified risk factors (other than age). Risk of breast cancer can be assessed using the National Cancer Institute online version of the Breast Cancer Risk Assessment Tool that is considered to be the most authoritative and accurate (www.cancer.gov/bcrisk-tool). This tool was designed for health professionals to project individualized 5-year and lifetime risks for invasive breast cancer.

Prevention of Breast Cancer

Even though breast cancer is not the most lethal malignancy, disease-related morbidity and mortality is still a major concern. Current efforts at breast cancer prevention are directed toward the identification and removal of risk factors. Unfortunately, a number of risk factors such as age and family or personal history of the disease or other gynecologic malignancies cannot be modified.

The idea that prevention can be achieved pharmacologically was based on clinical trials of tamoxifen, a selective estrogen receptor modulator (SERM), as adjuvant therapy for women with early, hormone receptor–positive breast cancer. These trials demonstrated a reduction of contralateral breast cancer events as well as a survival advantage of patients who received the drug for 2 to 5 years following mastectomy. Several clinical trials conducted with SERMs provided proof of principle that breast cancer risk reduction in premenopausal and postmenopausal women could be achieved through chemoprevention.[4,5]

In addition, a class of drugs known as the aromatase inhibitors (AIs) has been shown to be more effective than tamoxifen as adjuvant breast cancer therapy in postmenopausal women. This finding suggested that the AIs could also reduce the risk of developing breast cancer in postmenopausal women at high risk for the disease. Results of the International Breast Cancer Intervention Study (IBIS)-II demonstrated a 53% reduction in new breast cancer diagnoses with anastrozole compared to placebo.[6] Similar findings have been reported with the steroidal AI, exemestane, in high-risk postmenopausal women.

These positive findings are accompanied by a number of caveats. First, chemoprevention effectively reduces the incidence without a significant benefit in OS. Second, risk reduction appears to apply to hormone-dependent breast cancer only. Third, results of these trials confirmed the increased incidence of thromboembolic and gynecological adverse events associated with tamoxifen but not raloxifene. Fourth, AIs are not currently approved for preventing breast cancer, but if used off-label, they are only effective for postmenopausal women. Interestingly, adverse effects on the musculoskeletal system were not (or infrequently) observed in the prevention trials compared to the adjuvant trials of these agents. Fifth, the role of tamoxifen in *BRCA* mutation carriers is still not clear. In women with familial breast cancer, bilateral mastectomy remains the best, though not absolute, risk-reducing option. Sixth, in contrast to estrogen alone, the WHI study mentioned previously indicated that HRT with estrogen and progestin increased breast cancer risk and mortality.

It should be noted that even though the side-effect profiles of the SERMS and AIs negatively impact patient acceptance, pharmacological prevention could spare some patients from surgery, radiation, and even chemotherapy-related morbidity.

Table 89–2

Intrinsic Subtypes of Breast Cancer

Subtype	Tumor Features	Treatment Approach	Added Comment
Luminal A	All of the following: ER and PR positive, HER2 negative, and low Ki67 (proliferation marker)	Endocrine only (usually)	May add chemotherapy if four or more positive nodes, grade 3 disease, Oncotype Dx recurrence score > 25, or age < 35 years
Luminal B (HER2 negative)	ER positive, HER2 negative, and either high Ki67 or PR negative	Endocrine and chemotherapy (for most cases)	Add chemotherapy for most patients
Luminal B (HER2 positive)	ER positive, HER2 positive	Endocrine, HER2-targeted therapy and chemotherapy	
HER2 amplified or overexpressed (nonluminal)	HER2 positive	HER2-targeted therapy and chemotherapy	Opinion differs regarding use of anti-HER2 therapy in tumors < 5 mm
Basal (triple negative)	ER, PR, and HER2 negative	Chemotheraphy. First-line atezolizumab plus nab-paclitaxel approved for women with locally advanced surgically-unresectable or metastatic disease if tumors express PD-L1.	

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PATHOPHYSIOLOGY

Histologic evaluation of breast lesions serves to establish a pathologic diagnosis and confirm the presence of other factors believed to influence prognosis.

Invasive Breast Cancer

Breast cancers typically arise in the ducts or lobules of the mammary gland. When tumor cells infiltrate surrounding breast tissue, a diagnosis of invasive breast cancer is made. Even though the vast majority of tumors are adenocarcinomas, this does not imply that breast cancer is one disease. Furthermore, breast cancers can be grouped in one of four intrinsic subtypes with luminal B having two distinct surrogate features. When defined by clinical and pathological features, this classification system can be used for prognostication as well as a guide to treatment (Table 89–2*)*.

Noninvasive Carcinoma

Notably, the annual breast cancer incidence does not include thousands of cases of carcinomas *in situ* (ie, noninfiltrating tumors confined to the ducts and lobules). Ductal carcinoma *in situ* (DCIS) accounts for approximately 85% of all *in situ* breast cancers; while lobular neoplasia may not be a true cancer, rather a high-risk premalignant lesion that does not always require active treatment. The overwhelming majority of cases can be cured by surgery followed by whole breast radiation therapy after breast-conserving surgery (BCS). Although there is no proven role for the application of cytotoxic chemotherapy, patients with hormone receptor–positive tumors may benefit from the addition of tamoxifen.

Patient Encounter, Part 2

Discussion among the women progresses to early detection. Except for age within this group of mostly elderly women, most indicate they do not appear to have additional risk factors. The most commonly used screening tool is mammography. Even though performed, the role and utility of clinical breast examination have been questioned. Nonetheless, the ultimate goal of screening is to reduce breast cancer morbidity and mortality.

Discuss screening of "average-risk" women focusing on when to initiate discussion, when to start screening, mammographic interval, relative benefits of screening (in terms of decreased mortality) based on age, and potential harms associated with mammography.

CLINICAL PRESENTATION AND DIAGNOSIS

Early Detection

The rationale for early detection of breast cancer is based on the clear relationship between early-stage disease at diagnosis and greater probability of long-term survival. Screening guidelines for early detection of breast cancer have been published by the American Cancer Society (ACS), the United States Preventive Services Task Force (USPSTF), and the National Comprehensive Cancer Network (NCCN) (Table 89–3). All include recommendations that women aged 50 to 74 of average risk have annual or biennial screening. Controversy regarding the use of screening mammography is largely confined to women younger than 50 years. After many years of debate, NCCN and ACS recommend initiation of screening at age 40, while USPSTF recommends that in this age group, the decision should be an individual one.[7]

Diagnosis

Unless following up on abnormalities found during screening, the initial workup for women presenting with signs or symptoms (see the "Clinical Presentation and Diagnosis" section) suggestive of breast cancer should include a careful history, physical examination of the breast, three-dimensional mammography, and possibly other imaging techniques such as magnetic resonance imaging. Most (80%–85%) breast cancers are visualized on a mammogram as a mass, a cluster of calcifications, or a combination of both. A breast biopsy is indicated for a mammographic abnormality that suggests malignancy or a palpable mass on physical examination.

Table 89–3

Guidelines for Early Detection of Breast Cancer in Average-Risk Individuals

	American Cancer Society	US Preventive Services Task Force	National Comprehensive Cancer Network
BSE	NR (no clear benefit)	NR	25–39 years, breast awareness
CBE	NR (no clear benefit)	Not specifically addressed	25–39 years, every 1–3 years then annually > 39 years
Mammography	40–44 years, option to start 45–54 years, annual > 54 years, annual or biennial	Age 50–74 years: Every 2 years (with or without CBE)	Age 40, begin annual scans

BSE, breast self-examination; CBE, clinical breast examination; NR, not recommended.

Clinical Staging

The preferred method of staging includes the combination of anatomic (ie, tumor size [T], lymph node status [N], and metastasis [M]) and prognostic variables (ie, tumor grade and biomarkers such as human epidermal–related growth factor receptor [HER] 2 and estrogen and progesterone receptors [ER and PR]). In general, TNM (Tumor, node, metastasis [staging system]) stage (0–4) is defined as follows: carcinoma in situ (0), tumors less than 2 cm in diameter (1 or 2), 5 cm or greater (3), and metastatic (4). **KEY CONCEPT** Though dependent on multiple tumor and clinical characteristics, survival has improved across all stages of the disease. The overall 5-year survival rate is approximately 90%; nearly all of those with localized disease are alive at 5 years.

Clinical Presentation and Diagnosis of Breast Cancer

Common early signs and symptoms include the following:

Painless lump (90% of cases) that is:

- Solitary
- Unilateral
- Solid
- Irregular
- Nontender

Stabbing or aching pain (10% of cases) as the first symptom

Uncommon early signs and symptoms include the following:

Nipple discharge (3% of women and 20% of men), retraction, or dimpling

- Eczema appearance of the nipple (Paget carcinoma)
- Prominent skin edema, redness, warmth, and induration of the underlying tissue (inflammatory carcinoma)

Sites of metastases frequently include bone, liver, lung and brain. The following signs and symptoms of metastases are present in about 10% of patients when they first seek treatment:

- Bone pain
- Pathologic fracture
- Difficulty breathing
- Jaundice
- Abdominal pain
- Headache
- Mental status changes

Prognostic Factors

Good prognostic factors include the following:

- Luminal A subtype (ER and PR highly positive, Ki67 low)
- Absence of tumor cells in regional nodes (node-negative)
- Tumors smaller than 2 cm
- Early stage (1 or 2)
- Well-differentiated tumor
- Normal tumor grade

Poor prognostic factors include the following:

- Age younger than 35 years
- High nuclear grade (correlates with tumor growth)
- Triple-negative disease (ie, the absence of ER, PR, and HER2)
- Overexpression of HER2 alone

Patient Encounter, Part 3

After the above meeting, one of the younger women (age 50 and still having menstrual periods) makes an appointment with her family physician because of some unexplained pain in her right breast. Even though her doctor is unable to palpate a tumor or axillary node, a mammogram is ordered. Other than gender, the patient is not aware of any additional risk factors. Results of the mammogram showed a suspicious calcified lesion, approximately 1.6 cm in diameter, in the right upper outer quadrant. The radiologist recommended obtaining a core biopsy of the lesion. Pathologic review showed marked atypia with a focal nest of neoplastic cells. Tumor staining was notable for the absence of hormone receptors but overexpression of HER2. Additional tests indicated a poorly differentiated, high-grade tumor and high Ki67 proliferation index.

List important facets regarding screening in general. Discuss whether the woman had a screening mammogram. In addition, characterize the intrinsic subtype as well as predictive and prognostic features.

EARLY BREAST CANCER TREATMENT

Desired Outcome

KEY CONCEPT Most patients presenting with invasive breast cancer have small tumors with negative lymph nodes (stage 1 or 2). The goal of therapy for early breast cancer is cure. While surgery alone may be able to cure approximately one-third to one-half of all patients with early-stage breast cancer, certain tumor features warrant addition of systemic therapy.

Surgical procedures have changed significantly over the last 50 years. **KEY CONCEPT** Less aggressive surgical options for invasive early breast cancer include total mastectomy or BCS such as lumpectomy. The reason for favoring the latter is based on findings that BCS achieves similar survival outcomes as more extensive surgical procedures and is cosmetically superior. Additionally, breast conservation aids in preserving the emotional and psychological well-being of the patient.[8] Only two contraindications to BSC are considered absolute (or nearly absolute), including persistence of tumor on surgical margins and inability to perform postsurgery radiation, if indicated.

KEY CONCEPT Equally important is the issue related to axillary lymph node dissection (ALND). Because of the morbidity associated with the procedure, a clinical trial was conducted to determine the impact of sentinel lymph node (SLN) biopsy on disease outcomes. Results of this study indicated that ALND can be omitted with less than three positive sentinel nodes when postmastectomy radiation is planned.[9]

Except for the elderly and patients with substantial comorbid medical conditions, radiation therapy should be considered an integral adjunct to BCS especially in those with more than three positive nodes or those with positive sentinel nodes without ALND. However, a recent meta-analysis of trials indicated similar survival outcomes among subjects with stage 1, low-risk breast cancer regardless if they received radiation or not the following lumpectomy. What used to entail 4 to 6 weeks of external-beam radiation, newer clinical evidence supports the efficacy of a 3-week course of whole breast irradiation.[10] Complications associated with radiation therapy are usually minor and include erythema of the breast tissue and shrinkage of total breast mass beyond that predicted on the basis of surgical resection alone.

Systemic Adjuvant Therapy

Breast cancer cells can spread by contiguity, lymphatic channels, and blood to distant sites. Tumor cells often metastasize early in cancer growth. Because these deposits cannot always be detected with current diagnostic techniques, they are referred to as occult metastases. Hence, administration of adjuvant therapy (at a time when the tumor burden is low) should theoretically increase the likelihood of cure and minimize the emergence of drug-resistant tumor cell clones. **KEY CONCEPT** Most published results confirm that chemotherapy (in selected patients), hormonal therapy (in patients with hormone receptor–positive disease), anti-HER2 therapy (in tumors with amplification or overexpression of HER2), or appropriate combinations of these therapies improved disease-free survival (DFS) and/or OS in patients with early-stage breast cancer (see Table 89–2).

Among the most influential groups that provide treatment recommendations is the St. Gallen International Expert Consensus panel.[11]

▶ *Adjuvant Chemotherapy*

Cytotoxic drugs that are used most frequently as adjuvant therapy of breast cancer include the taxanes, anthracyclines, and cyclophosphamide. The most common chemotherapy regimens used in the adjuvant setting are listed in Table 89–4. Dose-limiting and other significant toxicities have been previously described in Chapter 88 and are discussed succinctly in Table 89–5.

Chemotherapy is usually initiated within 2 to 6 weeks from the surgical procedure; the efficacy of systemic therapy decreases if

Table 89–4

Common Chemotherapy Regimens for Breast Cancer

Adjuvant Chemotherapy Regimens

AC
Doxorubicin 60 mg/m^2 IV, day 1
Cyclophosphamide 600 mg/m^2 IV, day 1
Repeat cycles every 21 days for four cycles[a]

AC → Paclitaxel (CALGB 9344)
Doxorubicin 60 mg/m^2 IV, day 1
Cyclophosphamide 600 mg/m^2 IV, day 1
Repeat cycles every 21 days for four cycles
Paclitaxel 175 mg/m^2 on day 1

CMF
Cyclophosphamide 100 mg/m^2/day orally, days 1–14
Methotrexate 40 mg/m^2 IV, days 1 and 8
Fluorouracil 600 mg/m^2 IV, days 1 and 8
Repeat cycles every 28 days for six cycles[b,c]
or
Cyclophosphamide 600 mg/m^2 IV, day 1
Methotrexate 40 mg/m^2 IV, day 1
Fluorouracil 600 mg/m^2 IV, days 1 and 8
Repeat cycles every 28 days for six cycles[d]

Dose-Dense AC → Paclitaxel
Doxorubicin 60 mg/m^2 IV bolus, day 1
Cyclophosphamide 600 mg/m^2 IV, day 1
Repeat cycles every 14 days for four cycles (must be given with growth factor support)
Followed by:
Paclitaxel 175 mg/m^2 IV over 3 hours
Repeat cycles every 14 days for four cycles (must be given with growth factor support)[e]
Followed by:
Paclitaxel 175 mg/m^2 IV over 3 hours
Repeat cycles every 21 days for four cycles[f]

TC
Docetaxel 75 mg/m^2 IV over 60 minutes, day 1
Cyclophosphamide 600 mg/m^2 over 30–60 minutes, day 1
Repeat cycles every 21 days for four cycles

(Continued)

Table 89–4

Common Chemotherapy Regimens for Breast Cancer (*Continued*)

Metastatic Single-Agent Chemotherapy

Paclitaxel
Paclitaxel 175 mg/m^2 IV over 3 hours
Repeat cycles every 21 days
or
Paclitaxel 80 mg/m^2/week IV over 1 hour
Repeat dose every 7 days[g]

Docetaxel
Docetaxel 60–100 mg/m^2 IV over 1 hour
Repeat cycles every 21 days[i]
or
Docetaxel 30–35 mg/m^2/week IV over 30 minutes
Repeat dose every 7 days[j]

Capecitabine
Capecitabine 2000–2500 mg/m^2/day orally, divided twice daily for 14 days
Repeat cycles every 21 days[k,l]

Vinorelbine
Vinorelbine 30 mg/m^2 IV, days 1 and 8
Repeat cycles every 21 days
or
Vinorelbine 25–30 mg/m^2/week IV
Repeat cycles every 7 days (adjust dose based on absolute neutrophil count; see product information)[h]

Gemcitabine
Gemcitabine 600–1000 mg/m^2/week IV, days 1, 8, and 15
Repeat cycles every 28 days (may need to hold day 15 dose based on blood counts)[k]

Liposomal Doxorubicin
Liposomal doxorubicin 30–50 mg/m^2 IV over 90 minutes
Repeat cycles every 21–28 days[m]

[a] From Fisher B, et al. J Clin Oncol 1990;8:1483.
[b] From Bonadonna G, et al. N Engl J Med. 1976;294:405.
[c] From Levine MN, et al. J Clin Oncol. 1998;16:2651.
[d] From Fisher B, et al. N Engl J Med. 1989;32:473.
[e] From Citron, et al. J Clin Oncol. 2003;21;1431.
[f] From Henderson CI, et al. J Clin Oncol. 2003;21:976.
[g] From Perez EA, et al. Clin Oncol. 2001;19:4216.
[h] From Zelek L. Cancer. 2001;92:2267.
[i] From Taxotere (docetaxel) product information. Aventis Pharmaceuticals Inc., April 2003.
[j] From Hainsworth JD, et al. J Clin Oncol. 1998;16:2164.
[k] From Carmichael J, et al. J Clin Oncol. 1995;13:2731.
[l] From Michaud, et al. Proc Am Soc Clin Oncol. 2000; A402, and Xeloda product information.
[m] From Ranson MR, et al. J Clin Oncol. 1997;15:3185.
IV, intravenous.

Table 89–5

Toxicities of Common Chemotherapies Used for Breast Cancer

Class	Drug	Dose-Limiting Toxicities	Other Toxicities
Anthracyclines	Doxorubicin, epirubicin	Myelosuppression, cardiomyopathy	Alopecia, nausea, vomiting, stomatitis, ulceration, and necrosis with extravasation, red-colored urine, radiation recall effect
	Liposomal doxorubicin	Myelosuppression, palmar-plantar erythrodysesthesia (hand–foot syndrome)	Alopecia, infusion reactions, stomatitis, fatigue, nausea, vomiting
Taxanes	Paclitaxel	Neutropenia, peripheral neuropathy, hypersensitivity reactions	Alopecia, fluid retention, myalgia, skin reactions, ulceration, and necrosis with extravasation, bradycardia, stomatitis
	Docetaxel	Myelosuppression, severe fluid retention	Alopecia, fatigue, stomatitis, nausea, vomiting, diarrhea, peripheral neuropathy, nail disorder, skin reactions, hypersensitivity reactions
Antimetabolites	Capecitabine	Diarrhea, palmar-plantar erythrodysesthesia (hand–foot syndrome)	Myelosuppression, stomatitis, nausea, vomiting
	Gemcitabine	Myelosuppression (especially thrombocytopenia)	Flu-like syndrome (fever, chills, myalgias, and arthralgias), nausea
	Fluorouracil	Myelosuppression	Stomatitis, diarrhea, alopecia
	Methotrexate	Myelosuppression, stomatitis	Diarrhea, nausea, vomiting, renal toxicity
Vinca alkaloids	Vinorelbine	Neutropenia	Fatigue, nausea, vomiting, ulceration, and necrosis with extravasation
Alkylating agents	Cyclophosphamide	Myelosuppression, hemorrhagic cystitis	Alopecia, stomatitis, amenorrhea, aspermia

delayed more than 12 weeks following surgery. Currently, four to eight cycles of chemotherapy are administered for 12 to 24 weeks. Dose reduction for standard chemotherapy regimens should be avoided in the absence of severe acute toxicity because of the negative impact on DFS and OS. Even though most patients are able to maintain a reasonable level of functional, emotional, and social well-being during treatment, there are some compelling data indicating that some toxicities can have chronic debilitating effects on the quality of life.[12] Various forms of supportive therapy, including antiemetics and hematopoietic growth factors for patients receiving systemic adjuvant chemotherapy, are discussed in Chapter 99.

As mentioned previously, the usefulness of the intrinsic subtype classification also extends to treatment strategies. Since the magnitude of the 10-year survival benefit with cytotoxic agents appears to be only 5% and 10% for patients with negative and positive nodes, respectively, there has been intensive research to identify patients with low-risk disease that could avoid treatment with chemotherapy. One validated multigene assay known as Oncotype DX is used in patients with luminal A disease and limited nodal involvement, to determine who can be treated with endocrine therapy alone.[13]

KEY CONCEPT It is generally agreed that patients with high-risk luminal B, HER2 overexpression, and basal-like subtypes should receive chemotherapy (both anthracycline and taxane) with hormonal and/or HER2-targeted therapy if indicated.[14]

▶ *Adjuvant Anti-HER2 Therapy*

HER2 amplification or overexpression is found in approximately 15% to 20% of all breast cancers. Because of its aggressive features, treatment targeting the receptor (plus chemotherapy) is indicated in this subset of patients, especially for tumors greater than or equal to 0.5 cm in size. Most experts agree that HER2-positive tumors appear to derive greater benefit from anthracycline or taxane-based chemotherapy regimens. When used with these two classes of cytotoxic agents, trastuzumab is given either following completion of the anthracycline or concurrently with the taxane. However, the combination of trastuzumab and pertuzumab should be considered in patients with positive nodes or stage 2 or 3 tumors. One additional issue of relevance relates to the risk of trastuzumab-associated cardiac toxicity. Noninferiority of 6 months compared to standard 12 months trastuzumab has been demonstrated prospectively in one study; however, the shorter course is not standard of care.[15]

▶ *Adjuvant Endocrine Therapy*

Hormone receptors are used clinically to gauge prognosis, predict response to endocrine therapy, and discriminate luminal breast cancer subtypes. Approximately 50% to 70% of patients with breast cancer have hormone receptor–positive tumors. However, receptor positivity refers to tumors expressing both ER and PR, as well as either ER or PR alone. Furthermore, "ER-positive" tumors traditionally refer to ERα only. Although it is beyond the scope of this discussion, it is noteworthy to mention the existence, and accumulating data regarding the roles of ERβ and the ERα/ERβ heterodimer in breast cancer.[16,17] Tumors with high expression of both ER and PR (ie, luminal A subtype) are associated with favorable prognoses, superior responses to endocrine therapy, and longer disease-free intervals following initial treatment. Hormone receptor–positive tumors are more common in postmenopausal patients.

KEY CONCEPT Hormonal therapies that have been studied in the treatment of early breast cancer include tamoxifen, ovarian suppression (surgical and pharmacologic), and the AIs.

Duration of adjuvant endocrine therapy has historically been for 5 years. However, ER-positive tumors retain a substantial risk of recurrence beyond the initial 5-year period. Studies demonstrate a longer duration of endocrine therapy can reduce recurrence.[18,19] However, the greatest benefit appeared among women who initially received tamoxifen then switched to an AI. The strategies of extended monotherapy tamoxifen or AI were found to be proportionately less beneficial. Extended therapy can be considered after careful assessment of potential clinical benefits and risks related to tumor features and patient characteristics, including comorbidities, bone mineral density, and prior tolerance with AI therapy.

Another issue that may be related to overall prognosis is the observation that premenopausal breast cancer is biologically more aggressive than breast cancers diagnosed after menopause. Reduction in recurrence and an emerging survival benefit are being seen with long-term follow-up of a clinical trial of ovarian function suppression in combination with either tamoxifen or an AI in younger women with ER-positive breast cancer, particularly women with higher grades or higher stage cancers.[20]

Endocrine therapy is initiated shortly after surgery or as soon as pathology results are known. However, when chemotherapy is also indicated, endocrine therapy is given after all cytotoxic agents have been completed. This approach has been adopted based on possible harm and lack of convincing evidence of apparent benefit when given concurrently. In addition to tamoxifen, three AIs, anastrozole, letrozole, and exemestane are available (Table 89–6).

LOCALLY ADVANCED BREAST CANCER TREATMENT

Desired Outcome

Locally advanced breast cancer (LABC) is defined by size, 2 cm or greater, and nodal involvement, high likelihood, in the absence of measurable metastasis. Clinically, LABC includes stage 2 or 3, HER2-positive, triple-negative, and inflammatory breast cancers. The latter is a unique clinical entity that has, at times, been misdiagnosed as cellulitis. Notably, patients with stage 2B, 3A, and 3B tumors have much poorer prognosis with 5-year rates of 70%, 52%, and 48%, respectively.

Initial management for LABC is the use of cytotoxic or endocrine therapy as well as HER2-directed therapies (if indicated) prior to surgery. This approach, referred to as systemic neoadjuvant therapy (SNT), can render initially inoperable tumors resectable, even with the possibility of BCS. In addition, the application of SNT enables some patients to avoid some of the morbidities associated with axillary dissection. Furthermore, tailoring the initial approach to triple-negative and HER2-positive breast cancers can improve disease outcomes.

Pharmacologic Therapy

One of the treatment objectives for patients with high-risk LABC is to obtain tumor resectability. The guidelines for selection and duration of SNT are similar to the adjuvant setting. Available data support the use of anthracycline- and/or taxane-containing regimens as well as any approach to improve dose density or dose intensity. In patients with HER2-overexpressing tumors, the combination of a taxane, carboplatin, and trastuzumab with or

Table 89–6

Endocrine Therapies for Breast Cancer

Class	Drug	Dose	Side Effects
Aromatase inhibitors			
Nonsteroidal	Anastrozole	1 mg/day PO	Hot flashes, arthralgias, myalgias, headaches, diarrhea, mild nausea
	Letrozole	2.5 mg/day PO	
Steroidal	Exemestane	25 mg/day PO	
Antiestrogens			
SERMs	Tamoxifen	20 mg/day PO	Hot flashes, vaginal discharge, mild nausea, thromboembolism, endometrial cancer
	Toremifene	60 mg/day PO	
SERDs	Fulvestrant	250 mg IM every 28 days	Hot flashes, injection-site reactions, possibly thromboembolism
LHRH analogues	Goserelin	3.6 mg SC every 28 days	Hot flashes, amenorrhea, menopausal symptoms, injection-site reactions
Progestins	Megestrol acetate	40 mg PO 4 for a day	Weight gain, hot flashes, vaginal bleeding, edema, thromboembolism
	Medroxyprogesterone	400–1000 mg IM every week	

IM, intramuscular; LHRH, luteinizing hormone–releasing hormone; PO, oral; SC, subcutaneous; SERD, selective estrogen receptor downregulator; SERM, selective estrogen receptor modulator.

without pertuzumab avoids some of the risks and toxicities associated with anthracyclines. Furthermore, anti-HER2 therapy can be given concurrently with this regimen.

Neoadjuvant endocrine therapy may be an option for patients who have unresectable, strongly hormone receptor–positive tumors, low-risk factors, or are unable to receive chemotherapy because of comorbid medical conditions. Endocrine therapy is usually given for 4 to 8 months or until maximal response. Regardless of therapeutic approach, about two-thirds of the tumors can be downstaged; the pathological complete response rate is approximately 50%.

The extent of surgery will be determined by tumor response to neoadjuvant therapy, patient wishes, and cosmetic results likely to be achieved. Adjuvant anti-HER2 therapy improves the overall survival in patients with residual disease and should be administered.[21] Patients with HER2-negative breast cancer who do not achieve pathological complete responses (pCRs) following neoadjuvant chemotherapy have a high risk of relapse, especially those with TNBC. In the absence of any established adjuvant chemotherapy, a recent study demonstrated that 6 months of adjuvant capecitabine improved both the DFS and OS (though this is still not considered the standard of care).[22]

Patient Encounter, Part 4

Despite what appeared to be a small tumor on imaging, the multidisciplinary breast cancer team, in discussion with the patient, decided the best treatment strategy was systemic neoadjuvant therapy (SNT) followed by surgery and adjuvant therapy.

Discuss important aspects related to each component of the treatment plan including:

- *Selection of systemic agents and their toxicity profiles*
- *Extent of surgery*
- *Adjuvant therapy considerations*

METASTATIC BREAST CANCER (STAGE IV) TREATMENT

Desired Outcome

The goals of therapy for patients with metastatic breast cancer (MBC) are maintaining or improving quality of life and prolonging survival. In order to achieve these goals, an important consideration is selecting therapy with good activity and tolerability.

General Approach to Treatment

The choice of therapy for MBC disease is based on receptor expression status (ie, hormone and HER2) and distant disease sites. In many instances, age and comorbid medical problems will also be considered. While the choice between endocrine and cytotoxic chemotherapy is usually the hormone receptor status of the tumor, sites of metastatic disease may also influence treatment decisions. For example, in patients with ER-positive breast cancer with soft tissue or bone-only metastasis (without impending fracture), endocrine therapy alone is usually warranted. Hormonal therapy can even be considered in patients with asymptomatic visceral involvement. In contrast, chemotherapy is usually the initial treatment option for hormone-dependent breast cancer in patients who present with significant life-threatening metastasis to liver and/or lung. When used, chemotherapy is continued to maximal response. Patients with tumors responding initially to endocrine therapies are often treated with chemotherapy when endocrine options are exhausted or symptomatic visceral metastasis develops. Approximately 75% to 80% of tumors positive for both ER and PR respond to initial hormonal therapy; responses decrease to 50% to 60% for ER-positive/PR-negative tumors. The best predictor of response to second- and, possibly, third-line endocrine therapies is extent and duration of the initial response. Nevertheless, tumor responses are frequently lower and durations shorter with subsequent hormonal therapies.

KEY CONCEPT Endocrine therapy is not indicated for tumors that do not express at least one of the hormone receptors. Depending on functional status, patients with receptor-negative tumors should be treated with cytotoxic chemotherapy. Objective responses are achieved in 50% to 60% of patients who have not received prior chemotherapy though less than 20% of the responses are complete.

The duration of response to first-line therapy is usually less than 12 months. Although uncommon, responses to initial treatment can be extremely durable with patients living years without evidence of disease. The response rate to second- and third-line chemotherapy varies from 20% to 40%. Combinations of chemotherapy plus endocrine therapy are not used in the metastatic disease setting because of increased toxicity without added benefit.

Even though incurable, it has been recently reported that the 5-year relative survival rate has increased twofold from 18% to 36%. Notably, the improvement was observed primarily in women less than 50 years of age.

Pharmacologic Systemic Therapy

▶ *Endocrine Therapy*

The operative mode of all endocrine therapies is estrogen deprivation. The pharmacologic goal is to decrease the levels of circulating estrogen and/or prevent estrogen effect on tumor tissue through receptor blockade or downregulation. A number of new and effective agents are available. For postmenopausal women with hormone receptor–positive, HER2-negative MBC, an AI is recommended either alone or in combination with a cyclin-dependent kinase (CDK) 4/6 inhibitor as frontline therapy. Of note, the addition of palbociclib, ribociclib, or abemaciclib has demonstrated improvement in **progression-free survival (PFS)** and possibly, OS. One other biological target involves the PI3K pathway that is relevant because the development of acquired resistance remains a significant challenge. Activated in approximately 70% of all breast cancers, a recent study showed that an α-specific, PI3K inhibitor in combination with fulvestrant improved PFS in subjects with disease progressing on endocrine-based therapy.[23]

Until the turn of the century, evidence did not support the superiority of one type of endocrine therapy with regard to response or survival. Because of the similarity in efficacy, selection of endocrine therapy was based primarily on their toxicity profile (see Table 89–6), which favored tamoxifen. The only exception to this choice of therapy occurred in patients who received adjuvant tamoxifen and subsequently developed metastatic disease within 1 year of drug cessation.

Over the last 15 years, accumulating evidence related to the AIs has changed the way postmenopausal women with hormone-dependent MBC are treated. After menopause, estrogens continue to be produced by extragonadal conversion of androstenedione and testosterone to estrone and estradiol. This biosynthetic process, which is dependent on aromatase, occurs in peripheral tissue, including muscle, adipose, and even the breast itself. Therefore, AIs effectively reduce the level of circulating estrogens, as well as estrogens in the target gland. Their toxicity profile has been described in Chapter 88 and Table 89–6.

In general, the AIs are preferred as first-line therapy for ER-positive advanced breast cancer in postmenopausal women. Results of large clinical trials comparing these agents against tamoxifen demonstrated improved PFS among patients receiving AI therapy. A consistent observation in these trials was a lower incidence of thromboembolic events, endometrial cancer, and vaginal bleeding in patients treated with an AI. Of note also, several small studies indicated that regardless of which subclass of AI used initially, approximately 50% of the patients will have further antitumor benefit after switching to the other subclass suggesting that cross-resistance is incomplete. Therefore, postmenopausal patients may receive two AIs as first- and second-line therapies.

While the therapeutic benefit of the AIs is well accepted, targeted interruption of the cell cycle has been investigated to further enhance the treatment of patients with hormone-dependent MBC. The biological rationale is based on the critical role CDKs have in regulating phase transition related to cell cycle progression, cell division, and cell proliferation. Of the four stimulatory kinases, CDKs 4 and 6 are believed to be key promoters of tumor proliferation and hence, attractive targets for inhibition. Published results of three clinical trials demonstrating a significant reduction in risk of disease progression or death with combined CDK4/6 inhibitor plus AI compared to AI alone led to the recent approval of palbociclib with letrozole, and ribociclib or abemaciclib with any AI, as first-line therapy for ER-positive MBC in postmenopausal women.[24-26]

The use of AIs is approved for postmenopausal women. Even though ovarian estrogen production relies on the same enzymatic pathway discussed earlier, premenopausal or perimenopausal women with functioning ovaries are not appropriate candidates for these therapies. The reason is physiologic as evidence indicates that negative endocrine feedback will overcome aromatase inhibition. Clinical data also suggested that the strategy of combining an AI with ovarian suppression (ie, oophorectomy or luteinizing hormone–releasing hormone [LHRH] agonists) can also be considered in treatment-naïve premenopausal women.

Administration of AIs in men increases circulating levels of testosterone, which may antagonize the therapeutic effect of the drug. However, an AI plus gonadotropin-releasing hormone agonist with a CDK4/6 inhibitor is an option in men with **hormone receptor–positive** MBC.[27]

Antiestrogens bind to ERs, preventing receptor-mediated gene transcription, and therefore are used to block the effect of estrogen on the end target. This class of agents is subdivided into two pharmacologic categories, SERMs and selective ER downregulators (SERDs). SERMs like tamoxifen have tissue-specific estrogenic and antiestrogenic activities. The effort to minimize or eliminate the adverse estrogenic effects led to the development of SERDs, which are pure ER antagonists. The distinguishing feature of SERDs is their ability to degrade the ligand–ER complex.

Fulvestrant is the only SERD approved for clinical use in the United States. The drug received expanded indication as initial monotherapy for postmenopausal women with hormone receptor–positive, HER2-negative MBC.[28] However, clinical trial results have not consistently demonstrated improvements in PFS and OS with AI added to fulvestrant. The side-effect profile of fulvestrant is generally similar to the antiestrogens except for dermal reactions at the injection site. Even though fulvestrant is a good option for patients who are unable to take an oral medication, some patients may be averse to the drug because it must be given intramuscularly. There is no biological reason why fulvestrant should not produce similar outcomes in premenopausal women; however, safety or efficacy data are lacking.

Resistance to frontline therapy inevitably occurs in patients with advanced disease. One of the mechanisms of endocrine resistance appears to involve the mammalian target of rapamycin (mTOR), a protein downstream PI3K/Akt-signaling pathway. Results from a number of clinical trials demonstrated that everolimus, an mTOR inhibitor combined with an AI, tamoxifen, or fulvestrant is an effective treatment option for postmenopausal women with advanced disease.

Tamoxifen can be used in both premenopausal and postmenopausal women with ER-positive MBC. Toxicities associated with tamoxifen have been previously described. The only additional acute adverse effect, which occurs in about 5% of the patients with bone metastasis, is tumor flare or hypercalcemia following initiation of tamoxifen. Generally, this acute reaction is not an indication to discontinue treatment. Conversely, this finding appears to correlate with subsequent response to endocrine therapy.

Ovarian ablation or suppression in premenopausal women can be effectively achieved surgically or pharmacologically. Even though the efficacy of oophorectomy and tamoxifen are comparatively similar, secondary response rates to oophorectomy after tamoxifen treatment were somewhat higher than response rates achieved with tamoxifen after oophorectomy (33% vs 11%). Interpretation of these findings suggests that tamoxifen does not completely antagonize available estrogen, particularly in premenopausal women.

Castration can also be achieved pharmacologically with LHRH agonists. An initial surge in luteinizing hormone induces estrogen production, which can cause a tumor flare reaction similar to tamoxifen. Receptor downregulation occurs after a few weeks resulting in castrate levels of estrogen. With continued therapy, remission is achieved in about one-third of unselected patients. Of the three agents available in the United States, only goserelin is approved for the treatment of MBC.

Although tamoxifen alone can be considered, guidelines developed by the American Society of Clinical Oncology recommend offering ovarian ablation or suppression in combination with antiestrogen or AI in premenopausal women with endocrine-responsive MBC.

In randomized trials, progestins such as megestrol acetate and medroxyprogesterone acetate have been shown to induce noninferior response rates when compared with tamoxifen. Megestrol acetate is used more frequently in the United States. Despite their efficacy, these agents have been relegated to third-line status. The most common side effects are listed in Table 89–6. One side effect, weight gain, occurs in 20% to 50% of patients. Patients experiencing weight gain may have fluid retention, but fluid retention is not responsible for all of the weight gain. In cachectic cancer patients, the weight gain may be desirable, but this is not uniformly true of all patients with MBC.

High-dose estrogens and androgens are rarely used because they are more toxic than other hormonal agents and, in some cases, less effective. About one-third of patients placed on high-dose estrogens will discontinue the use of these agents because of side effects, the most important of which are thromboembolic events, vomiting, and fluid retention.

▶ *Cytotoxic Chemotherapy*

Except for brain and spine (with impending cord compression), chemotherapy is given as initial treatment of metastasis in patients with hormone receptor–negative tumors. The median time to an objective response is 2 to 3 months, but this period depends largely on the site of measurable disease. For example, time to response is 3 to 6 weeks for disease localized primarily to skin and lymph nodes; 6 to 9 weeks lung lesions; 15 weeks for liver metastasis; and 18 weeks for bone involvement. Once chemotherapy has been initiated, it is usually continued until maximal response, disease progression, or intolerable toxicity.

Unlike endocrine or anti-HER2 therapy, no clinical characteristic or established test has been shown to predict benefit from chemotherapy. However, a number of factors are associated with likelihood of tumor response, including good performance status, limited number (one or two) of disease sites, treatment-naïve status, and previous response to chemotherapy with a long disease-free interval. Tumors that progress while being treated may respond to different agents. Importantly, tumors that do not respond to endocrine therapy are as likely to respond to chemotherapy as tumors treated with cytotoxic agents first. If not used initially, chemotherapy can be an effective therapeutic option in appropriately selected patients with advanced breast cancer.

KEY CONCEPT The most active classes of chemotherapy in MBC are the anthracyclines and the taxanes with response rates as high as 50% to 60% in patients who have not received prior chemotherapy for metastatic disease. Although many chemotherapeutic agents have demonstrated activity in the treatment of breast cancer, the most frequently used agents include all of the agents used in the adjuvant setting. A brief discussion of the taxanes, capecitabine, and gemcitabine extends upon what is described in Chapter 88.

Taxanes

In the metastatic setting, the most effective weekly dose of paclitaxel is 80 to 100 mg/m^2 days 1, 8, and 15 of a 28-day cycle. With this approach, the toxicity profile of paclitaxel changes with less myelosuppression and delayed onset of peripheral neuropathy, but slightly more fluid retention and skin and nail changes.

A dose-response relationship has been demonstrated with docetaxel. The preferred regimen is 80 to 100 mg/m^2 given every 21 days. While less neuropathy, myalgia, and hypersensitivity reactions are observed with docetaxel (compared to paclitaxel), the incidence of febrile neutropenia, fluid retention, and skin reactions is higher. A weekly schedule of docetaxel, 30 to 40 mg/m^2 for 3 weeks followed by a week off may be more tolerable in some patients. Premedication with dexamethasone reduces the risk of hypersensitivity reactions and fluid retention associated with paclitaxel and docetaxel, respectively.

Antimetabolites

Capecitabine has activity against tumors progressing on anthracycline- and taxane-containing regimens. Moreover, the drug exhibits somewhat selective activity against cancer cells. This belief is supported by the presence of higher tumor cell levels of thymidine phosphorylase, the enzyme that catalyzes the final step in the conversion of capecitabine to 5-FU. In previously treated patients, capecitabine produced response rates of about 25%, which was impressive compared with other tested chemotherapy agents.

Gemcitabine is another agent that is used frequently in patients with advanced breast cancer. This nucleotide analogue has a unique mechanism of action and a favorable toxicity profile. As a single agent, response rates of nearly 40% have been achieved in the first-line setting. Response rates to gemcitabine monotherapy in the second- and third-line settings are approximately 18% to 26%. When combined with one other agent such as a taxane, vinorelbine, cisplatin, or an anthracycline, results of clinical studies consistently demonstrated higher efficacy than either single agent. In patients who have been exposed to an anthracycline and a taxane, gemcitabine appears to provide a similar benefit to capecitabine.

General Comments

Combination chemotherapy regimens are usually associated with higher response rates than single-agent therapies, but the higher response rates do not necessarily translate into significant differences in OS. The use of sequential single-agent therapy versus combination chemotherapy regimens has been debated widely for MBC. In the advanced disease setting, the least toxic approach is preferred when efficacy is considered equal. In clinical practice, patients who require a rapid response to chemotherapy (ie, those with symptomatic bulky metastases) often receive combination therapy despite the added toxicity. This decision is complex and should be made on an individual patient basis.

Because many patients receive adjuvant chemotherapy, regimens that are chosen for first-line use in the metastatic setting often are different from those used in the adjuvant setting with the following caveat. If the patient's cancer recurs more than 1 year after the end of adjuvant chemotherapy, the same agents may have activity in the metastatic disease setting.

▶ *Targeted Biologic Therapy*

Anti-HER2 therapies are only indicated for breast cancers that meet the definition for HER2 positivity (ie, 3+ by immunohistochemistry and/or *HER2* gene/chromosome 17 ratio ≥ 2 by fluorescence in situ hybridization).

Trastuzumab targets a specific extracellular epitope of HER2. Single-agent treatment with trastuzumab produces responses in approximately 15% to 20% of patients; the clinical benefit rate, which includes CRs, PRs, and stable disease, is nearly 40%. Trastuzumab has additive and perhaps synergistic activity with chemotherapeutic agents.[29] The issue regarding concomitant administration with other cytotoxic agents has been discussed previously.

The most notable adverse effects associated with trastuzumab include cardiac dysfunction, infusion-related hypersensitivity reactions, and pulmonary toxicity. Close monitoring for clinical signs and symptoms of heart failure is imperative. Although cardiac toxicity is usually reversible, some patients may require pharmacologic therapy. In addition, it is important to educate patients regarding the latter two adverse effects because they may occur up to 24 hours after the infusion and can be fatal if not treated promptly.

Three oral agents have been tested in clinical trials involving women with HER2-positive MBC. Lapatinib inhibits the intracellular kinase domains of HER2 and HER1 (epidermal growth factor receptor). A pivotal phase 3 clinical trial assessed the efficacy and safety of lapatinib plus capecitabine versus capecitabine alone in patients with disease progressing on trastuzumab. The trial was terminated early when a preplanned interim analysis indicated a significant reduction in the risk of disease progression that favored the combination arm. Of note, the incidence of brain metastasis was significantly lower in the lapatinib-treated group.[30] Neratinib, a pan-HER receptor blocker, was approved initially as extended adjuvant therapy (following completion of trastuzumab) in July 2017. Both drugs are approved in combination with capecitabine as third-line therapies for women with advanced disease. In April 2020, tucatinib was approved as part of a three-drug combination with trastuzumab and capecitabine as 3rd-line therapy for patients with metastatic HER2-positive breast cancer including those with brain metastases.

The side-effect profiles of these three tyrosine kinase inhibitors are similar. Diarrhea, especially with neratinib, is the most distressing untoward effect. Dyspepsia and rash occurred more frequently when these agents were combined with capecitabine. Importantly, cardiac toxicity in the phase 3 trials of both agents was minimal compared to trastuzumab.

Pertuzumab is another HER2-targeted agent. Although both pertuzumab and trastuzumab are monoclonal antibodies that block HER2-mediated signaling, a number of differences exist. First, each agent recognizes different extracellular epitopes. Second, the unique binding site of pertuzumab induces structural changes that hinder receptor dimerization. Theoretically, by inhibiting HER2 signaling initiated by ligand-activated HER1 or HER3, pertuzumab could provide even greater inhibition of HER2 signaling than trastuzumab. However, this does not appear to be case. In fact, compared to trastuzumab, pertuzumab has exhibited less activity. Based on results of a phase 3 clinical trial, pertuzumab was initially approved as first-line therapy (in combination with trastuzumab and docetaxel) for HER2-positive MBC.[31] The antibody received additional indications as part of the treatment regimens in the neoadjuvant and adjuvant settings. The most frequently reported adverse observed in clinical trials involving pertuzumab was diarrhea; cardiac toxicity was similar to, but does not appear to be increased when used concurrently with, trastuzumab.

One of the most significant limitations of cytotoxic chemotherapy is the lack of tumor specificity. Coupling target selectivity with the observation that trastuzumab's modest antitumor effect was substantially improved by the addition of chemotherapy led to the idea that antibodies could be used to deliver chemotherapy rather specifically to tumor cells. However, the efficacy of antibody–chemotherapy (drug) conjugates (ADCs) has historically been limited by variable expression of the target antigen, defective tumor cell uptake mechanisms, and unreliable linkers used in the conjugation process.

A novel therapeutic compound known as trastuzumab-DM1 (T-DM1, trastuzumab emtansine) has been developed that appears to have resolved all of the above issues. Because HER2 is overexpressed in approximately 15% to 20% of breast cancers, trastuzumab was identified as a reasonable vehicle for drug delivery. In order to improve the therapeutic index of the attached chemotherapeutic agent, a maytansine derivative was synthesized. The resulting maytansinoid, emtansine, was configured to have an easily cleavable linker to trastuzumab. The resulting ADC has the potential not only of retaining the antitumor properties of the individual agents but also maintaining a tolerable side-effect profile. T-DM1 is effective both for women with progressing disease and in the adjuvant setting.[32,33] A second ADC, fam-trastuzumab deruxtecan, was recently approved as third-line therapy for HER2-positive, metastatic breast cancer. Other HER2-targeted agents and immune checkpoint inhibitors are in clinical development and appear promising.[34-36]

▶ *Bisphosphonates*

The inclusion of bisphosphonates as part of standard adjuvant therapy should be considered for all postmenopausal women. For women whose breast cancer has metastasized to bone, bisphosphonates are recommended, in addition to chemotherapy or endocrine therapy, to reduce bone pain and fractures. Zoledronic acid, a potent bisphosphonate, is used most frequently. Although usually dosed every 4 weeks, a 12 weekly schedule has been reported to be noninferior.[37] Supplemental calcium and vitamin D are usually prescribed.

Local-Regional Control

▶ *Radiation Therapy*

Radiation is an important modality in the treatment of symptomatic metastatic disease. The most common indication for treatment with radiation therapy is painful bone metastases or other localized sites of disease refractory to systemic therapy. Approximately 90% of patients who are treated for painful bone metastases experience significant pain relief with radiation therapy. Additionally, radiation is an important modality in the palliative treatment of metastatic brain lesions and spinal cord lesions, which respond poorly to systemic therapy.

Patient Encounter, Part 5

Two months after the case above, the president of the Sierra Club, a woman 63 years of age, reported that she too has been diagnosed with invasive breast cancer after routine biennial mammography. Pathological evaluation indicated the tumor was positive for both ER and PR, HER2 negative, low tumor grade, and low proliferation index. Surgically, a total mastectomy was performed with sentinel node biopsy. Tumor was 2.1 cm at its widest margin, and sentinel node was negative for tumor. Final diagnosis was $T_2N_0M_0$ (stage 2, node-negative), hormone receptor–positive breast cancer. Her overall prognosis is very good. Even though the decision to receive systemic therapy following surgery is ultimately a patient's decision, appropriately used enhances the 5-year survival rate.

Detail the process regarding recommendations for adjuvant therapy in this patient focusing on:

- *Choice and duration of endocrine therapy*
- *Quality-of-life issues and treatment-related adverse events*
- *Clinical benefit of adding chemotherapy*
- *Supplemental supportive care measures*
- *Counseling regarding physical activity and weight gain*

OUTCOME EVALUATION

Early breast cancer is resected completely with curative intent and adjuvant chemotherapy and/or hormonal therapy plus trastuzumab with or without pertuzumab, in selected patients who are initiated to prevent a recurrence. During adjuvant chemotherapy, clinical and laboratory assessments to monitor patient tolerance to therapy-related toxicities are performed before each cycle of treatment. After completion of adjuvant therapy, patients are monitored every 3 months for the first few years after diagnosis, with intervals between examinations extended as time from diagnosis lengthens. Evaluation includes the following:

- Physical examination to detect breast cancer recurrence
- Annual mammography
- Symptom-directed workup
- Assess vitamin D status, especially in postmenopausal women

Patients with LABC are often treated with neoadjuvant therapy to enable tumor resectability. However, many believe that neoadjuvant therapy may have benefits that extend beyond downstaging. In addition, physical and ultrasound examinations are conducted to determine the size of the tumor following a complete course of neoadjuvant therapy. Surgical resection is then performed. Although no further chemotherapy is usually given following surgery, there is one confirmed exception, adjuvant T-DM1 and, possibly, capecitabine in patients with pathologically assessed residual tumor cells after preoperative chemotherapy. MBC is not curable, and therapy is intended to palliate symptoms and prolong survival. In most cases, hormonal therapy is the mainstay for tumors that are ER positive. While on therapy, patients are monitored monthly for signs of disease progression or metastasis to common sites, such as the bones, brain, or liver. Evaluations include the following:

- Pain
- Mental status or other neurologic findings
- Laboratory tests
- Liver function tests
- Complete blood count
- Calcium, electrolytes

Patient Care Process: Breast Cancer

Collect Information:

- Review medical/medication history and current laboratory values
- Document components of the medical history related to risk factors, breast cancer screening and surveillance programs, and menopausal status
- Discuss the overall health and performance status with the patient
- Address issues related to quality of life, psychosocial support, and survivorship needs
- Gather information related to insurance coverage

Assess the Information:

- Detail key aspects of the patient's history related to breast cancer risk level (ie, age, family history of breast/ovarian and other cancers, exposure to estrogens and ionizing radiation, and atypia)
- Determine the circumstance(s) that led to the diagnosis
- Determine the intrinsic subtype and stage of the disease
- Evaluate the overall prognosis for a patient with early breast cancer based on intrinsic subtype, stage, regional node status, proliferation markers, and tumor grade

Develop a Care Plan:

- Provide sufficient time for patient to process and cope with the diagnosis
- Explore the appropriateness of testing for possible hereditary cancers and fertility preservation in premenopausal women
- Assess treatment goals
- Formulate treatment strategy based on tumor burden, nodal involvement, tumor biology, health and menopausal status, and patient preference
- Identify key endpoints (especially with regard to quality-of-life issues) related to pharmacotherapeutic management of the patient
- Develop a supportive care plan

Implement the Care Plan:

- Ensure that the patient understands details related to the overall treatment plan (ie, timing and duration of systemic therapy relative to other treatment modalities)
- Assess pharmacologic treatment for drug interactions
- Address concerns and appraise comprehension and communication of drug-related side effects and possible adverse events (both acute and delayed)

(*Continued*)

Patient Care Process: Breast Cancer (*Continued*)

Follow-up: Monitor and Evaluate:

- Reinforce compliance regarding clinic visit and medications prescribed
- Address acute therapy-related complications and recommend or modify therapy as appropriate
- Recommend treatment of delayed therapy-related complications (ie, menopausal symptoms, and osteoporosis)
- Reeducate patient regarding any change(s) in medication(s)
- Assess quality-of-life issues especially for women receiving long-term endocrine therapy

Abbreviations Introduced in This Chapter

AI	Aromatase inhibitor
BCS	Breast-conserving surgery
CDK4/6	Cyclin-dependent kinases 4 and 6
ER	Estrogen receptor
HER2	Human epidermal–related growth factor receptor
HRT	Hormone replacement therapy
LABC	Locally advanced breast cancer
LHRH	Luteinizing hormone–releasing hormone
MBC	Metastatic breast cancer
PD-L1	Programmed death ligand 1 (PD1-binding protein)
PR	Progesterone receptor
SERD	Selective estrogen receptor downregulator
SERM	Selective estrogen receptor modulator
TNBC	Triple-negative breast cancer
TNM	Tumor, node, metastasis (staging system)

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90 Lung Cancer

Ninh M. La-Beck and Christopher Selby

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Identify major risk factors for the development of lung cancer.
2. Explain the pathologic progression of lung cancer and its relationship with signs and symptoms of the disease.
3. Make appropriate recommendations for screening and preventive measures in high-risk patients.
4. Understand staging of lung cancer patients and how it influences treatment decisions.
5. Explain how histology, biomarkers, and genetic mutational testing are used to select therapy.
6. List the rationale, advantages, and disadvantages for neoadjuvant and adjuvant chemotherapy in non–small cell lung cancer (NSCLC).
7. Identify the treatment of choice and treatment goals for limited and extensive small-cell lung **carcinoma**.
8. Identify the treatment of choice and treatment goals for local, locally advanced, and advanced non–small cell lung carcinoma.

INTRODUCTION

Lung cancer continues to be one of the most commonly diagnosed cancers and the leading cause of cancer-related mortality. Although treatment can cure some patients, most therapies are aimed at prolonging survival and reducing symptoms. Recent advances in lung cancer research have provided a number of new targeted therapies that provide significant benefit for some populations of patients; however, prevention and risk-reduction still appear to be the best strategies for reducing lung cancer incidence and mortality.

EPIDEMIOLOGY AND ETIOLOGY

Incidence and Mortality

Lung cancer, including cancer of the bronchus, is the second most common cancer diagnosis in the United States behind breast cancer[1] and the number one cause of cancer-related mortality, comprising more than 25% of cancer-related deaths in the United States. A close correlation exists between incidence and mortality of lung cancer, reflecting the reality that approximately 80% of patients with lung cancer ultimately die of the disease.[1]

Risk Factors

▶ *Tobacco Smoke*

KEY CONCEPT The most important risk factor for the development of lung cancer is tobacco smoke. Although rates of lung cancer have nearly doubled in never-smokers over the past 25 years, this population still only represents about 15% of all cases while the remaining 85% of cases occur in current or former smokers.[2] The correlation between smoking and lung cancer continues to drive anti-smoking and clean indoor air campaigns. Both total smoke exposure (reported as pack-years where one pack-year is the equivalent of smoking one pack per day for 1 year) and current use correlate with the individual's risk of developing malignancy. The risk of lung cancer decreases over time after a patient stops smoking, with at least 5 years needed to see appreciable decreases in cancer risk.[3] However, a former smoker will never see their risk return to that of a nonsmoker. Therefore, smoking cessation plays an important role in reducing lung cancer risk, making this a critical element of lung cancer prevention and treatment in at-risk patients. In addition to direct inhalation of cigarette smoke, environmental tobacco smoke, also known as passive smoking, is thought to cause 3000 cases of lung cancer per year.[3]

▶ *Other Environmental Risks*

Other environmental risk factors include **radon**, arsenic, nickel, and carcinogens such as chloromethyl ethers and coal products. Radon is the second leading cause of lung cancer overall, and the leading cause in never-smokers.[4] Those who live in an urban environment are also at increased risk for lung cancer due to exposure to high concentrations of combustion fumes.[4] Asbestos exposure increases the risk of developing **mesothelioma**, a distinct and rare type of lung cancer.

▶ *Hereditary Risk Factors*

Although smoking is a key risk factor for lung cancer, the majority of smokers never develop lung cancer. It is likely that genetic risk factors exist that may predispose certain smokers to lung cancer. After adjustments for age, smoke exposure, occupation, and gender, relatives of a lung cancer patient have approximately a two-fold higher risk of developing lung cancer.[5] The degree of inherited risk inversely correlates with the age of the relative at the time of diagnosis. First-degree relatives of a lung cancer patient diagnosed between the ages of 40 and 59 years have a six-fold higher risk for lung cancer. Although familial lung cancer that develops at an early age in nonsmokers fits a Mendelian codominant inheritance model, no gene has been identified that is specific for lung cancer.

▶ *Uncertain or Unproven Risk Factors*

Smoking marijuana may increase the risk of lung cancer similarly to tobacco smoking. However, this has not been well-studied due to the illicit status of marijuana in most places and due to confounding factors, such as concurrent tobacco smoking. E-cigarettes, which deliver nicotine without tobacco or by-products of smoking, are relatively new and no long term studies are currently available. However, emerging studies suggest that e-cigarette products may contain high levels of heavy metals such cadmium and nickel which may be risk factors for lung cancer.

Chemoprevention

Many potential chemoprevention agents, including nonsteroidal anti-inflammatory drugs, retinoids, inhaled glucocorticoids, vitamin E, selenium, and green tea extracts have been studied.[6-8] However, none have met regulatory criteria for drug approval[8] and two large randomized trials found that beta carotene supplements may actually increase the risk of lung cancer in smokers.[9] Therefore there are currently no chemoprevention strategies for smokers.

Screening and Early Detection

The 5-year survival for patients diagnosed with localized lung cancer is greater than 60% whereas for regional and distant disease, 5-year survival rates are 35% and 6%, respectively.[10] Unfortunately, most patients have advanced disease at the time of diagnosis (Figure 90–1), therefore, improved early detection of lung tumors could improve overall survival.

The National Lung Screening Trial (NLST) randomized over 53,000 patients at high risk for lung cancer to three annual low-dose spiral computed tomography (CT) scans or chest X-rays.[11] Chest X-ray has been shown in large trials to be equivalent to no screening and can be considered a placebo control for mortality. In the CT screening arm, 6.9% of patients were diagnosed with localized lung cancer with over 90% having surgery with curative intent, resulting in a 20% reduction in lung cancer mortality compared to the control arm.[11] In this study, high-risk patients were defined as having all of the following criteria:

1. Age between 55 and 74 years old
2. If former smoker, had quit within the previous 15 years
3. Greater than or equal to a 30 pack-year history

While screening reduces lung cancer mortality, implementation has been slow. This is likely due to the small absolute change in mortality of 0.3% (1.3% vs 1.6%) combined with the high false positive findings.[11] In the NLST, the CT screening arm had positive findings in 26% of scans and nearly 40% of all patients, and 96.4% of the lesions discovered were benign (false positive).[11] Due to this high false positive rate, research continues to look for methods to improve the specificity of lung screening strategies.[12]

Based on these data, the United States Preventative Services Task Force guidelines give a category B recommendation (indicating moderate benefit) that CT screening be offered to high-risk patients in combination with tobacco cessation where applicable.[12]

PATHOPHYSIOLOGY

Histologic Classification

Most lung cancers arise from the respiratory epithelium and are classified as carcinomas. Based on histological characteristics, lung cancer is classified into two major types, small-cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC), that have major differences in invasiveness, disease prognosis and treatment. Small-cell lung cancer represents about 15% of cases but has a significantly higher mortality rate than NSCLC, which accounts for about 85% of cases.[13] NSCLC is further categorized into three major histologic subtypes: squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma. It is important to note that there are other rare lung malignancies and lung cancers may consist of multiple histologic subtypes. Furthermore, pharmacologic treatments may selectively kill different components of the tumor, resulting in a conversion of the remaining tumor to a different subtype. Therefore, tumor histological classification is critical for therapy selection and clinical staging at the time of

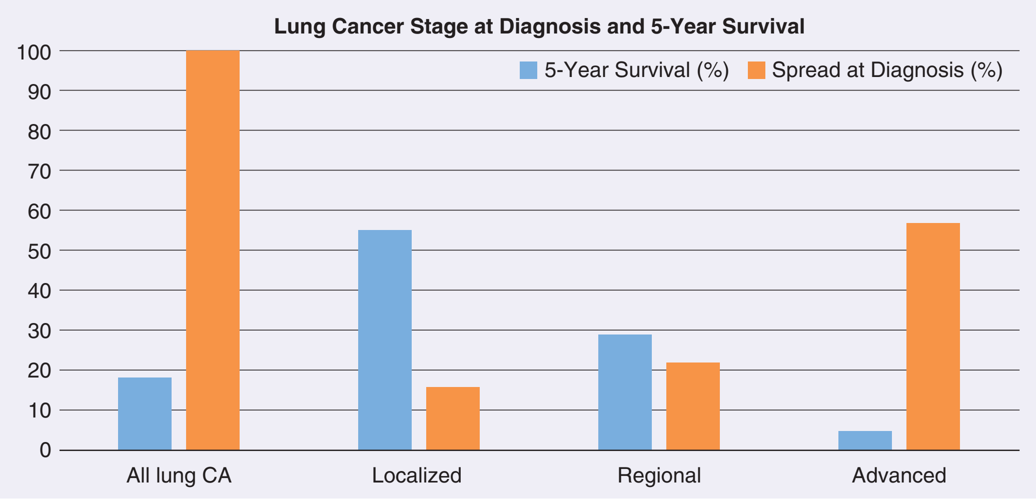

FIGURE 90–1. Lung cancer stage at diagnosis and corresponding 5-year survival in the United States. Data from National Cancer Institute. SEER Database https://seer.cancer.gov/statfacts/html/lungb.html accessed 8/14/2017.

Table 90–1

Lung Tumor Histopathology[14]

Tumor Type	Percent of Tumors	Targetable Mutation	Frequency
Small cell	15–20	None	
Non–small cell			
Adenocarcinoma	35–40	*EGFR*	15%–20%
		ALK	2%-7%%
		BRAF	3%–5%
		ROS1	1%–2%
		MET	1%-4%
		RET	1%–2%
		NTRK	<1%
Squamous (epidermoid)	25–30	Rare	
Large cell (giant)	10	None	

From F.R. Hirsch, G.V. Scagliotti, J.L. Mulshine, R. Kwon, W.J. Curran, Jr., Y.L. Wu, L. Paz-Ares, Lung cancer: current therapies and new targeted treatments, Lancet, 389 (2017) 299–311.

diagnosis, and also after disease progression/recurrence in order to guide patient care decisions.

Molecular Classification

In addition to histology, tumors are described by the presence of driver mutations or biomarkers[14] as outlined in Table 90–1. All patients with metastatic disease and nonsquamous histology are tested for actionable oncogenes, eg, sensitizing epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase 1 (ALK-1), ROS proto-oncogene 1 (ROS1), B-Raf proto-oncogene (BRAF), c-mesenchymal-epithelial transition factor exon 14 skipping mutation (MET), rearranged during transfection (RET) rearrangements, and neurotrophic-tropomyosin receptor kinase (NTRK; also referred to as neurotrophic tyrosine receptor kinase) gene fusions.[15] These driver mutations have a total prevalence of approximately 27% in newly diagnosed NSCLC patients with low overlapping probability (1%–3%).[16,17] In NSCLC, tumors with driver mutations or mutation/rearrangement of *ALK, BRAF, EGFR, MET, NTRK, RET,* or *ROS1* should be treated first line with molecular targeted therapies since they have been shown to improve response rates and survival compared to traditional cytotoxic therapies in this scenario.[16] Notably, targeted therapy can induce molecular changes in tumors that may lead to treatment resistance. Approximately 50% of NSCLC patients initially treated with EGFR targeting tyrosine kinase inhibitors (TKIs) (erlotinib, gefitinib, osimertinib, or afatinib) acquire resistance[18] leading to disease progression within 1 to 2 years in the majority of patients.[19]

It is estimated that 73% of NSCLC patients have oncogenic drivers that are not eligible for treatment with the currently approved molecular targeted therapies.[17] These patients are potentially eligible for immune checkpoint inhibitor (ICI) therapy targeting programmed cell death protein 1 receptor (PD-1), programmed death ligand 1 (PD-L1), or cytotoxic T-lymphocyte antigen 4 (CTLA4).[15] These checkpoints are immunoinhibitory coreceptors expressed on lymphocytes, myeloid immune cells, and tumor cells that are implicated in mediating cancer-associated immunosuppression and immune evasion.[20,21] Immune evasion is an emerging hallmark of cancer that involves upregulation of immune checkpoints such as the PD-1/PD-L1 pathway.[22] Blockade of this pathway using monoclonal antibodies against PD-1 or PD-L1, restored tumor-specific T-cell immunity and inhibited tumor growth in preclinical models.[22] Since then, evidence from multiple randomized trials have led to the approval of several immune checkpoint inhibitors for the treatment of lung cancer as monotherapy or as part of combination chemo-immunotherapy or dual immunotherapy regimen.[23-26] Although it involves monoclonal antibodies, it is considered separate from other antibody therapeutics because the goal is to activate the immune system to attack tumor cells, rather than the monoclonal antibody being directly responsible for cytotoxicity. A retrospective cross-sectional study found that about 40% of cancer patients were eligible for immunotherapy, with NSCLC patients accounting for about 20% of these patients.[27] Tumor PD-L1 expression and mutational testing should be performed on all NSCLC patients with metastatic disease who are considering systemic treatments.[15] Tumor mutational burden (TMB) is a measure of somatic nonsynonymous mutations,[28] and high TMB (10 or greater) is another indication for immunotherapy use.[28]

Patient Encounter Part 1

A 68-year-old man presents at your clinic complaining of worsening cough with occasional hemoptysis. He has had 1 to 2 severe upper respiratory infections annually for the past 4 to 5 years and 1 last month. He smoked about a pack of cigarettes per day beginning since he was 15 years old. He lives in a small rural town where he worked as a coal miner. A year after retiring at age 62 he purchased a restaurant/bar where he now works.

What risk factors for lung cancer are present?

Calculate this patient's pack-year history.

CLINICAL PRESENTATION AND DIAGNOSIS

The signs and symptoms of lung cancer depend on tumor location, size, and extent of invasion/metastasis. Tumors that are centrally located near the bronchus and trachea tend to present earlier with symptoms such as coughing, hoarseness (from tracheal compression), and dysphagia (from esophageal compression). In contrast, tumors that are peripherally located may not be symptomatic until lesions have progressed much longer. Nonetheless, the early clinical signs and symptoms of lung cancer are nonspecific and can also be attributed to other more common conditions such pulmonary or cardiovascular diseases. Consequently, 75% of patients will have advanced disease (regional and distant metastases) at the time of diagnosis.

KEY CONCEPT Signs and symptoms of lung cancer can be classified into three categories: pulmonary, extrapulmonary, and paraneoplastic syndromes. Distinguishing among these classes of symptoms is important in determining disease severity and prognosis, and guiding treatment selection.

Clinical Staging

The diagnosis of lung cancer is confirmed through visualization and biopsy (Table 90–2), then the extent of disease must be determined by clinical staging. Clinical staging serves two primary purposes: predicting prognosis and guiding therapy. Both NSCLC (squamous and nonsquamous subsets) and SCLC are staged using the American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) staging system. However,

Clinical Presentation and Diagnosis[29]

Pulmonary Symptoms

Symptoms related to the direct effects of the primary tumor often appear first and are the most common. These include:

- Cough
- Chest pain
- Shortness of breath
- Pneumonitis
- Dysphagia
- Hemoptysis
- Hoarseness
- Pleural effusion

Extrapulmonary Symptoms

Once the tumor invades tissues outside the pleural cavity, it can produce a wide array of symptoms, including:

- General bone pain
- Adrenal insufficiency
- Confusion
- Personality changes
- Enlarged lymph nodes
- Weight loss
- Seizures
- Nausea and vomiting
- Focal neurologic symptoms
- Horner syndrome
- Fatigue
- Headache
- Pancoast syndrome
- Subcutaneous skin nodules

Paraneoplastic Syndromes

Symptoms that are not a result of the direct effects of the tumor are termed paraneoplastic syndromes. They may be caused by substances secreted by the tumor or in response to the tumor and often occur in tissues far from the site of malignancy. Paraneoplastic syndromes are numerous and affect a wide variety of systems, including the endocrine, neurologic, skeletal, renal, metabolic, vascular, and hematologic systems.

- Cushing's syndrome
- Hypercalcemia
- Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
- Hypercoagulable state
- Anemia

Diagnosis

Diagnosis requires visualization of one or more lesions as well as a biopsy to confirm malignancy. Both visualization and sampling can be performed by invasive or noninvasive methods. These methods are summarized in Table 90–2.

clinical staging, management and prognosis of these two types of lung cancer are distinct. Lung cancer diagnosis can be confirmed through a number of diagnostic biopsies including direct tissue biopsies via bronchoscopy, mediastinoscopy, and transthoracic fine needle aspiration or core sample. These tests all carry risk to the patient as they require a surgical procedure, typically under anesthesia, to confirm a lung cancer diagnosis, and some patients may not be physically fit enough to tolerate such procedures. Less invasive methodologies include cytology testing on samples collected from sputum or thoracentesis to look for cancerous cells.[15] The newest and least invasive form of testing is a plasma or liquid biopsy which is a PCR-based test that can detect tumor-associated mutations in circulating cell-free DNA. At this time, liquid biopsies are not recommended in lieu of traditional histologic diagnostics, but can be used to help identify targetable mutations in a minimally invasive way.[15]

▶ *Non–Small Cell Lung Cancer*

Clinical staging of NSCLC with the TNM system is based on the size of the tumor (T), extent of nodal involvement (N), and presence of metastatic sites (M). Clinical stages are grouped together as localized, regional, or metastatic disease for real world prognosis by the National Cancer Institute Surveillance Epidemiology and End Results (SEER) Database. Local disease (stages 1 and 2) includes tumors that are confined to a single hemithorax and those cancers which have spread to the ipsilateral hilar lymph nodes. Once malignancy invades the mediastinal lymph nodes or contralateral hilar nodes, the disease becomes locally advanced (regional, stage 3). When lung cancer is detected outside the pleural cavity, it is considered advanced metastatic disease (stage 4). Local disease is associated with the highest cure and survival rates, whereas those with advanced disease have a 5-year survival rate of less than 5%.[10]

▶ *Small-Cell Lung Cancer*

The staging system for SCLC, originally developed by the Veterans Administration Lung Cancer Study Group, has now been incorporated into the TNM staging system.[30] This system categorizes SCLC into two classifications, limited disease or extensive disease, that guide treatment.

- Limited disease: Stages I to III that can be treated with definitive radiation therapy.
- Extensive disease: Stage IV or T3 and T4 characterized by multiple tumor/nodal lesions that are too extensive for a single radiation field.

TREATMENT

General Treatment Considerations

The treatment of lung cancer depends on tumor histology, stage of disease, biomarkers (eg, driver mutations, PD-L1 expression), patient characteristics and comorbidities, and performance status (PS). Treatment modality based on histology and stage is outlined in Figure 90–3. In the development of a patient care plan, the ultimate goals of therapy should be determined and treatment decisions made based on discussions between the treatment team and a well-informed patient. Some treatments may prolong survival by a few months, but at the expense of significant decrease in patient quality of life. Approximately half of patients diagnosed with NSCLC are greater than 70 years old[31] and compared to patients greater than 65 years old, they have more complex disease presentation with physiological changes and comorbidities[32,33]

Table 90–2

Diagnostic Tools[75,76]

	Technique	Description
Visualization	Chest X-ray	The least expensive visualization method in the diagnosis of lung cancer. Readily accessible and does not require systemic administration of contrast dye. However, it often detects lesions that are not cancerous and is not capable of assessing lymph node status.
	CT	More accurate when providing information on size, location, and invasion than chest radiography. It is recommended as part of the standard workup in most cases.
	PET scanning	Uses a substance called 5-FDG to produce a functional image of the lungs. Cells that are actively growing and dividing use greater amounts of glucose and therefore take up more 5-FDG. Focal regions of fluorescence can be visualized in cancerous lesions. PET scanning combined with a CT scan is more accurate than CT scan alone; however, the exact role of PET scanning in staging and monitoring is unclear. The apparent benefit and common role in staging is to evaluate mediastinal disease when it can influence the tumor resectability.
Tumor sampling	Fine needle aspiration	A method of aspirating cells from the tumor via insertion of a small-bore needle into the lesion and aspirating. Commonly used to evaluate lymph nodes or other poorly accessible sites, it has the advantage of being faster and less invasive than other biopsy methods; however, it does not preserve the architecture of the tumor and may return cells that are undergoing cell death, which negates histologic analysis.
	Bronchoscopy	A fiberoptic camera is inserted through the airways to examine the site of the suspected lesion. Once the lesion is visualized, a tool attached to the camera allows for a tissue biopsy. Newer technologies incorporate fluorescence to differentiate malignant tissue from premalignant lesions.
	Core needle biopsy	A method of obtaining tissue and preserving the tumor architecture. A large-bore needle is inserted into a lesion, where it cuts a core of tissue out that then can be evaluated.
	Liquid Biopsy	A method in which a peripheral blood sample is assessed for the presence of cancer biomarkers and oncogenes. This is considerably less invasive than direct tumor sampling, but is not yet considered to be as reliable as conventional sampling.
	Thoracentesis	Involves removal of fluid in the pleural cavity via a needle. The fluid then is assayed for the presence of cancerous cells. This procedure has low sensitivity and depends on the presence of a pleural effusion.
	Sputum cytology	Detects cancerous cells that become dislodged from the airways into the sputum. Sputum cytology is useful because it is not invasive, but it has much lower sensitivity for detecting cancer.

CT, computed tomography; 5-FDG, 5-fluorodeoxyglucose; PET, positron-emission tomography.

that may affect response to therapy and/or increase risk of adverse effects. KEY CONCEPT In patients with early stage disease, a definitive cure is the primary goal of treatment, although this end point is not always met. Additional goals of treating lung cancer patients include prolongation of survival and improvement of quality of life through alleviation of symptoms.

▸ *Performance Status*

The Eastern Cooperative Oncology Group (ECOG) performance status (PS) (see Chapter 88) is an independent prognostic indicator for survival in patients with lung cancer.[34] The performance status (PS) also predicts response and likelihood of toxicity to chemotherapy. Patients with localized disease tend to be treated with more aggressive measures as the intent of treatment is curative. However, these aggressive treatments also increase the risks of treatment related adverse events, some of which can be dose-limiting or fatal. Patients with good PS (0–1) are more likely to tolerate the full treatment intensity, while patients with PS 2 may require dose reductions or experience treatment delays due to adverse events. Patients with PS 3 to 4 usually receive palliative therapy and/or supportive care.

KEY CONCEPT Categorizing patients by their ECOG PS allows for a standardized approach to predict the capability to tolerate systemic therapies that have significant drug toxicities.

Treatment Modality

▸ *Surgery (NSCLC)*

KEY CONCEPT Of all treatment modalities, surgical resection is associated with the greatest improvement in survival for patients with early stage NSCLC tumors (clinical stage IA, IB, or IIA). Surgery is not recommended in locally advanced and metastatic disease as it has not been proven to prolong survival. However, surgery for advanced disease is an important palliative treatment that can improve quality of life in some patients. In this respect, surgery is limited to local sites where the tumor is causing significant morbidity (eg, spinal cord compression).[15]

▸ *Surgery (SCLC)*

Historically, patients with SCLC were rarely treated with surgery as the results of a randomized trial published in 1969 showed that surgery did not result in any 5- or 10-year survivors in comparison to radiation which produced a 4% survival rate at 5 and 10 years.[35] More recently, a retrospective study was published in 2018 showing that patients with limited stage SCLC who received surgery with adjuvant chemotherapy were found to have increased overall survival at 5 years (47.6%) as compared to patients who received concurrent chemoradiation (32.5%).[36] With improved imaging, surgical techniques, and better application of pharmacotherapy these numbers are significantly improved compared

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnosis

PMH: Moderate hypertension (controlled)

FH: Father died from lung cancer at age 62, mother is 85, alive, and living in a nursing home due to heart failure and dementia

Meds: Lisinopril 20 mg daily

ROS: (+) Chest pain, shortness of breath, hemoptysis; (–) recent weight loss

PE:

VS: BP 125/69 mm Hg, RR 26 breaths/min, P 80 beats/min, T 99°F (37.2°C)

CV: RRR

Labs: Slightly elevated LFTs and platelets, mild anemia (Hgb 11.8 g/dL); all others WNL; CXR reveals a solitary nodule in right lobe; fine needle aspiration confirms squamous cell carcinoma of the lung that stains positive for PD-L1; further evaluation with CT and PET scans reveal a 3-cm mass, with bilateral mediastinal lymph node involvement and a lesion on his adrenal gland.

What clinical stage is this patient's disease?

What is the estimated survival time for this stage of NSCLC?

Does this patient have any factors that may negatively or positively influence survival?

to the data from the 1960s. However, the review did note that only 30% of SCLC patients in the study received surgery while 70% were treated with chemoradiation, suggesting that we may be able to continue to improve upon the 5-year overall survival numbers for this patient population.

▸ *Radiotherapy (NSCLC)*

Patients with localized NSCLC are best treated with surgery, however, many of these patients are considered inoperable due to comorbidities (eg, lung disease from smoking).[37] In these situations, radiation therapy can be used with curative intent in place of surgery, and the success rate is approximately 50% that of surgery.[38] Patients with locally advanced (stage IIIB, nonsurgically resectable) disease have prolonged survival with combined chemotherapy and radiotherapy, while patients with metastatic NSCLC can receive radiation therapy to palliate symptomatic metastases. Although radiation is less invasive than surgery, it is associated with significant toxicities affecting normal tissue in the radiated area. Patients may experience esophagitis, pneumonitis, cardiac abnormalities, myelosuppression, and skin irritation. These adverse events can be decreased by using stereotactic radiation and/or hyperfractionated administration.[39]

Postoperative radiotherapy (PORT) is thought to eliminate remnants of the resected tumor that might be deposited in nearby tissue, but is only recommended for patients with positive margins after surgical resection when a local recurrence is of concern.[15]

▸ *Radiotherapy (SCLC)*

Radiotherapy, with concurrent chemotherapy, is the treatment of choice for limited-stage SCLC. Radiation may also be used for extensive-stage patients for symptomatic management. Limited- and extensive-stage SCLC patients who respond to therapy should also receive prophylactic cranial irradiation, which treats micrometastatic disease in the CNS. This improves cure rates for limited-stage disease and prolongs survival for extensive-stage disease.[37]

▸ *Systemic therapy (NSCLC)*

Traditional cytotoxic chemotherapy is the mainstay of lung cancer treatment for patients with locally advanced disease (ie, stage IIb or IIIa) although osimertinib was recently approved for patients with early stage EGFR mutant disease. In advanced or metastatic disease (stage IV), patients who are eligible for immunotherapy or whose tumors express a targetable mutation are treated first with targeted therapies. Cisplatin and carboplatin are considered the most effective traditional chemotherapy agents regardless of histology and are combined with a second agent to comprise a regimen known as a "platinum doublet".[14] **KEY CONCEPT** Platinum doublet chemotherapy offers superior response rates compared with single-agent chemotherapy regimens and should be used when the patient can tolerate the increased toxicity of multiple agents. Effective chemotherapy agents that may be combined with a platinum agent include paclitaxel, albumin bound paclitaxel, docetaxel, gemcitabine, vinorelbine, etoposide, and pemetrexed. Patients with squamous histology do not benefit from pemetrexed, while they seem to benefit more from gemcitabine (see Table 90–3 for regimen details). The duration of therapy has also been intently studied. Doublet therapy is generally given for four to six cycles; patients with nonsquamous histology receive benefit from maintenance therapy with pemetrexed with or without bevacizumab. Those with squamous histology can be treated with maintenance gemcitabine.[15]

PD-1 and PD-L1 inhibitors have become a mainstay in advanced NSCLC treatment. Pembrolizumab, targeting PD-1, is approved for first-line therapy both as monotherapy in PD-L1 positive patients, and in combination with chemotherapy regardless of PD-L1 expression. Atezolizumab, targeting PD-L1, is approved first-line for NSCLC regardless of PD-1 expression when used in combination with chemotherapy and bevacizumab, an antibody against VEGF.[40,41] Durvalumab, targeting PD-L1, was recently approved as consolidation immunotherapy after definitive platinum-based chemoradiation in unresectable stage 3 NSCLC.[15] Nivolumab (PD-1 target), atezolizumab, and pembrolizumab are also efficacious as second-line therapy. Key studies are shown in Table 90–4.

TKIs are the front-runners in molecular-targeted therapy for advanced NSCLC. Monotherapy with a TKI in genetically selected patients frequently outperforms cytotoxic chemotherapy. Multiple agents are approved for *EGFR, BRAF, and MET* mutations, *ALK, ROS1*, and *RET* rearrangements, and *NTRK* gene fusions. These TKIs are oral medications. Optimizing outcomes requires clinicians to obtain a complete medication history and be knowledgeable about preventing and managing therapy-induced toxicity (see Chapter 88) and drug interactions. Everyone involved in this process should be knowledgeable about toxicity prevention and management.[15] Results of key studies for targeted therapies are shown in Table 90–5.

Monoclonal antibodies targeting vascular endothelial growth factor (VEGF) signaling (bevacizumab and ramucirumab) and epidermal growth factor receptor (EGFR; necitumumab) have

Table 90–3

Select Chemotherapy Regimens and Their Efficacy

Regimen	Histology	Comparison	PFS	OS
		NSCLC Adjuvant Therapy[77]		
Cisplatin-vinorelbine (JBR.10)		Cisplatin 50 mg/m^2 IV day 1 and 8 q4 week × 4 weeks Vinorelbine 25 mg/m^2 IV day 1 q3 week for 16 weeks vs Observation		Median 7.8 years vs 6.1 years (P = 0.05)
		NSCLC First-Line for Advanced Disease[78-82]		
Cisplatin-paclitaxel	Not reported	Paclitaxel 135 mg/m^2 CIV over 24 h day 1 + cisplatin, 75 mg/m^2 IV day 2 repeat q3 week	Median 3.4 months vs	Median 7.8 months vs
Cisplatin-docetaxel		Cisplatin 75 mg/m^2 IV day 1 and docetaxel 75 mg/m^2 IV day 1 repeat q3 week	3.7 months vs	7.4 months vs
Cisplatin-gemcitabine		Cisplatin 100 mg/m^2 IV day 1 and gemcitabine 1000 mg/m^2 IV days 1, 8, and 15 repeat q4 week	4.2 months vs	8.1 months vs
Carboplatin paclitaxel (ECOG 1594)		Carboplatin AUC 6 IV day 1 and paclitaxel 225 mg/m^2 IV over 3 hours day 1 repeat q3 week	3.1 months (P = NS)	8.1 months (P = NS)
Cisplatin-pemetrexed	Squamous and nonsquamous	Cisplatin 75 mg/m^2 IV day1 + Pemetrexed 500 mg/m^2 IV day 1 Repeat q3 week × 6	Median 4.8 months vs	Median 12.6 months (adenocarcinoma) (P = 0.03) 9.4 months (squamous)
Cisplatin-gemcitabine		Cisplatin 75 mg/m^2 IV day 1 + Gemcitabine 1250 mg/m^2 IV days 1 and 8 Repeat q3 week × 6	5.1 months (P = NS)	Median 10.9 months (adenocarcinoma) 10.8 months (squamous) (P = 0.05)
Carboplatin-pemetrexed	Nonsquamous	Carboplatin AUC 6 IV day 1 + Pemetrexed 500 mg/m^2 IV day 1 Repeat q3 week	5.7 months vs	10.5 months vs
Oxaliplatin-pemetrexed		Oxaliplatin 120 mg/m^2 IV day + Pemetrexed 500 mg/m^2 IV day 1 Repeat q3 week	5.1 months (P = NS)	10.5 months (P = NS)
Carboplatin-albumin-bound paclitaxel	Squamous and nonsquamous	Carboplatin AUC 6 IV day 1 + albumin-bound paclitaxel 100 mg/m^2 IV days 1, 8, 15 Repeat q3 week	6.3 months vs	12.1 months vs
Carboplatin-paclitaxel		Carboplatin, AUC 6 IV day 1 + Paclitaxel 200 mg/m^2 IV over 3 hours day 1 Repeat q3 week	5.8 months (P = NS)	11.2 months (P = NS)
Carboplatin-paclitaxel +/– Bevacizumab (ECOG 4599)		Paclitaxel 200 mg/m^2 IV Day 1 + Carboplatin AUC 6 IV Day 1 Repeat q3 week × 6 vs Paclitaxel 200 mg/m^2 IV Day 1 + Carboplatin AUC 6 IV Day 1 + Bevacizumab 15 mg/kg IV day 1 Repeat q3 week × 6	Median 4.5 months vs 6.2 months (P < 0.001)	Median 10.3 months vs 12.3 months (P = 0.003)
		SCLC First-Line Regimens[83,84]		
Limited stage				
EP	Etoposide 100 mg/m^2/d IV days 1–3 + Cisplatin 80 mg/m^2 IV day 2 + Radiation Repeat q4 week vs		Median 1.1 year vs	Median 3.2 years vs
IP	Irinotecan 60 mg/m^2 IV days 1, 8, 15 + Cisplatin 60 mg/m^2 IV day 1 Repeat q4 week		1.0 year (P = 0.74)	2.8 years (P = 0.70)
Extensive stage				
Carboplatin-etoposide-atezolizumab	Etoposide 100 mg/m^2/d IV days 1–3 + Carboplatin AUC 5 IV day 1 + Atezolizumab 1200 mg day 1 Repeat q3 week x 4 followed by Atezolizumab 1200 mg day 1 Repeat q3 week vs		Median 5.2 months vs	Median 12.3 months vs
Carboplatin-Etoposide	Etoposide 100 mg/m^2/d IV days 1–3 + Carboplatin AUC 5 IV day 1 Repeat q3 week × 4–6		4.3 months (P = 0.02)	10.3 months (P = 0.007)
Platinum-Etoposide-Durvalumab	Carboplatin AUC 5–6 OR Cisplatin 75–80 mg/m^2 IV day 1 + Etoposide 100 mg/m^2/d IV days 1–3 + Durvalumab 1500 mg day 1 Repeat q3 week x 4 followed by Durvalumab 1500 mg day 1 Repeat q4 week vs			Median 13 months vs
Platinum-Etoposide	Carboplatin AUC 5–6 OR Cisplatin 75–80 mg/m^2 IV day 1 + Etoposide 100 mg/m^2/day IV days 1–3			10.3 months (P = 0.007)

Table 90–4

Select Clinical Trials in Advanced NSCLC with Immunotherapy

Regimen	Comparator	Histology	Median PFS	Median OS
Any PD-L1 Status and Driver Mutation Negative				
Platinum + Pemetrexed + **Pembrolizumab** q3 week (KEYNOTE-189)[62]	Platinum + Pemetrexed + Placebo q3 week	Nonsquamous	9.0 months vs 4.9 months	22.0 months vs 10.7 months
Paclitaxel 200 mg/m^2 IV Day 1 OR nab-Paclitaxel 100 mg/m^2 Days 1, 8, 15 Carboplatin AUC 5 IV Day 1 + **Pembrolizumab** 200 mg Day 1 IV q3 week (KEYNOTE-407)[85]	Paclitaxel 200 mg/m^2 IV Day 1 OR nab-Paclitaxel 100 mg/m^2 Days 1, 8, 15 Carboplatin AUC 5 IV Day 1 + Placebo q3 week	Squamous	6.5 Months vs 4.8 months ($P < 0.001$)	15.9 Months vs 11.3 months ($P < 0.001$)
Paclitaxel 200 mg/m^2 IV + Carboplatin AUC 5 IV + Bevacizumab 15 mg/kg IV + **Atezolizumab** 1200 mg q3 week (IMPower150) [86]	Paclitaxel 200 mg/m^2 IV + Carboplatin AUC 5 IV + Bevacizumab 15 mg/kg IV q3 week	Nonsquamous (also included subset with ALK and EGFR mutation positive who had progressed on TKI)	8.3 months vs 6.8 months ($P < 0.001$)	19.2 months vs 14.7 months ($P = 0.002$)
Nab-Paclitaxel 100 mg/m^2 Days 1, 8, 15 Carboplatin AUC 5 IV Day 1 + **Atezolizumab** 1200 mg Day 1 IV q3 week (IMPower130) [87]	Nab-Paclitaxel 100 mg/m^2 Days 1, 8, 15 Carboplatin AUC 5 IV Day 1 + Placebo q3 week	Nonsquamous	7 months vs 5.5 months ($P < 0.001$)	18.6 months vs 13.9 months ($P = 0.033$)
PD-L1 Positive and Driver Mutation Negative				
Pembrolizumab 200 mg IV q3 week (KEYNOTE-024)[88] (KEYNOTE-042)[89]	Histologically appropriate Platinum Doublet	Squamous and nonsquamous PD-L1 $\geq$50% Squamous and nonsquamous PD-L1 1%–49%	10.3 months vs 6.0 months ($P < 0.001$)	30 months vs 14.2 months ($P = 0.002$) 13.4 months vs 12.1 months (P = NS)
Atezolizumab 1200 mg q3 week (IMPower110)[90]	Histologically appropriate Platinum Doublet	Squamous and nonsquamous PD-L1 $\geq$50%		20.0 months vs 13.1 months ($P = 0.0106$)
PD-L1 Positive Second-Line[91-93]				
Atezolizumab (OAK)		Atezolizumab 1200 mg IV q3 week vs Docetaxel 75 mg/m^2 IV q3 week	Median 2.8 months vs 4 months	Median 13.8 months vs 9.6 months ($P = 0.0003$)
Nivolumab (CheckMate 017)	Squamous	Nivolumab 3 mg/kg IV q2 week vs Docetaxel 75 mg/m^2 IV q3 week	[a]3 year PFS Rate 10% (Nivolumab) vs <1% (Docetaxel)	[a]Median 11.1 months (Nivolumab) vs 8.1 months (Docetaxel)
Nivolumab (CheckMate 057)	Nonsquamous	Nivolumab 3 mg/kg IV q2 week vs Docetaxel 75 mg/m^2 IV q3 week		
Pembrolizumab (KEYNOTE-010)		Pembrolizumab 2 mg/kg IV q3 week vs Docetaxel 75 mg/m^2 IV q3 week	Median 3.9 months vs 4 months	Median 10.4 months vs 8.5 months ($P = 0.0008$)

[a] Outcomes data at 3 years pooled for Checkmate 017 and Checkmate 057.

Table 90–5

Select Clinical Trials in Advanced NSCLC with a Targetable Mutation

Agent	Comparison	PFS	OS
EGFR Positive First-Line[47,94-98]			
Osimertinib[a] (FLAURA)	Osimertinib 80 mg PO Daily vs Erlotinib 150 mg PO Daily OR Gefitinib 250 mg PO Daily	Median18.9 months vs 10.2 months($P < 0.001$)	18 month survival rate 83% vs 71% ($P = 0.007$)
Dacomitinib vs Gefitinib (ARCHER1050)	Dacomitinib 45 mg PO Daily vs Gefitinib 250 mg PO Daily	Median 14.2 months vs 9.2 months ($P < 0.0001$)	Not reported
Gefitinib vs Erlotinib	Gefitinib 250 mg PO daily vs Erlotinib 150 mg PO Daily	Median 10.4 months vs 13 months ($P = 0.108$)	Median 20.1 months vs 22.9 months ($P = 0.250$)
Gefitinib (IPASS)	Gefitinib 250 mg PO Daily vs Paclitaxel 200 mg/m^2 IV + Carboplatin AUC 5–6 IV every 3 weeks	In EGFR+ patients: HR 0.48 (95% CI 0.34–0.67)	In EGFR+ patients: HR 1.00 (95% CI 0.76–1.33)
Erlotinib (EURTAC)	Erlotinib 150 mg PO Daily vs Chemotherapy	Median 9.7 months vs 5.2 months ($P < 0.0001$)	Median 19.3 months vs 19.5 months ($P = 0.87$)
Afatinib (LUX-Lung 3)	Afatinib 40 mg PO Daily vs Cisplatin 75 mg/m^2 IV + Pemetrexed 500 mg/m^2 IV every 3 weeks	Median 11.1 months vs 6.9 months ($P = 0.001$)	Median 28.2 months vs 28.2 months ($P = 0.39$)
EGFR T790M Positive Second-Line[48]			
Osimertinib (AURA3)	Osimertinib 80 mg PO Daily vs Pemetrexed 500 mg/m^2 IV + Carboplatin AUC 5 IV or Cisplatin 75 mg/m^2 IV q3 week	Median 10.1 months vs 4.4 months ($P < 0.001$)	Not yet reached
ALK Positive First-Line[49,50,99]			
Alectinib[a] Vs Crizotinib (ALEX)	Alectinib 600 mg PO BID vs Crizotinib 250 mg PO BID	Median 25.7 months vs 10.4 months ($P < 0.001$)	Not yet reached
Crizotinib (PROFILE 1014)	Crizotinib 250 mg PO BID vs Pemetrexed 500 mg/m^2 IV + Cisplatin 75 mg/m^2 IV or Carboplatin AUC 5–6 IV every 3 weeks	Median 10.9 months vs 7.0 months ($P < 0.001$)	Median Not yet reached vs 47.5 months
Ceritinib (ASCEND-4)	Ceritinib 750 mg PO Daily vs Pemetrexed 500 mg/m^2 IV + Cisplatin 75 mg/m^2 IV or Carboplatin AUC 5–6 IV every 3 weeks	16.6 months vs 8.1 months ($P < 0.00001$)	Overall survival rate at 24 months 70.6% vs 58.2%
ALK Positive Second-Line[51,52,100]			
Ceritinib (ASCEND-5)	Ceritinib 750 mg PO Daily vs Pemetrexed 500 mg/m^2 IV OR Docetaxel 75 mg/m^2 IV every 3 weeks	5.4 months vs 1.6 months ($P < 0.0001$)	HR 1.0 (95% CI 0.67–1.49; $P = 0.5$)
Brigatinib (ALTA)	Brigatinib 90 mg PO Daily OR 180 mg PO daily	9.2 months Arm A and 12.9 months Arm B	1 year OS probability 71% Arm A and 80% Arm B
Lorlatinib (Phase I data)	Lorlatinib 10–200 mg PO Daily OR Lorlatinib 35–100 mg PO Daily	Estimated median PFS 13.5 months	Not reported

(Continued)

Table 90–5

Select Clinical Trials in Advanced NSCLC with a Targetable Mutation (*Continued*)

Agent	Comparison	PFS	OS
ROS1 Positive First-Line[56,101,102]			
Crizotinib[a]	Crizotinib 250 mg PO BID	Median 19.2 months	12 month OS 85%
Ceritinib	Ceritinib 750 mg PO Daily	Median 9.3 all patients Median 19.3 in crizotinib-naïve patients	Median 24 months
Entrectinib[a] (Phase I data)	Entrectinib at least 600 mg PO Daily	Median Duration of response 24.6 months	Not reported
***BRAF* V600E Positive First-Line[53,54]**			
Dabrafenib[a] and Trametinib[a] (1st line)	Dabrafenib 150 mg PO BID + Trametinib 2 mg PO daily	Median 14.6 months	Median 24.6 months
Dabrafenib[a] and Trametinib[a] (BRF113928) (Previously treated)	Dabrafenib 150 mg PO BID + Trametinib 2 mg PO daily	Median 9.7 months	Not mature
RET Positive First-Line[60]			
Selpercatinib[a]	Selpercatinib 160 mg PO BID	Median duration of response 20.3 months	Not reported
MET exon 14 Skipping Mutation Positive[59]			
Capmatinib[a]	Capmatinib 400 mg PO BID	Median 5.4 months–pretreated 12.4 months–treatment-naive	Not reported
Tepotinib	Tepotinib 500 mg PO Daily	Median response 11.1 months	Not reported
TRK Gene Fusion Positive First-Line[55,103]			
Entrectinib[a] (Phase I Data–multiple tumor types)	Entrectinib at least 600 mg PO Daily	Median 11.2 months	Estimated median 21 months
Larotrectinib[a]	Larotrectinib 100 mg PO BID	Median not reached at median follow up of 9.4 months	1 year PFS rate 55%

[a] Denotes preferred therapy for patients with the matched driver mutation.

been combined with traditional chemotherapy to improve outcomes. Their use is currently limited to stage IV NSCLC.

Therapeutic decisions must include the full consent and understanding of risks by the patient. Counseling on the therapeutic regimen and risk of toxicity is imperative before dosing. Refer to Chapter 88 for dosing recommendations in renal and hepatic failure.

▶ *Systemic therapy (SCLC)*

A platinum-based doublet regimen, either carboplatin or cisplatin combined with etoposide, is the cytotoxic chemotherapy backbone of treatment for SCLC. With limited-stage disease, cisplatin is thought to be slightly more efficacious than carboplatin, but also more toxic. The preferred treatment regimen for extensive-stage disease is four to six cycles of a platinum agent in combination with etoposide and an ICI, either atezolizumab or durvalumab, followed by maintenance therapy with the ICI.[37] If ICI therapy is contraindicated, carboplatin with etoposide, or cisplatin combined with irinotecan or etoposide, are acceptable alternatives. While molecular targeted therapies such as those targeting VEGF and EGFR have been investigated in SCLC, they have not been found to significantly improve outcomes.

Treatment of Non–Small Cell Lung Cancer

The first step in treatment of NSCLC involves confirmation of the clinical stage, histological subtype, and determination of likelihood of resection of the tumor. All patients should undergo histological evaluation since the subtype will impact clinical management. Moreover, patients with advanced (nonresectable) disease should also undergo genetic and biomarker analysis in addition to their histologic classification. PD-L1 testing needs to be done on all tumors in this setting, while the genomic analysis of driver mutations is required in nonsquamous NSCLC subtypes (adenocarcinoma and large cell). Mutation testing should also be considered in never smokers with squamous NSCLC. Treatment options depend on the stage of disease (ie, eligibility for resection), performance status, histology (squamous versus nonsquamous NSCLC), PD-L1 expression, and genetic findings.[15]

▶ *Local Disease (Stages IA, IB, and IIA)*

Local disease encompasses stages IA through IIA and is associated with a favorable prognosis. Approximately 60% of these patients are expected to live more than 5 years from time of diagnosis. The goal of therapy is curative in local disease, and surgery is the mainstay of treatment regardless of histology. Stage IA tumors are rarely seen clinically and may be treated with surgery alone. If surgical margins are positive, radiotherapy or repeat resection is recommended.[15] Stage IB and IIA may be treated with adjuvant chemotherapy, if surgical margins are positive for disease or if they are particularly high-risk patients. The rationale behind adjuvant chemotherapy is to eradicate micrometastases or other tumor cells that may have been missed during removal of the primary tumor. The results of five prospective trials suggest that there is benefit from adjuvant chemotherapy leading to a survival advantage of 4% to 15%.[42,43] Consequently, adjuvant therapy has become the standard of care in resectable NSCLC and should be offered to patients, particularly those with stage II or III disease.

Although the regimen of choice is unclear, studies evaluating pemetrexed in squamous NSCLC indicate that it has minimal to no activity in this histology. Thus, regimens containing pemetrexed should be avoided in patients with squamous NSCLC, regardless of stage. Cisplatin and vinorelbine regimens appear to have the most evidence supporting efficacy, regardless of histology or genetics. Carboplatin-based regimens may be used in patients unable to tolerate cisplatin or with comorbidities precluding cisplatin use.

▶ *Locally Advanced Disease (Stages IIB and IIIA)*

Patients with locally advanced disease should also be considered for surgery, followed by adjuvant chemotherapy as outlined in local disease. However, neoadjuvant chemotherapy could also be considered before surgery. The rationale behind neoadjuvant chemotherapy is to decrease the size of the tumor so that it can be resected more easily with clean margins, as well as to eliminate distant micrometastases before invasive local treatment. A meta-analysis of neoadjuvant trials suggests that neoadjuvant chemotherapy in all early stages improves 5-year survival by 5%.[44] Notably, in many of these studies, there was no adjuvant chemotherapy, which could theoretically improve survival to a similar extent as neoadjuvant chemotherapy. One concern with neoadjuvant chemotherapy is that the toxicity of these regimens may delay surgery, and if the tumor does not respond to the treatment, there is a risk of disease progression. However, current data suggest that more than 90% of patients who are treated with neoadjuvant chemotherapy maintained their scheduled surgery.[45] The utilization of neoadjuvant chemotherapy is inconsistent, but is most common in patients with locally advanced tumors (stage III).[46] Neoadjuvant chemotherapy regimens are platinum-based doublets. Three cycles of carboplatin and paclitaxel administered on a 3-week schedule is a common and supported approach. The benefit of combining neoadjuvant chemotherapy and surgery with additional adjuvant chemotherapy is being investigated but is of unknown value at this time. Relatively small studies have compared using three treatment modalities (chemotherapy, radiation, and surgery) to two treatment modalities (chemotherapy and radiation). Improvements have been shown for progression-free survival, but not overall survival. Consequently, the value of trimodal therapy is unclear.

▶ *Advanced or Metastatic Disease (Stages IIIB, IIIC, and IV)*

Advanced disease is treated with systemic therapy if the patient has an acceptable performance status. The selection of therapy is determined by the stage, histology, presence/absence of biomarkers/targetable mutations, and patient characteristics. Tumor PD-L1 expression and mutational analysis should be performed since these will determine selection of the treatment regimen. Patients with targetable tumor mutations do significantly better with a molecular-targeted agent than with traditional chemotherapy or immunotherapy. Currently, there are seven families of targetable mutations that have been reported in NSCLC: (a) *EGFR*, (b) *ALK*, (c) *BRAF*, (d) *ROS1*, (e) *MET*, (f) *RET*, (g) *NTRK*; they occur almost exclusively in nonsquamous histologies and are generally mutually exclusive. The *EGFR* activating mutations (most commonly exon 19 deletion and exon 21 substitution) are present in about 15% of nonsquamous tumors, *ALK* mutations (most commonly *ALK-EML4* rearrangement) are found in about 7% of nonsquamous NSCLC, while *BRAF* (most commonly V600E), *ROS1*, *MET* (most commonly exon 14 skipping mutation), *RET*, and *NTRK* mutated tumors are all less common, appearing in <5% of NSCLC patients.[15] Once patients fail appropriate targeted therapies, treatment options are similar to first-line treatment for no driver mutation (consider PD-L1 status and histology) (Figure 90–2).

EGFR mutation positive patients should be treated with osimertinib, afatinib, dacomitinib, erlotinib, or gefitinib in the first-line setting. In large randomized trials they have all been shown to be superior to chemotherapy with a median PFS of about 11 months. Osimertinib was recently compared to erlotinib and gefitinib in the first-line setting of *EGFR*-mutated NSCLC. Osimertinib demonstrated superior progression-free survival (18.9 vs 10.2 months) with fewer serious adverse effects, therefore it is now considered the preferred first-line agent.[15,47] Ultimately, all patients have a recurrence and the most common acquired mutation conveying resistance to EGFR-targeted TKIs is *T790M*. Upon recurrence patients should be tested for this mutation and those who are positive should be treated with osimertinib, which is active against this gatekeeper mutation, if they have not received osimertinib in the first-line setting. A prospective randomized trial compared second-line osimertinib to a platinum doublet. The results showed that osimertinib was superior in terms of ORR (71% vs 31%) and PFS (10.1 vs 4.4 months); however, the overall survival data were not mature at the time of analysis.[48]

ALK mutation positive patients should be treated with alectinib. Recently second-generation alectinib was studied head to head with crizotinib and demonstrated superiority. The median PFS with crizotinib was just 10.4 months (similar to previous trials), compared to 25.7 months with alectinib.[49] Moreover, the 5 year survival rates were 63% and 46% for alectinib and crizotinib, respectively. Ceritinib, another second-generation ALK inhibitor was approved as first-line therapy based on a trial showing its superiority to chemotherapy. In that trial the ceritinib PFS was 16.6 months.[50] Brigatinib is approved as second-line therapy for patients who have failed crizotinib.[51] *In vitro* studies suggest that it is active against resistance mutations, but the clinical significance of this is unknown. Lorlatinib is the most recently approved ALK inhibitor and demonstrates activity against resistance mutations and has good CNS penetration to reach brain metastases.[52] Ceritinib, alectinib, brigatinib, and lorlatinib are all approved as second-line options and the selection of therapeutic agent should be based on avoiding the agent used in the previous line of therapy.

A small number of lung cancer patients (~1%) harbor a mutation in *BRAF*, where dabrafenib with trametinib are indicated. A pivotal single arm, phase II trial enrolled 57 previously treated patients and reported an overall response rate of 63%. The progression-free survival for this trial was 9.7 months with a median duration of response of 9 months. Although large randomized trials are lacking, nonrandomized comparison of dabrafenib to dabrafenib plus trametinib support the combination based on ORR (27% vs 63%), and duration of response (9.9 vs 12.6 months).[53,54] For this population, dabrafenib with trametinib is recommended to be used first line. The other *BRAF* and *MEK* inhibitors do not have enough data to be used in this setting at this time. When patients fail dabrafenib and trametinib, they should be treated similarly to patients with no targetable mutations (Figure 90–2).

The *NTRK* driver mutation is found in less than 0.5% of NSCLC patients, but is targetable by tropomyosin receptor kinase (TRK)

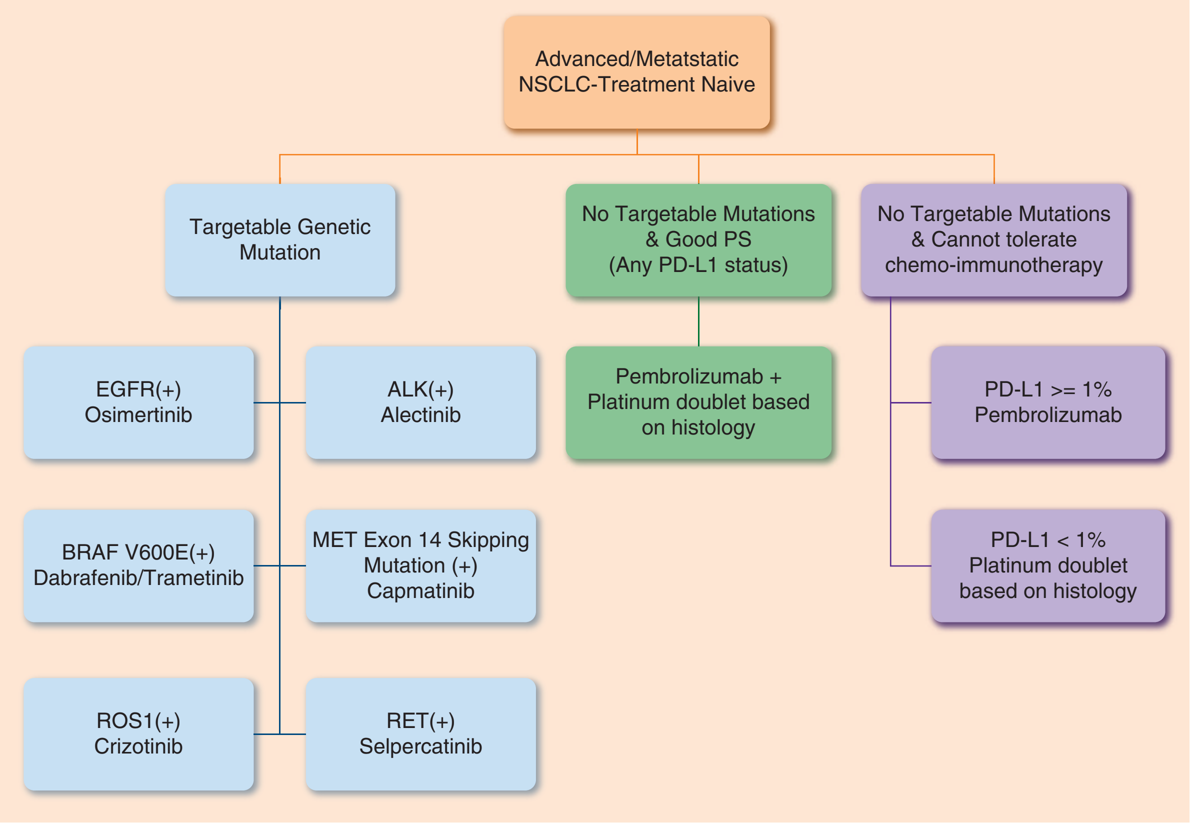
Advanced/Metatstatic NSCLC-Treatment Naive
Targetable Genetic Mutation
No Targetable Mutations & Good PS (Any PD-L1 status)
No Targetable Mutations & Cannot tolerate chemo-immunotherapy
EGFR(+) Osimertinib
ALK(+) Alectinib
BRAF V600E(+) Dabrafenib/Trametinib
MET Exon 14 Skipping Mutation (+) Capmatinib
ROS1(+) Crizotinib
RET(+) Selpercatinib
Pembrolizumab + Platinum doublet based on histology
PD-L1 >= 1% Pembrolizumab
PD-L1 < 1% Platinum doublet based on histology

FIGURE 90–2. First-line treatment algorithm with preferred agents for advanced stage NSCLC based on biomarkers, genetic mutations, and histology. (NSCLC, non–small cell lung cancer; PD-L1, PD-1 targeting immunotherapy; EGFR, Epidermal Growth Factor Receptor; ALK, Anaplastic Lymphoma Kinase; MET, C-mesenchymal-epithelial transition factor; RET, rearranged during transfection.)

inhibitors. The presence of *TRK* mutations in other tumor types, including salivary gland cancers, sarcomas, and thyroid cancers, led to the FDA approval of larotrectinib for any *TRK* mutation positive cancers, making it the first oral anticancer therapy with an indication that is agnostic to tissue type or anatomical location.[55] Both larotrectinib and entrectinib have shown response rates between 75% and 80% when used as monotherapy in *NTRK* positive advanced NSCLC patients.

Patients whose tumors harbor an *ROS1* mutation should be treated with crizotinib. Since this mutation is only present in ~1% of tumors it is relatively uncommon and randomized controlled trial data are lacking. Studies have reported 70% to 80% response rates in ROS1 positive patients receiving crizotinib.[56] Other first-line agents include ceritinib and entrectinib, though neither have matched crizotinib's response rate, and lorlatinib is approved for patients with a ROS1 mutation in the second line setting.[15]

For patients with a *MET* mutation, capmatinib and tepotinib are FDA approved targeted therapy. The phase II GEOMETRY trial showed a 71.4% response rate in patients receiving capmatinib with a reported 9 months PFS.[57,58] Additionally, 54% patients with brain metastases who enrolled in GEOMETRY, saw improvement of those brain metastases on study.

Selpercatinib and pralsetinib targeted options for patients with *RET* rearrangements.[59] In a phase I/II trial, first-line therapy with selpercatinib showed an overall response rate of 85%, patients receiving selpercatinib after progressing on chemotherapy showed an almost 70% overall response rate and a median PFS of just over 18 months.[60] Selpercatinib also showed good CNS penetration with 91% of patients who enrolled with brain metastases showing a response to therapy.

For advanced NSCLC patients with no targetable mutations, first-line chemotherapy with a platinum-based doublet is the most commonly used regimen. Patients with stage IIIB or IIIC disease should receive concurrent chemotherapy and radiation, followed by therapy with durvalumab if unresectable disease.[15] Historically, four to six cycles of a platinum-based doublet regimen were used, with an overall response rate of 25% to 35% and 1-year survival rates of 30% to 40%. The PACIFIC trial, which studied the effects of adding maintenance durvalumab to concurrent chemoradiation in patients with stage III unresectable disease, found that durvalumab maintenance therapy had a 2-year overall survival rate of 66%, compared to the placebo maintenance arm at 55%.[61] These data strongly support the use of durvalumab maintenance therapy in advanced, unresectable NSCLC. However, durvalumab therapy is not recommended in patients who have definitive surgical resection. Consolidation chemotherapy (two additional cycles of chemotherapy after concurrent chemoradiation) is an option in patients who are not candidates for consolidation therapy with durvalumab. However, concurrent chemotherapy and durvalumab is not recommended in this setting due to increased risk of pneumonitis. Cisplatin and etoposide are an example of a preferred platinum doublet that can be given with radiotherapy, though many combinations have been studied. Guideline recommended platinum doublets that are considered equivalent and key trials are listed in Table 90–3.

For metastatic patients with nonsquamous NSCLC and no targetable mutational drivers, pembrolizumab with a platinum and pemetrexed chemotherapy doublet is the preferred regimen, regardless of tumor PD-L1 expression, unless there are contraindications to ICI therapy. The addition of pembrolizumab to a platinum and pemetrexed doublet chemotherapy regimen demonstrated a median progression-free survival that was 4 months longer than chemotherapy with placebo, and median overall survival of 22 versus 10.7 months, respectively.[62] If PD-L1 expression is greater than equal to 50% (NCCN category 1) or between 1% and 49% (category 2B), then pembrolizumab monotherapy may be considered. Other acceptable chemoimmunotherapy regimens, irrespective of PD-L1 expression levels, include atezolizumab with carboplatin/paclitaxel/bevacizumab or carboplatin/albumin-bound paclitaxel, or dual immunotherapy with nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor). In patients with contraindications to ICI therapy, combination chemotherapy with or without bevacizumab are acceptable options. The addition of bevacizumab to carboplatin and paclitaxel improved survival by 2 months (median OS = 12.3 months); however, the survival curve did not plateau at the end, indicating that lung cancer deaths were delayed and not prevented.

Patients who progress after first-line therapy will benefit from second-line therapy. The choice of therapy depends on prior therapies, comorbidities, PS, PD-L1 status, and mutation status. For those not previously treated with immunotherapy, the preferred second-line therapy is a PD1 or PD-L1 inhibitor. Second-line treatment with atezolizumab, nivolumab, or pembrolizumab improved overall survival by 2 to 4 months when compared to docetaxel (the prior standard).[15] If patients received immunotherapy in the first-line setting, their subsequent treatment options include docetaxel, pemetrexed, ramucirumab + docetaxel and gemcitabine. For patients treated with front-line chemoimmunotherapy, second-line treatment with docetaxel would be the standard and adding ramucirumab could be considered. The pivotal study that led to FDA approval of ramucirumab in this setting reported a statistically significant overall survival benefit (10.5 vs 9.1 months); however, the clinical significance of this difference is questionable and this has not become a clear standard of care.

Patients with squamous NSCLC are treated similarly to nonsquamous NSCLC with several notable exceptions. As mentioned earlier, pemetrexed does not provide benefit for this population and should be avoided. Similarly, bevacizumab is not recommended for patients with squamous histologic subtype, due to an increased risk of hemoptysis. Based on secondary endpoints, it appears that a platinum-gemcitabine or platinum-paclitaxel regimen are effective chemotherapy regimens. Immune checkpoint monotherapy, combination chemoimmunotherapy, or dual immunotherapy are treatment options as in nonsquamous NSCLC.[15]

▶ *Special Populations*

Patients who cannot tolerate platinum agents can be treated with gemcitabine-paclitaxel or gemcitabine-docetaxel. Randomized trials have produced response durations and survival times similar to the platinum-containing doublet regimens. However, these regimens are only recommended for patients who are unlikely to tolerate the toxicity of platinum regimens owing to comorbidities or other factors.[15]

Patients with poor PS, defined as those with a PS of 2 or greater, is a subject of debate. Although patients with a PS of 2 typically have inferior survival rates and increased treatment toxicity than higher performing patients, low-toxicity single-agent regimens may offer a survival advantage in this subset. Use of these regimens also presents a method of providing symptomatic care for advanced stage patients. Agents such as pemetrexed, gemcitabine, and docetaxel may be used in this scenario. In patients with a PS of 3 or 4, chemotherapy typically results in high rates of toxicity and without a significant survival benefit. Consequently, treatment should be reserved for cases where it may provide symptomatic relief. Because targeted agents typically have lower rates of severe toxicity, they also have been used in appropriate subsets of patients with a poor PS (ECOG PS of 2 or 3). Unfortunately, there is not adequate clinical trial data regarding the efficacy and toxicity of immunotherapy or targeted agents in these patients. In summary, patients with poor PS should not be treated with combination chemotherapy with or without targeted agents because of historically high rates of toxicity and no evidence of survival benefit. Single-agent therapy is associated with less toxicity and can be used to help palliate symptoms.[15]

▶ *Duration of Therapy*

Because advanced stage lung cancer is not curable, therapeutic goals should include extending the number of quality days, rather than just overall survival. With this in mind and the assumption that quality of life is lower while receiving chemotherapy, it is important to consider the duration of treatment. Over the last decade, treatment has moved toward fewer chemotherapy cycles. Typical cytotoxic doublet therapy regimens have decreased from eight planned cycles to four cycles with the option of two additional cycles if treatment is well tolerated.[15] However, maintenance therapy with a single cytotoxic chemotherapy, targeted therapy, or immunotherapy agent has become the standard.[15]

The duration of therapy for NSCLC also depends on the presence/absence of biomarkers and the agents that are used. For patients without a targetable genetic mutation the duration is determined by the order in which patients received therapies. Patients receiving first-line immunotherapy, with or without chemotherapy, should receive maintenance immunotherapy for 2 years or the development of intolerable side effect. Patients receiving immunotherapy in the second-line or later setting can receive immunotherapy maintenance until progression or the development of intolerable side effects. All of the targeted therapies (oral TKIs) for targetable mutational drivers are continued until disease progression or unacceptable toxicity. At this point, subsequent therapy will be determined based upon the mutation in question, the presence or absence of brain metastasis, and the presence or absence of symptoms and adverse effects. It is possible that patients will continue with the same targeted therapy agent after progression, or may be switched to a different agent within the same class. However, in general, patients will typically remain on a therapy that targets their specific mutation until intolerable side effects. Additionally, any patient with a targetable mutation may switch over to cytotoxic chemotherapy if necessary. However, this is reserved for cases that appear to be refractory to targeted agents and in whom cytotoxic chemotherapy is not contraindicated due to comorbidities or performance status.

In summary, the duration of therapy depends highly on treatment pathway, histology, and initial therapy; cytotoxic chemotherapy rarely exceeds six cycles, while monotherapy and targeted therapies are commonly administered until disease progression except in patients with squamous cell histology, in whom switch maintenance therapy is an option. This involves rotating or switching between monotherapy maintenance options based on patient performance status, history of adverse events, and response to therapy.

Treatment of Small-Cell Lung Cancer

SCLC typically presents as extensive disease (approximately 60%–70% of new cases) and progresses very quickly. SCLC is very responsive to chemotherapy and radiation but has a short

Patient Encounter Part 3

The patient is treated with pembrolizumab 200 mg IV q3 weeks as first-line treatment. Six weeks after starting therapy a repeat CT scan is performed, which shows that the primary 3 cm lesion is now 5 cm in diameter.

Does that mean he has progressed on this treatment?

Discuss how this influences assessment moving forward and propose a treatment and monitoring plan.

duration of response. Radiotherapy became the standard in 1969, when a randomized trial showed that it offered the potential for cure, whereas surgery did not.[63] In the vast majority of patients, chemotherapy, augmented with either radiotherapy or immunotherapy is the treatment of choice. Even after a complete response to therapy, the cancer usually recurs within 6 to 8 months and the survival time following recurrence is short (approximately 4 months). This yields an average survival rate of 24 to 30 months for limited disease and 10 to 13 months for extensive disease.[37]

▶ *Limited Disease*

The regimen of choice for limited-disease SCLC is etoposide with cisplatin. In patients who are able to tolerate combined modality therapy, concomitant chemoradiotherapy offers the greatest survival benefit. Carboplatin may be substituted for cisplatin in patients who cannot tolerate cisplatin toxicity. Cisplatin is associated with significantly more nephrotoxicity and more emetogenicity than carboplatin. Cisplatin is preferred over carboplatin because of a small study that randomized patients to cisplatin or carboplatin plus etoposide. There was a numerically higher complete response rate with cisplatin, which is believed to be requisite for cure. Consequently, the guidelines recommend that the etoposide-platinum regimen be used with concurrent radiotherapy.[37]

Because patients with SCLC commonly have a recurrence in the CNS, trials have been performed to evaluate the benefit of prophylactic cranial irradiation. A pivotal study showed that prophylactic cranial irradiation reduces the incidence of brain metastasis and increases the 3-year survival rate from 15% to 21%.[64] Patients with limited-stage SCLC who achieve a complete response with treatment should be offered prophylactic cranial irradiation.

▶ *Extensive Disease*

In the first-line setting, etoposide-platinum doublet, combined with either atezolizumab or durvalumab is the treatment of choice for extensive disease. Carboplatin is commonly used in place of cisplatin because it is generally thought to have less toxic and demonstrated similar outcomes in progression-free survival and overall survival. The choice of atezolizumab or durvalumab appears to be of little clinical consequence as each showed similar outcomes of 12.3 and 13 months of overall survival, respectively, for first-line treatment of extensive-stage SCLC. At this time there is not thought to be any meaningful difference in the adverse event profile between these two PD-L1 inhibitors and either agent in combination with etoposide-platinum are considered to be preferred regimens.[37] Patients with contraindications to ICI therapy can be treated using these doublet chemotherapy regimens without the PD-L1 inhibitor.

Patient Encounter Part 4

The patient's condition has caused symptoms and periodic interruptions to his tasks, but he has been able to work and complete daily activities up to this point.

What is this patient's ECOG PS score?

Are there any nonpharmacologic interventions you would suggest?

Concurrent radiotherapy is not used routinely in extensive disease; however, prophylactic cranial irradiation provides significant benefit in patients responding to systemic treatment. A pivotal study demonstrated that median survival from the time of randomization increased from 5.4 to 6.7 months and 1-year survival rates increased from 13.3% to 27.1% with prophylactic cranial irradiation.[65] An additional benefit was a lower rate of brain metastases (14.6% vs 40.4%), thought this has not been tested with the addition of immunotherapy to the front-line setting.

▶ *Recurrent Disease*

The treatment of recurrent SCLC depends on the time to recurrence. If the time to recurrence is less than 6 months, nonplatinum based second-line therapy should be considered if the patient has an acceptable PS (0–2) (see Patient Care Process). The most widely accepted second-line therapies in SCLC are topotecan and lurbinectedin, although other acceptable options include nivolumab with or without ipilimumab, pembrolizumab, paclitaxel, docetaxel, irinotecan, oral etoposide, and others. Lurbinectedin is new cytotoxic agent, approved for use in small-cell lung cancer in 2020. This alkylating agent binds to DNA and bends the helix towards the minor groove, disrupting the actions of some transcription and DNA repair pathways.[66] Relapses occurring more than 6 months after treatment warrant a repeat of the initial platinum-based regimen, or lurbinectedin. Patients with a poor PS (3–4) are typically managed with best supportive care, including palliative therapies.[37]

▶ *Duration of Therapy*

For patients with limited stage SCLC, four to six cycles of cytotoxic chemotherapy with radiation is the standard of care. First-line treatment beyond six cycles has not been shown to be beneficial.[37] However, in patients with extensive-stage disease, the standard of care has shifted to four cycles of cytotoxic chemotherapy with an immunotherapy agent, followed by single agent immunotherapy maintenance until disease progression or unacceptable toxicity.[37] Second-line therapy, regardless of stage, is generally continued until progression or intolerable toxicity.

OUTCOME EVALUATION IN LUNG CANCER

Evaluating outcomes is a goal-oriented process and should begin from that perspective. Patients with localized disease are treated with localized therapy with or without systemic therapy, with curative intent as the goal. Monitoring for toxicity and response on a regular basis is essential.

Following surgery or pharmacologic treatment, the patient should be monitored regularly to detect recurrence or progression of disease. Methods include a physical examination and chest X-ray every 3 to 4 months for 2 years. If no disease is detected during this time, follow-up frequency can be prolonged to every 6 months for 3 years and then annually. Low-dose spiral CT scanning is also recommended annually.[15]

For patients who have advanced stage disease, response of target lesions is performed with a radiologic scan every 6 to 12 weeks. Response Evaluation Criteria in Solid Tumors (RECIST)[67] are applied to classify response as follows: complete remission (CR) is complete disappearance of tumor, partial remission (PR) is a reduction in target tumor volume in unilateral diameters by 30% or more, progressive disease (PD) is defined as new lesions or a growth of the target lesion diameter by more than 20%, and stable disease (SD) is defined by not meeting the PR or PD criteria. These criteria have been modified for patients on immunotherapy because the checkpoint inhibitors have a delayed time to antitumor effect due to their mechanisms of action. The process for T-cell activation against tumors, migration to and infiltration of tumor tissue, and then exertion of tumoricidal activity requires more time than the direct cytotoxic and antiproliferative effects typical of traditional chemotherapies. Moreover, immune activation by immunotherapies may transiently increase cellular mass and inflammation-related edema, causing tumors to appear larger on radiologic evaluation prior to observations of antitumor responses. The revised guidelines most commonly used in this scenario is the immune RECIST (iRECIST).[68] The primary difference is that the first progression based on RECIST is considered an immune Unconfirmed Progressive Disease (iUPD). The confirmatory radiology would then occur 4 to 8 weeks later and PD is confirmed if target lesions continue to grow. If they do not grow or shrink to any degree, it would become the new set point and repeat radiologic assessments would reevaluate for iUPD prior to having confirmed PD.[68]

Smoking cessation counseling with or without pharmacologic treatment should be a priority. Although studies have shown that patients who continue to smoke through treatment in NSCLC do not perform more poorly compared with those that quit before treatment, those who respond to treatment and continue to smoke probably have an increased risk of developing secondary malignancies.[69] In contrast to NSCLC, data in SCLC patients suggests increased toxicity in those who continue to smoke during treatment.[37]

For those with advanced disease, the goal of treatment is to prolong the duration of life, particularly the number of quality days. Ultimately, most lung cancer patients succumb to their disease or related complications. Palliative care focuses on the management of symptoms and improvement of quality of life. Symptomatic metastases can be removed by surgery (depending on location) or can be treated with radiotherapy to reduce tumor size. In selecting options in this setting, it is important to keep the goals of therapy (ie, maximizing the duration and quality of life) in mind. Low-toxicity single-agent chemotherapy, targeted therapy, and best supportive care (including fatigue and pain management) may all be employed to attempt to prolong quality days of life in the advanced disease population.

COST-EFFECTIVENESS AND QUALITY OF LIFE CONSIDERATIONS

Cancer treatments such as the molecular and immune targeted therapies currently are much more expensive than traditional chemotherapy. Where there is a clear survival benefit, they should be used over traditional chemotherapy. However, where the efficacy benefit is marginal or minor, cost-effectiveness should be considered because they can pose long-term financial burdens for patients and their families. This is especially the case when immunotherapy is added to another regimen which adds not only significantly more cost but also more toxicities. In cost-effectiveness analyses of pembrolizumab plus chemotherapy versus chemotherapy the incremental cost-effectiveness ratio

Patient Care Process

Collect Information:

- Determine stage and histology of cancer.
- Perform PD-L1 expression and mutation analysis if advanced disease.

Assess the Information:

- Comorbidities and organ and hematological function.
- Starting doses and schedules of planned treatment regimen.
- Need for supportive care therapies.

Develop a Care Plan:

- Ensure the patient has access and insurance coverage for chemotherapy and supportive therapies.
- Educate the patient on expected outcomes, potential adverse effects, and their management.

Implement the Care Plan:

- Evaluate the appropriateness of a patient's regimen at every visit (every week, 3 weeks, or 4 weeks).
- Inquire about toxicity and quality of life issues.
- Include a medication reconciliation process.
- Laboratory and/or radiology evaluations can be prompted by the initial assessment or at a scheduled interval for the treatment regimen.
- Findings of tumor growth or significant toxicity should prompt a change in the therapeutic plan.
- Grade and monitor toxicity—Grade 3 or 4 toxicity (see Chapter 88) requires a change in therapy with the next cycle of treatment. Common changes include a chemotherapy dose reduction or pharmacologic intervention to prevent or treat the toxicity.
- Manage toxicity—*Knowing when and how to treat adverse events from therapy is an important aspect of patient care. Unmanaged events may cause delays in therapy administration and reduced therapy doses and may contribute to treatment failure.* This includes managing neutropenic episodes (see Chapter 99) and chemotherapy-induced nausea and vomiting (see Chapter 99). The emetogenic potential of selected chemotherapy regimens is listed in Chapter 99. For patients on immunotherapy, they must be monitored for immune-related adverse events with early recognition and intervention (see Chapter 88).
- Counsel patients on appropriate use and adherence of oral medications.

Follow-up: Monitor and Evaluate:

- Monitor for recurrence. Follow recommendations of the NCCN, as outlined in Outcome Evaluation.
- Smoking cessation plans. For NSCLC patients, all long-term care plans should include options and recommendations for smoking cessation (see Chapter 36).

(ICER) for the combination regimen was $86,293 to $104,823/quality-adjusted life year (QALY).[70,71] This can be considered cost-effective using either the World Health Organization threshold of $180,000/QALY[71,72] or the traditional USA threshold of $100,000/QALY.[73] The chemo-immunotherapy combination was shown to extend life expectancy in tumors with PD-L1 greater than equal to 50% compared with pembrolizumab monotherapy at an ICER of $147,365/QALY and $118,879/life years, respectively.[70] However, cost-analysis of atezolizumab plus bevacizumab plus chemotherapy versus chemotherapy reported an ICER of $568,967/QALY and $516,114, respectively,[74] suggesting that this may not be cost effective. While additional cost-effectiveness and quality of life studies are needed, these are factors that warrant discussion with the patient when potential efficacy benefits are marginal and treatment toxicities may diminish quality of life.

Abbreviations Introduced in This Chapter

5-FDG	5-Fluorodeoxyglucose
ALK	Anaplastic lymphoma kinase
BRAF	A proto-oncogene kinase that is a sarcoma viral oncogene homolog B
CT	Computed tomography
CTLA-4	Cytotoxic T-Lymphocyte Antigen 4
ECOG	Eastern Cooperative Oncology Group
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EML4	Echinoderm microtubule-associated protein-like 4
EP	Etoposide-cisplatin
ETS	Environmental tobacco smoke
ICI	Immune Checkpoint Inhibitor
Met	c-Mesenchymal-Epithelial Transition Factor
NSCLC	Non–small cell lung cancer
NTRK	Neurotrophic-tropomyosin receptor kinase or neurotrophic tyrosine receptor kinase
PD1	Programmed cell death protein 1 receptor
PD-L1	Programmed death ligand 1 (aka B7-H1 and CD274)
PET	Positron-emission tomography
PS	Performance status
RET	Rearranged during transfection
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	ROS Proto-Oncogene 1, Receptor Tyrosine Kinase
SCLC	Small-cell lung cancer
TNM	Tumor, node, and metastasis staging
TRK	Tropomyosin Receptor Kinase
VEGF	Vascular endothelial-derived growth factor

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91 Colorectal Cancer

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Identify the risk factors for colorectal cancer.
2. Outline preventive and screening strategies for individuals at average and high risk for colorectal cancer.
3. Recognize the signs and symptoms of colorectal cancer.
4. Describe the treatment options for colorectal cancer based on patient-specific factors, such as stage of disease, age of patient, genetic mutations, and previous treatment received.
5. Outline the pharmacologic principles for agents used to treat colorectal cancer.
6. Develop a monitoring plan to assess the efficacy and toxicity of agents used in colorectal cancer.
7. Educate patients about the adverse effects of chemotherapy that require specific patient counseling.

INTRODUCTION

Colorectal cancer is one of the four most common cancers diagnosed in the United States and includes cancers of the colon and rectum. In 2021, an estimated 149,500 new cases of colorectal cancer are expected to be diagnosed, with an estimated 52,980 deaths expected, making colorectal cancer the second leading cause of cancer-related deaths in the United States.[1] The prognosis is primarily determined by the stage of disease with the majority of patients with early stage (I or II) disease cured. Treatment options for colorectal cancer include surgery, radiation, chemotherapy, and targeted molecular therapies.

EPIDEMIOLOGY AND ETIOLOGY

Colorectal cancer occurs more frequently in industrialized regions such as North America and Europe, while the lowest rates are seen in less-developed areas, suggesting that environmental and dietary factors influence the development of colorectal cancer. In addition to environmental factors, colorectal cancers develop more frequently in certain families, and genetic predisposition to this cancer is well known.

The incidence of colorectal cancer in men is approximately 1.2 times greater than observed in women. Overall, colon and rectal cancers make up approximately 7.9% of all cancer diagnoses in men and women in the United States. The median age at diagnosis is 67 years with few cases occurring in individuals younger than 45 years of age.[2] KEY CONCEPT Age appears to be the biggest risk factor for the development of colorectal cancer with 56% of cases diagnosed in adults older than 65 years of age.

Although still the second leading cause of cancer death, mortality rates for colorectal cancer have declined over the past 30 years as a result of better and increasingly used screening modalities and more effective treatments.

RISK FACTORS

In addition to age, dietary or environmental factors, inflammatory bowel disease, and genetic susceptibility increase the risk of colorectal cancer. Table 91–1 lists well-known risk factors for developing colorectal cancer.

KEY CONCEPT Diets high in fat and low in fiber are associated with increased colorectal cancer risk. While data are not entirely consistent, long-term consumption of red and processed meats is associated with an increased risk of colorectal cancer. A large pooled analysis of 13 prospective cohort studies found dietary fiber intake to be inversely associated with the risk of colorectal cancer; however, upon multivariate analysis for other dietary risk factors, the benefit was no longer observed.[3] This analysis does not consider the known benefits of a fiber-rich diet for noncancerous conditions such as diabetes and coronary artery disease.

Foods that are high in fiber include vegetables, fruit, and grains. The protective effects of fiber may be a result of reduced absorption of carcinogens in the bowel, reduced bowel transit time, or a reduction in dietary fat intake associated with high-fiber diets.[3]

Physical inactivity and elevated body mass index (BMI) are associated with up to a twofold increase in the risk of colorectal cancer. Increasing physical activity, decreased bowel transit time and exercise-induced alterations in body glucose, insulin levels, and other hormones may reduce tumor cell growth.[4,5] Type 2 diabetes mellitus, independent of body mass size and physical activity level, is also associated with an increased risk of colorectal cancer in women and supports a role for hyperinsulinemia as a possible link between obesity, sedentary lifestyle, diabetes mellitus, and colorectal cancer.[5] Additional lifestyle choices that increase the risk of colorectal cancer include alcohol consumption and smoking, which may increase the risk of colorectal cancer by generating carcinogens with direct toxic effects on bowel tissue.[4]

Table 91–1

Risk Factors for Colorectal Cancer

Risk Factors for Colorectal Cancer
General
Age is the primary risk factor
Dietary
High-fat, low-fiber diets
Lifestyle
Alcohol
Smoking
Obesity or physical inactivity
Comorbid Conditions
Inflammatory bowel disease (ulcerative colitis and Crohn disease)
Hereditary or Genetic
FAP and HNPCC
Family history

FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer.

Patient Encounter Part 1

A 67-year-old man presents to your clinic with a chief complaint of bloating and distention, abdominal discomfort, and intermittent changes in his bowel movements over the past 3 to 4 months. He has a medical history positive for type 2 diabetes mellitus, hyperlipidemia, diabetic neuropathy, and obesity. He states that he quit drinking alcohol almost 30 years ago but is a current smoker (50-pack-year history). He reports he used to eat healthy until his wife passed away almost 10 years ago. Currently his diet mostly consisted of red meats and processed foods. He reports that he hasn't exercised in years.

What risk factors does this patient have for colon cancer?

Does he have clinical symptoms suggestive of colon cancer?

What additional tests need to be ordered to diagnosis colon cancer?

Inflammatory bowel diseases, such as chronic ulcerative colitis, particularly when it involves the entire large intestine, and to lesser extent Crohn disease, confer increased risk for colorectal cancer. Overall, individuals with inflammatory bowel disease account for about 1% to 2% of all new cases of colorectal cancer each year.

Finally, as many as 10% of cases are thought to be hereditary. The two most common forms of hereditary colorectal cancer are familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC). FAP is a rare autosomal dominant trait that is caused by mutations of the **adenomatous polyposis coli (*APC*)** gene and accounts for 1% of all colorectal cancers. The disease is manifested by hundreds to thousands of **polyps** arising during adolescence.[6] The risk of developing colorectal cancer for individuals with untreated FAP is nearly 100%, and patients require early screening for the disease and likely a prophylactic total colectomy. HNPCC, also an autosomal dominant syndrome, accounts for up to 5% of colorectal cancer cases.[6] In contrast to FAP, juvenile polyps occur rarely, and the average age of colorectal cancer in these patients is closer to that of average-risk patients, with most patients diagnosed in their 40s. Testing for HNPCC mutations is available but reserved for individuals who meet diagnostic criteria.

Up to 20% of patients who develop colorectal cancer have a family history of colorectal cancer unrelated to a mutation described earlier.[7] First-degree relatives of patients diagnosed with colorectal cancer have an increased risk of the disease that is at least two to four times that of persons in the general population without a family history.

Summary of Risk Factors

In summary, the true association between most dietary factors and the risk of colorectal cancer is unclear. The protective effects of fiber and a diet low in fat are not completely known at this time. Physical inactivity, alcohol use, and smoking appear to increase the risk of colorectal cancer. Certain genetic mutations are well-known risks for colorectal cancer.

SCREENING

KEY CONCEPT Effective colorectal cancer screening programs incorporate annual fecal occult blood testing or regular examination of the entire colon starting at age 45 years for average-risk individuals and should be recommended by all healthcare providers. Appropriate screening of patients at normal and high risk for colorectal cancer leads to the detection of smaller, localized lesions and higher cure rates.[8] Screening techniques include fecal occult blood tests (FOBTs) and imaging of the colon. The use of FOBTs annually in combination with digital rectal examinations has led to the diagnosis of early stages of disease and may reduce colorectal cancer mortality by up to one-third.[8] However, FOBT using a single stool sample collected during a digital rectal examination is not a recommended option for screening because this method has a decreased sensitivity for detecting advanced disease. Recommendations for adequate FOBT require the patient to collect two stool samples from three consecutive specimens using at-home testing procedures.[8] Two main methods are available to detect occult blood in the feces: guaiac dye and immunochemical methods. The Hemoccult II is the most commonly used FOBT in the United States and is a guaiac-based test. Proper counseling by healthcare providers is required to receive accurate test results. Consumption of red meat, blood sausages, peroxidase-containing vegetables, iron products, or nonsteroidal anti-inflammatory drugs (NSAIDs) may result in false-positive results. Vitamin C and dehydrated samples may lead to false-negative results. These products should be avoided for 3 days prior to testing. Fecal immunochemical tests (FITs) (InSure and others), which use antibodies to detect hemoglobin, are also available for use. Though more expensive, an advantage of FITs is that they do not react with dietary factors or medications. Both FOBTs can be recommended in screening protocols for patients.

Imaging of the colon with a sigmoidoscopy, colonoscopy, or CT colonography is recommended every 5 to 10 years for most individuals. Colonoscopy is the preferred procedure as it allows for greater visualization of the entire colon and simultaneous removal of lesions found during screening.[8] A sigmoidoscopy only examines the lower half of the colon. Several revisions to the colorectal cancer screening guidelines have been made in an attempt to increase the compliance to screening guidelines. These include the use of computed tomographic colonography (CTC) and stool DNA testing as acceptable screening methods. CTC, also known as "virtual colonoscopy," uses integrated two- and three-dimensional images to detect and characterize polyps. Although noninvasive compared with colonoscopy, adequate bowel preparation, which is often cited as the reason for noncompliance, is still required. In addition, any lesions found on examination require a follow-up colonoscopy.

Table 91–2

Colon Cancer Screening Guidelines

Average risk	Annual FOBT or FIT after age 45 years Stool DNA testing may be used as an alternative *or* One of the following after age 45 years: Sigmoidoscopy every 5 years Colonoscopy every 10 years CTC every 5 years
Family history	Screening at ages 40 years or 10 years before the youngest case in the immediate family, whichever is earlier
HNPCC	Screening at age 20–25 years or 10 years before the youngest case in the immediate family, whichever is earlier
FAP	Screening at ages 10–12 years
IBD	8 years after the onset of pancolitis; 12–15 years after onset of left-sided colitis

CTC, computed tomographic colonography; FAP, familial adenomatous polyposis; FIT, fecal immunochemical tests; FOBT, fecal occult blood tests; HNPCC, hereditary nonpolyposis colorectal cancer; IBD, inflammatory bowel disease.

Multitarget stool DNA tests with fecal immunochemical testing detect molecular markers (KRAS and methylation biomarkers) as well as FIT for hemoglobin. Advantages of this test are it can be done at home, requires only a single stool collection, and is recommended once every 3 years. However, like virtual CT, positive tests require follow-up colonoscopy. KEY CONCEPT Table 91–2 is a summary of the current NCCN guidelines for screening and surveillance for early detection of colorectal polyps and cancer.[8]

COLORECTAL CANCER PREVENTION

There are currently no pharmacologic agents approved for colorectal cancer prevention. Strategies under investigation to prevent colorectal cancer include pharmacologic and surgical interventions and involve either preventing the initial development of colorectal cancer (primary prevention) or preventing cancer in patients who demonstrate early signs of colorectal cancer (secondary prevention).

The most widely studied agents for the chemoprevention of colorectal cancer are agents that inhibit cyclooxygenase-2 (COX-2) (aspirin, NSAIDs, and selective COX-2 inhibitors) and calcium supplementation.[9] Individual studies have demonstrated that regular (at least two doses per week) NSAID and aspirin use is associated with a 20% to 40% reduction in risk of colorectal cancer in individuals at average risk.[10,11] However, a meta-analysis of over 40 trials suggests the benefit of these agents may be limited to individuals at high risk for developing colorectal cancer.[12] Chronic use of aspirin and other NSAIDs are associated with significant potential adverse effects, including gastrointestinal (GI) and cardiovascular toxicities. These risks limit healthcare professionals from making routine recommendations for use in patients of average risk for colorectal cancer.

The risk of colorectal cancer appears to be inversely related to calcium and folate intake. Calcium supplementation appears to be associated with a moderate reduction in risk of recurrent colorectal adenomas with prospective studies demonstrating a nonstatistical decrease in adenoma recurrence, its role as a chemoprevention agent in the average-risk patient remains under investigation.[9,12]

Exogenous hormone use, particularly postmenopausal hormone replacement therapy, is associated with a significant reduction in colorectal cancer risk in most studies with the greatest benefit in women who are on current hormone replacement therapy.[13] Unfortunately, the known risks of hormone replacement therapy outweigh this benefit, and routine use of hormone replacement therapy to prevent colorectal cancer is not recommended.

Surgical resection remains an option to prevent colorectal cancer in individuals at extremely high risk for its development such as patients diagnosed with FAP. Individuals with FAP who are found to have polyps on screening examinations require total abdominal colectomy. In addition, removal of noncancerous polyps detected during screening colonoscopy is considered the standard of care to prevent the progression of premalignant polyps to cancer.

PATHOPHYSIOLOGY

Anatomy and Bowel Function

The large intestine consists of the cecum; ascending, transverse, descending, and sigmoid colon; and rectum (Figure 91–1).

Four major tissue layers, from the lumen outward, form the large intestine: the mucosa, submucosa, muscularis externa, and serosa. Complete replacement of surface epithelial cells occurs every 7 to 10 days with the total number of epithelial cells remaining constant in normal colonic tissue. As patients age, abnormal cells accumulate on the surface epithelium and protrude into the stream of fecal matter; their contact with fecal mutagens can lead to further cell mutations and eventual adenoma formation.[6]

Colorectal Tumorigenesis

The development of a colorectal neoplasm is a multistep process of several genetic and phenotypic alterations of normal bowel epithelium leading to unregulated cell growth, proliferation, and tumor development. A genetic model has been proposed for colorectal tumorigenesis that describes a process of transformation from adenoma to carcinoma. This model of tumor development reflects an accumulation of mutations within colonic epithelium that gives a selective growth advantage to the cancer cells.[6] Genetic changes include activating mutations of oncogenes,

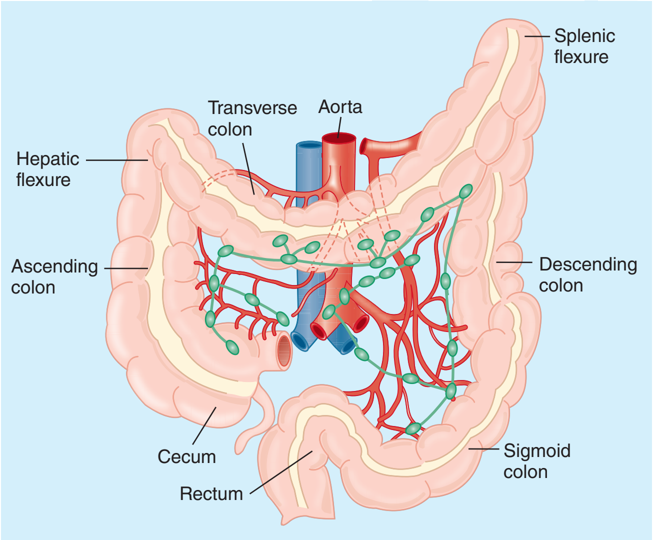

FIGURE 91–1. Colon and rectum anatomy. (From Davis LE, Sun W, Medina PJ. Colorectal Cancer. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill, 2014; Figure 107–2.)

Clinical Presentation and Diagnosis of Colorectal Cancer

General

Patients are often asymptomatic in early stages of disease

Symptoms

Changes in bowel habits, abdominal pain, anorexia, nausea and vomiting, weakness (if anemia is severe), and tenesmus

Signs

Blood in stool and weight loss

Laboratory Tests

- Patients may have a low hemoglobin level from blood loss
- Positive FOBT
- Liver function tests (INR, activated partial thromboplastin time, and bilirubin) may be abnormal if disease has metastasized to the liver.
- CEA level may be high; normal level is less than 2.5 ng/mL (2.5 mcg/L) in nonsmokers and less than 5 ng/mL (5 mcg/L) in smokers.

Imaging Tests

Chest X-ray, CT scan, or PET scan results may be positive if cancer has spread to the lungs, liver, or peritoneal cavity.

mutations of tumor suppressor genes, and defects in DNA mismatch repair genes.

Additional genes and protein receptors are believed important in colorectal tumorigenesis. COX-2, which is induced in colorectal cancer cells, influences apoptosis and other cellular functions in colon cells, and overexpression of EGFR, a transmembrane glycoprotein involved in signaling pathways that affect cell growth, differentiation, proliferation, and angiogenesis, occurs in the majority of colon cancers.[14] These mechanisms are potentially important because of the availability of pharmacologic agents targeted to inhibit these processes.

CLINICAL PRESENTATION AND DIAGNOSIS

The signs and symptoms associated with colorectal cancer can be extremely varied, subtle, and nonspecific. Most patients are asymptomatic but may develop changes in bowel or eating habits, fatigue, abdominal pain, and blood in the stool.

TREATMENT

Desired Outcomes

Patients are staged with the tumor, node, metastasis (TNM) classification system (see Chapter 88) to determine treatment options and assess prognosis. Figure 91–2 depicts how the three categories are used in combination to determine the stage of disease. **KEY CONCEPT** The stage of colorectal cancer upon diagnosis is the most important prognostic factor for survival and disease recurrence. Stages I, II, and III disease are considered potentially curable and are aggressively treated in an attempt to cure these patients. Patients who develop stage IV disease are treated to reduce symptoms, avoid disease-related complications, and prolong survival.

General Approach to Treatment

The treatment approaches for colorectal cancer reflect two primary treatment goals: curative therapy for localized disease (stages I–III) and palliative therapy for metastatic cancer (stage IV). Surgical resection of the primary tumor is the most important part of therapy for patients in whom cure is possible.[16] Depending on the stage of disease and whether the tumor originated in the colon or rectum, further adjuvant chemotherapy or chemotherapy plus radiation may be needed after surgery to cure these patients. In the metastatic setting, pharmacologic intervention is the main treatment option.

Pharmacogenetic and pharmacogenomic testing has become an integral component to designing the optimal pharmacologic intervention for patients with colorectal cancer. The choice of treatment agents is largely dictated by individualized patient and tumor-specific factors. For example, data have demonstrated specific tumor characteristics that may assist clinicians in predicting who will respond to EGFR inhibitors. Early immunohistochemical staining for EGFR status is not useful in predicting response because both EGFR-positive and EGFR-negative patients respond at the same rate. However, *RAS* gene mutation status has demonstrated predictive value. Patients should be tested for both *KRAS*

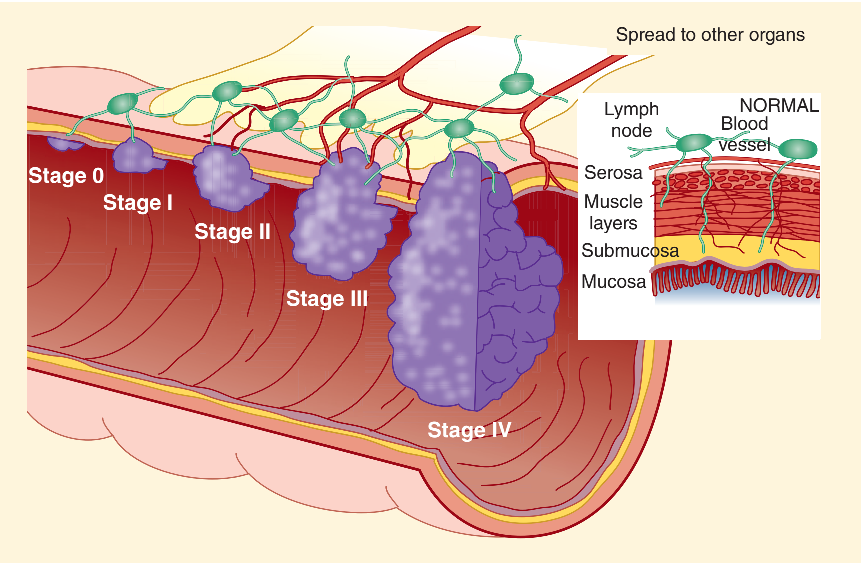

FIGURE 91–2. Stage I: cancer is confined to the lining of the colon. Stage II: cancer may penetrate the wall of the colon into the abdominal cavity but does not invade any local lymph nodes. Stage III: cancer invades one or more lymph nodes but has not spread to distant organs. Stage IV: cancer has spread to distant locations in the body, which may include the liver, lungs, or other sites. (From National Cancer Institute, Washington, DC).

and *NRAS*; patients with mutated *RAS* are unlikely to benefit from cetuximab or panitumumab therapy.[15] In particular, testing for *RAS* mutational status is now part of the disease workup to define patients who may derive benefit from cetuximab or panitumumab. Characteristics of the tumor are also vital in making treatment decisions for patients with stages II and III disease. The degree of microsatellite instability (MSI) within a tumor tells clinicians information about both prognosis and treatment options. More detail on specific pharmacogenetic and pharmacogenomic information is provided in the pertinent pharmacologic therapy sections.

Nonpharmacologic Therapy

▶ *Operable Disease (Stages I–III)*

Surgery Individuals with stages I to III colorectal cancer should undergo a complete surgical resection of the tumor mass with removal of regional lymph nodes as a curative approach for their disease.[16] Surgery for rectal cancer depends on the region of tumor involvement with attempts to retain rectal function as a goal of the surgical procedure. Overall, surgery for colorectal cancer is associated with low morbidity and mortality rates. Common complications include infection, anastomotic leakage, obstruction, adhesion formation, and malabsorption syndromes.

Radiation Therapy There is currently no role for adjuvant radiation in colon cancer. However, patients who receive surgery for rectal cancer receive radiation therapy to reduce local tumor recurrence. Adjuvant radiation plus chemotherapy is considered standard treatment for patients with stage II or III rectal cancer after the surgical procedure is complete.[17] Preoperative chemoradiation using either capecitabine or fluorouracil may be used to reduce the initial size of rectal cancers to make the surgical procedure less extensive.

▶ *Metastatic Disease (Stage IV)*

Surgery Unlike stages I to III disease, the benefit of surgical resection in most patients with metastatic disease is limited to symptomatic improvement. Selected patients who have one to three small nodules isolated to the liver, lungs, or abdomen may have a prolongation of survival, although cure is rare. Five-year survival for patients who undergo surgical resection of metastases isolated to the liver is approximately double than that of patients who are not surgical candidates with approximately 38% of patients alive at 5 years.[18] Alternatives to surgery include destroying the tumor through freezing and thawing (cryoablation), heat (radiofrequency), or alcohol injection, although these appear to be less successful than surgical resection.[15,16,18]

Radiation Symptom reduction is the primary goal of radiation for patients with advanced or metastatic colorectal cancer.

Pharmacologic Therapy

Table 91–3 lists common chemotherapy regimens used in colorectal cancer and the abbreviations used in the literature to describe them.

Table 91–3

Dosing Schedules of Chemotherapy Regimens for Colon Cancer[a]

Regimen	Dosing
5-FU + leucovorin (continuous infusion)	Leucovorin 200 mg/m² IV 5-FU 400 mg/m² IV bolus and then 600 mg/m² of 5-FU as a 22-hour continuous infusion on days 1 and 2; repeat every 2 weeks
FOLFIRI	Irinotecan 180 mg/m² IV day 1 Folinic acid (leucovorin) 400 mg/m² IV day 1 5-FU 400–500 mg/m² IV bolus after folinic acid; then 2400–3000 mg/m² of 5-FU IV over 46 hours Repeat every 14 days
FOLFOX4	Oxaliplatin 85 mg/m² IV + leucovorin 200 mg/m² IV followed by 5-FU 400 mg/m² IV bolus and then 5-FU 600 mg/m² IV over 22 hours day 1 Leucovorin 200 mg/m² IV, followed by 5-FU 400 mg/m² IV bolus and then 5-FU 600 mg/m² IV over 22 hours day 2 Repeat every 2 weeks
mFOLFOX6	Oxaliplatin 85 mg/m² IV day 1 Leucovorin 400 mg/m² IV over 2 hours, followed by 5-FU 400 mg/m² IV bolus day 1 followed by 2400 mg/m² IV over 48 hours Repeat every 2 weeks
FOLFOXIRI	Irinotecan 165 mg/m² IV day 1 Oxaliplatin 85 mg/m² IV day 1 Leucovorin 200 mg/m² IV over 2 hours, followed by 5-FU 3200 mg/m² IV over 48 hours Repeat every 2 weeks
Bevacizumab + 5-FU regimen	Bevacizumab 5 mg/kg IV every 2 weeks + a 5-FU–containing regimen (FOLFOX, FOLFIRI, or 5-FU + leucovorin) Bevacizumab 7.5 mg/kg IV every 3 weeks with CapeOX
Cetuximab ± irinotecan	Cetuximab 400 mg/m² IV first infusion, then 250 mg/m² weekly ± irinotecan 125 mg/m² IV every week for 4 weeks Repeat irinotecan every 6 weeks (after a 2-week break)
Panitumumab	6 mg/kg IV every 2 weeks
Capecitabine	1250 mg/m² twice a day orally for 14 days Repeat every 3 weeks
CapeOX	Capecitabine 1000 mg/m² twice a day orally for 14 days Oxaliplatin 130 mg/m² IV on day 1 Repeat every 3 weeks

[a] Note that many variations exist, and current literature should be checked before administering any chemotherapy regimen.

5-FU, 5-fluorouracil; IV, intravenous.

Patient Encounter Part 2

PMH: Type 2 diabetes mellitus since 60 years, hyperlipidemia since 40 years, diabetic neuropathy since 65 years, obesity; the patient is 40% over his ideal body weight.

FH: Father died at age 74 years of lung cancer; mother died at age 81 of congestive heart failure; older sister with breast cancer; maternal uncle died at age 53 years from rectal cancer.

SH: Retired from the sales industry. Widowed with three grown children. Volunteers at local organization delivering meals.

Meds: Metformin 1000 mg po daily BID, liraglutide 1.2 SUBQ daily; gabapentin 300 mg po TID, pravastatin 40 mg daily.

ROS: (+) Abdominal cramping, diarrhea, constipation, and fatigue.

PE:

VS: 146/94 mm Hg, P 74 beats/min, RR 18 breaths/min, T 37.1°C (98.8°F), Ht 187 cm (74 in.), Wt 115 kg (253 lb).

Abd: Distended and tender to touch, (+) bowel sounds.

Labs: Positive hemoglobin 12.0 g/dL (120 g/L or 7.45 mmol/L) decreased from 13.9 g/dL (139 g/L or 8.63 mmol/L) last year. Positive lipid panel: triglycerides 279 mg/dL (3.15 mmol/L). Hemoglobin A1C 6.9% (goal:<7%)

Imaging and Diagnostic Studies

- Colonoscopy revealed multiple polyps in his transverse colon.
- Biopsy revealed two polyps positive for adenocarcinoma of the colon.
- T4 lesion present with disease spreading through the bowel wall.
- Staging CT scan negative for disease outside of the colon.
- Biopsied lymph nodes were negative for disease.
- Tumors positive for low levels of microsatellite instability.

Because the patient has stage II colon cancer, how does this affect the goal of your treatment plan compared with stage IV disease?

What nonpharmacologic and pharmacologic options are available to this patient?

▶ *Operable Disease (Stages I–III)*

KEY CONCEPT Adjuvant chemotherapy is administered after tumor resection to decrease relapse rates and improve survival in patients with colon cancer by eliminating micrometastatic disease that is undetected on imaging studies. Patients diagnosed with stage I colon or rectal cancer are usually cured by surgical resection, and adjuvant chemotherapy is not indicated in these patients.[16] The role of adjuvant chemotherapy for stage II colon cancer is controversial but may benefit certain high-risk groups. Adjuvant chemotherapy is standard therapy for patients with stage III colon cancer. Table 91–4 lists adjuvant treatment regimens based on stage and performance status (PS). Adjuvant chemotherapy for patients with stage II disease has not been shown to be superior to surgery alone with the possible exception of high-risk patients, including those with inadequate nodes sampled for staging, bowel perforation upon diagnosis, T4 lesions, and those with unfavorable histology.[15] The risks and benefits of adjuvant chemotherapy should be discussed with medically fit patients who have stage II disease with high-risk features. However, the American Society of Clinical Oncology does not recommend the routine use of adjuvant chemotherapy in the general patient population with stage II disease unless part of a clinical trial.[19]

Table 91–4

Adjuvant Treatment Regimens for Colon Cancer

Stage II[a]	Stage III
High Risk	**Good Performance Status**
• Capecitabine or 5-FU plus leucovorin	• FOLFOX
• FOLFOX	• CapeOX
• CapeOx	• FLOX
• FLOX	• Capecitabine or 5-FU plus leucovorin
Low Risk[b]	**Poor Performance Status**
• Observation or clinical trial	• Capecitabine
• Capecitabine or 5-FU plus leucovorin	

[a] Individualized assessment of patient risk is necessary to determine if treatment is required. Clinical trials or observation may be an appropriate option.

[b] T3 lesions may be considered high risk by some clinicians.

5-FU, 5-fluorouracil.

There are currently insufficient data to recommend the use of tumor gene profiling to determine the need for adjuvant therapy in stage II disease, but it is an area of active research.[15] An additional consideration for deciding on adjuvant therapy is the status of MSI within the tumor. MSI results from defective DNA mismatch repair (dMMR) genes leading to damaged DNA. Patients with tumors that display high levels of MSI may have better prognosis than patients with microsatellite-stable (MSS) tumors. Despite being associated with a better prognosis, tumors that display high levels of MSI (MSI-H) do not respond as well to certain chemotherapy, including 5-fluorouracil (5-FU).[20] It is recommended that stage II patients should be tested for the status of MSI if 5-FU is being considered for therapy, and an alternative therapy should be considered if high levels of MSI are displayed.[15] In general, patients with stage II colon cancer should be enrolled into clinical trials to assess the impact of new agents and prognostic models.

Adjuvant chemotherapy is standard therapy for patients with stage III colon cancer. The presence of lymph node involvement in the resected specimen places patients with stage III colon cancer at high risk for relapse; the risk of death within 5 years of surgical resection alone is as high as 70%.[16] In this population of patients, adjuvant chemotherapy significantly decreases the risk of cancer recurrence and death and is considered standard of care.

KEY CONCEPT 5-FU, leucovorin, and oxaliplatin (FOLFOX)-based chemotherapy is the standard regimen used in adjuvant colon cancer. It is usually given for 6 months. Refer to Tables 91–3 and 91–4 for recommended treatment regimens and schedules. 5-FU alone results in a small improvement in survival that can vary based on the method of 5-FU administration and the status of MSI.[20]

The combination of 5-FU plus leucovorin has undergone extensive study in the adjuvant setting with decreased rates of recurrence and improved survival seen in patients receiving 5-FU plus leucovorin compared with surgery alone. Though various schedules of 5-FU and leucovorin can be administered, continuous infusions may be less toxic and have improved response rates (although no survival advantage) compared with bolus regimens. Capecitabine is an oral prodrug of 5-FU that is also effective in the adjuvant setting and is being used as a replacement in certain regimens for 5-FU. Data suggest that capecitabine is at least equivalent to bolus 5-FU and leucovorin in efficacy and is better tolerated by patients in the adjuvant setting.[21] An increase in hand–foot syndrome and decreased mucositis and neutropenia are seen with capecitabine compared with bolus 5-FU.

More often, 5-FU or capecitabine is administered as part of a combination regimen with oxaliplatin and leucovorin (FOLFOX or CapeOx). FOLFOX is considered standard of care for patients with stage III disease unless their PS is so poor that clinicians do not believe the patients could tolerate intensive combination therapy. Every effort should be made to minimize adverse treatment effects and use this regimen in patients with stage III colon cancer because this is the only regimen demonstrated to improve overall survival.[16,22] Several variations on the original FOLFOX regimen have been studied with mFOLFOX6 being the most routinely used in clinical practice (refer to Table 91–4). CapeOx resulted in improved disease-free survival (DFS) compared with bolus 5-FU-leucovorin, but no overall survival benefit in stage III patients and is considered an acceptable adjuvant regimen in this patient population.[15,23]

Targeted therapies, including cetuximab and bevacizumab, have been evaluated for their role in their adjuvant treatment of colon cancer. At this time, no targeted agents are approved for use as adjuvant therapy in stage II or III colorectal cancer patients. Additionally, irinotecan should not be used in the adjuvant setting because its addition to 5-FU–based regimens has increased toxicity without therapeutic benefit.[15]

▶ *Metastatic Disease (Stage IV)*

Traditional chemotherapy and targeted biological therapies are the mainstay of treatment for metastatic colon or rectal cancer and have improved the median survival time of these patients to more than 2 years.[16] Most often, a combination of chemotherapy agents with biological therapies is administered to these patients. Currently, metastatic colorectal cancer is incurable, and treatment goals are to reduce patients' symptoms, improve quality of life, and extend survival. Combination chemotherapy regimens have been demonstrated to result in prolongation of survival with tolerable adverse effects. Similar to the adjuvant setting, 5-FU plus leucovorin continues to be in most first-line chemotherapy regimens used for metastatic colorectal cancer. A variety of continuous intravenous (IV) infusion 5-FU and bolus regimens can be used; however, compared with IV bolus 5-FU, response rates with the continuous infusion 5-FU are approximately doubled. In a large meta-analysis of patients with advanced colorectal cancer, continuous infusions of 5-FU had a significantly higher tumor response rate, a small increase in survival, and lower incidence of myelosuppression, diarrhea, and mucositis when compared with bolus regimens.[24]

Additional agents including irinotecan and oxaliplatin have been added to 5-FU and leucovorin regimens with superior response and survival rates compared to the two drugs used alone.[25,26] A large European study compared a combined bolus and infusional 5-FU regimen plus irinotecan (FOLFIRI) with the FOLFOX regimen (using a slightly different schedule) with crossover to the opposite arm upon relapse.[27] No difference in patient survival was seen with either regimen, and toxicity was as expected. Neuropathy and neutropenia were more common with FOLFOX, while diarrhea, nausea, vomiting, dehydration, and febrile neutropenia were more common with FOLFIRI. Based on improved survival data with the FOLFOX and FOLFIRI regimens, irinotecan-based regimens should be administered outlined as described in Table 91–3.

Capecitabine also has activity in the metastatic setting. When combined with oxaliplatin in regimens known as CapeOx or XELOX, capecitabine appears to be as safe as 5-FU–based regimens.[15] Additionally, progression-free survival (PFS) with CapeOX is similar to that of FOLFOX and is considered noninferior to the FOLFOX regimen as first-line therapy in advanced disease.[28] This noninferiority with capecitabine may be specific to its use with oxaliplatin because capecitabine in combination with irinotecan (CAPIRI) demonstrated decreased PFS compared with FOLFIRI and the routine substitution of 5-FU with capecitabine in irinotecan-based regimens is not recommended.[15,29]

5-FU plus leucovorin, or capecitabine alone, are appropriate first-line treatment options for individuals for whom three-drug combination regimens are believed to be toxic. The site(s) of tumor involvement, history of prior chemotherapy, and patient-specific factors help define the appropriate management strategy. **KEY CONCEPT** The most important factor in patient survival is not the initial regimen but whether or not patients receive all three active chemotherapy drugs (5-FU, irinotecan, and oxaliplatin) at some point in their treatment course.[30] Some clinicians choose to use all three agents in combination in the first-line setting in a regimen termed FOLFOXIRI, although only in patients who are able to tolerate intensive therapy.

Targeted or biologic agents are approved for use in metastatic colorectal cancer. Bevacizumab in combination with IV 5-FU–based chemotherapy (either FOLFOX or FOLFIRI) is approved by the FDA for initial treatment of patients with metastatic colorectal cancer. Results from randomized trials show increased benefit compared with chemotherapy alone.[15] The efficacy of bevacizumab in this patient population shows the relevance of angiogenesis as an important target for the treatment of metastatic colorectal cancer. The addition of bevacizumab to first-line oxaliplatin-based chemotherapy has also been demonstrated to improve PFS but did not positively impact response rates or overall survival.[31] Similar results were demonstrated with bevacizumab in combination with capecitabine and oxaliplatin.[42]

Based on these results, bevacizumab is recommended as part of 5-FU–based chemotherapy regimens used for the first-line treatment of metastatic colorectal cancer unless contraindicated. Bevacizumab is contraindicated in patients with GI perforation or fistulas involving a major organ, recent (within 28 days) major surgeries or open wounds, wound dehiscence requiring medical intervention, hypertensive crisis or uncontrolled severe hypertension, hypertensive encephalopathy—serious bleeding, a severe arterial thromboembolic event, moderate or severe proteinuria (urine protein excretion 2 g/24 hours or more), nephrotic syndrome, and reversible posterior leukoencephalopathy syndrome.

Monoclonal antibody EGFR inhibitors, cetuximab and panitumumab, demonstrate improved PFS as first-line therapy in the metastatic setting when individually combined with either the FOLFOX or FOLFIRI regimens in *RAS* wild-type individuals.[32-35] In addition, pembrolizumab may be considered in patients with MSI-H cancers and encorafenib with cetuximab or panitumumab for those with a BRAF V600E mutation. **KEY CONCEPT** Before using these agents, testing for *RAS* (*KRAS* and *NRAS*), *BRAF* and *MSI-H* mutation status should occur. Extensive literature exists, demonstrating poor response rates of EGFR inhibitors in patients whose tumors have a mutation in exons 2, 3, or 4 of the *KRAS* or *NRAS* genes.[15,36] Consequently, cetuximab or panitumumab may be used in the first-line setting in combination with traditional chemotherapy agents in *RAS* WT patients only.[15]

Attempts to combine the vascular endothelial growth factor (VEGF) inhibitor bevacizumab with cetuximab and panitumumab as part of traditional chemotherapy regimens have resulted in inferior outcomes to regimens with bevacizumab alone.[37] Based on these results, the use of bevacizumab with either EGFR inhibitor is not recommended.[15]

KEY CONCEPT In summary, most practitioners select first-line treatment for metastatic colorectal cancer from among these treatments: oxaliplatin plus 5-FU plus leucovorin (FOLFOX); irinotecan plus 5-FU plus leucovorin (FOLFIRI); capecitabine plus oxaliplatin (CapeOx or XELOX); oxaliplatin plus irinotecan plus 5-FU plus leucovorin (FOLFOXIRI); bevacizumab plus 5-FU- or capecitabine-based chemotherapy (FOLFIRI or FOLFOX or CapeOx or FOLFOXIRI); or cetuximab or panitumumab plus 5-FU–based chemotherapy (FOLFOX or FOLFIRI) in *RAS* WT patients.[15]

▶ *Second-Line Therapy*

KEY CONCEPT Treatment of relapsed or refractory metastatic disease uses agents not given in the first-line setting. Patients who receive all effective chemotherapy options have improved outcomes compared with those who do not. Because most patients will have received a combination of 5-FU or capecitabine with either irinotecan or oxaliplatin, second-line therapy with the alternate regimen should be considered.[15] For example, a patient who received FOLFOX plus bevacizumab as first-line therapy for metastatic disease should be offered FOLFIRI as part of their second-line regimen. EGFR inhibitors are an additional option for use in the second-line setting in patients with WT *RAS* only. Patients who did not have an EGFR inhibitor in their first-line regimens are candidates for single-agent cetuximab or panitumumab or either agent in combination with 5-FU and irinotecan (FOLFIRI + EGFR inhibitor). Additionally cetuximab plus irinotecan can be used without the inclusion of 5-FU. The use of EGFR inhibitors may be beneficial as monotherapy, but response rates and PFS appear to be increased in combination with irinotecan-based chemotherapy.[38-42] The results appear to be best when irinotecan is continued because of synergy demonstrated between the two classes of agents.[15,38]

If targeted agents such as bevacizumab were not part of the initial regimen, addition to the second-line regimen should be strongly considered. The addition of bevacizumab to FOLFOX has been shown to increase overall survival.[43] Bevacizumab as monotherapy was shown to be inferior to FOLFOX4 in efficacy and should not be considered a treatment option in the second-line setting. In patients receiving bevacizumab as part of first-line therapy, continuation of bevacizumab with second-line therapy is associated with increased survival.[44] Based on these findings, continuation of bevacizumab in combination with traditional second-line chemotherapy regimens (5-FU-irinotecan- or 5-FU-oxaliplatin–based) can be considered in patients treated with a first-line bevacizumab-containing regimen. Additional agents targeting VEGF, ziv-aflibercept or ramucirumab, in combination with FOLFIRI can also be considered for use in the second-line setting in patients who have progressed following an oxaliplatin-based first-line regimen. A modest increase in overall and PFS was found in patients receiving FOLFIRI plus ziv-aflibercept compared to FOLFIRI alone.[45] In two separate clinical trials, the addition of ramucirumab or ziv-aflibercept to FOLFIRI led to a modest increase in overall and PFS when compared to FOLFIRI alone.[45,46] Adverse events and warnings for use with ziv-aflibercept or ramucirumab are similar to those with bevacizumab and described in the section of specific agents. Table 91–5 lists treatment options for first- and second-line treatment of metastatic colorectal cancer. Patients with good PS are treated more aggressively than those with poor PS because of their ability to better tolerate chemotherapy.

Table 91–5

Treatment Options for Metastatic Colon Cancer[a]

First-Line Therapy	Second-Line Therapy
Good Performance Status	**If First-Line Irinotecan**
• FOLFOX or FOLFIRI with bevacizumab • FOLFOX or FOLFIRI with cetuximab or panitumumab[c] • FOLFOXIRI with or without bevacizumab • 5-FU + leucovorin or capecitabine with or without bevacizumab	• FOLFOX with or without bevacizumab[b] • Irinotecan with or without cetuximab[c,d] • Capecitabine or 5-FU plus leucovorin
Poor Performance Status	**If First-Line Oxaliplatin**
• Capecitabine or 5-FU plus leucovorin with or without bevacizumab	• FOLFIRI with or without bevacizumab • FOLFIRI with ziv-aflibercept • Irinotecan with ziv-aflibercept • FOLFIRI or irinotecan with or without cetuximab or panitumumab[c,d]

[a]CapeOX may replace FOLFOX in selected patients.

[b]Bevacizumab may be given if not part of the first-line therapy.

[c]If *RAS* wild type.

[d]Cetuximab or panitumumab may be given if not part of first-line therapy.

5-FU, 5-fluorouracil.

▶ *Salvage Therapy*

Several salvage therapy options exist for patients with colorectal cancer who have progressed beyond standard first- and second-line therapy. Panitumumab is approved for patients who have progressed after 5-FU, oxaliplatin, and irinotecan. Compared with best supportive care, it improves time to disease progression.[15] Based on improvement in PFS compared to best supportive care, the multiple tyrosine kinase inhibitor, regorafenib, was approved as a single agent for metastatic colorectal cancer in the third- or fourth-line setting.[47] Trifluridine and tipiracil is another oral treatment option for patients who have been previously treated with all standard therapies. This agent gained FDA approval after demonstrating improved overall survival when compared with placebo.[48]

An additional option in patients with metastatic colorectal cancer and who also demonstrate high MSI or dMMR disease is pembrolizumab. Patients with these particular tumor characteristics have demonstrated notable clinical benefit in early clinical trial data, thus prompting FDA approval in this setting.[49] Although several salvage options exist, patients who fail standard treatment for metastatic colorectal cancer should be encouraged to participate in a clinical trial evaluating new treatment approaches for this incurable disease.

Patient Encounter Part 3

Based on the information presented, create a care plan for this patient's colon cancer. Your plan should include:

(a) The patient's drug- and nondrug-related needs and problems.

(b) The goals of therapy.

(c) A treatment plan specific to this patient that includes strategies to prevent adverse effects of chemotherapy.

(d) A follow-up plan to determine whether the goals have been achieved and the adverse effects of chemotherapy have been minimized.

SPECIFIC AGENTS USED IN COLORECTAL CANCER

Table 91–6 lists FDA-approved drugs used in colorectal cancer along with their mechanisms of action, common toxicities, and recommended dose adjustments for hepatic and renal dysfunction as well as pharmacogenetic considerations.

5-Fluorouracil

5-Fluorouracil (5-FU) acts as a "false" pyrimidine inhibiting the formation of the DNA base thymidine as described in Chapter 88.[16]

5-FU is commonly used in the adjuvant and metastatic treatment of colon and rectal cancers with common regimens listed in Table 91–3. Clinical studies comparing efficacy of bolus and continuous infusion schedules generally favor continuous infusion of 5-FU. This is consistent with evidence that suggests that the duration of infusion may be an important determinant of the biologic activity of 5-FU, particularly because of its short plasma half-life, S-phase specificity, and relatively slow growth of colon tumors.[16,50]

Clinically significant differences in toxicity also differ based on the dose, route, and schedule of 5-FU administration. Leukopenia and mucositis are the primary dose-limiting toxicities of bolus 5-FU, whereas palmar–plantar erythrodysesthesia ("hand–foot syndrome") and diarrhea occur most frequently with continuous infusions of 5-FU.[16,50] Healthcare practitioners can offer valuable patient advice to decrease the impact of these adverse effects. Patients can be informed to suck on ice chips before and for up to 30 minutes after 5-FU boluses to decrease the incidence of mucositis. Hand–foot syndrome, characterized by painful swelling and redness of the soles of the feet and palms of the hand, can be minimized with loose-fitting clothing and keeping skin moist. Additional toxicities include moderate nausea and vomiting, skin discoloration, nail changes, photosensitivity, and neurologic toxicity.

An additional determinate of 5-FU toxicity, regardless of the method of administration, is related to its catabolism and pharmacogenomic factors. Dihydropyrimidine dehydrogenase (DPD) is the main enzyme responsible for the catabolism of 5-FU to inactive metabolites.[48] A number of polymorphisms in DPD have been identified in which patients have a complete or near-complete deficiency of this enzyme. This results in unusually severe toxicity, including death, after the administration of 5-FU. Approximately 3% of patients have a complete lack of DPD activity with other patients demonstrating a partial deficiency in enzyme activity. Although patients may be tested for level of DPD activity, it is not routinely done but may be considered in patients who develop severe toxicity after 5-FU administration. The response to 5-FU is also influenced by the status of MSI within the tumor. Tumors with high levels of MSI are generally more resistant to 5-FU despite being associated with better prognosis.

Leucovorin is commonly given with 5-FU. Leucovorin acts to increase the affinity of 5-FU to thymidine synthase, thus increasing the pharmacologic activity of 5-FU.[16] Leucovorin is most effective when administered before 5-FU and can be given by IV bolus or as a continuous infusion. 5-FU toxicities (leukopenia, mucositis, and diarrhea) are increased when leucovorin is given in combination with 5-FU.

Capecitabine

Capecitabine (Xeloda) is an oral prodrug of 5-FU that is designed to be selectively activated by tumor cells. Capecitabine undergoes a three-step conversion to 5-FU, the last step being phosphorylation by thymidine phosphorylase (TP). TP levels are reported to be higher in tumor cells than normal tissues; therefore, the systemic exposure of active drug is minimized, and tumor concentrations of the active drugs are optimized.[16,22] After the drug is converted to 5-FU, it has the same mechanism of action. The current FDA-approved indication for capecitabine is for use in metastatic and adjuvant colorectal cancer when monotherapy is desired, although it is actively being investigated as a replacement for 5-FU in most combinations of colon and rectal cancer regimens. Hand–foot syndrome and diarrhea are common with capecitabine because its toxicities (and pharmacologic activity) appear to mimic those of continuous infusions of 5-FU.

The dose of capecitabine ranges from 1000 to 1250 mg/m^2 twice a day when used alone; lower doses are often used when it is given in combination with irinotecan or oxaliplatin or in patients with renal insufficiency. The dose should be taken on a full stomach with breakfast and dinner. Capecitabine administered with warfarin can result in significant increases in patients' international normalized ratio (INR) and requires close monitoring. The convenience of oral administration, potentially requiring fewer clinic visits, and an improvement in toxicity make capecitabine a useful alternative to IV 5-FU both by itself and incorporated into other regimens used in colorectal cancer.

Irinotecan

Irinotecan (Camptosar) is a topoisomerase-I inhibitor that forms a complex with the covalently bound DNA topoisomerase I enzyme and interferes with the DNA breakage–resealing process. Binding permits uncoiling of the double-stranded DNA, but it prevents subsequent resealing of the DNA, resulting in double-stranded DNA breaks. Irinotecan is a prodrug that is converted by carboxylesterases to its active form, SN-38. Irinotecan is indicated for the first-line treatment of metastatic colorectal cancer in combination with 5-FU and leucovorin or as a single agent in patients who fail first-line therapies. Irinotecan is not recommended as part of the adjuvant treatment of colorectal cancer at this time.

The major toxicity of irinotecan is diarrhea, which can occur both early and late in therapy.[15,50] The early diarrhea is a cholinergic reaction that occurs in the first 24 hours (often during the infusion) in up to 10% of patients and responds to atropine 0.25 to 1 mg IV. The late diarrhea seen in a larger percent of patients occurs 7 to 14 days after the irinotecan infusion. Healthcare practitioners have to be diligent in counseling patients on this adverse reaction and counseling them on the proper use of antidiarrheals. At the first change in bowel habits, an intensive loperamide regimen should be started by patients (4 mg initially followed by 2 mg every 2 hours until diarrhea free for 12 hours). If diarrhea does not stop or if it worsens, patients should be instructed to

Table 91–6

FDA-Approved Drugs Used in Colon Cancer

Generic Name (Trade Name)	Mechanism of Action	Common Toxicities	Dosing Adjustments for Renal or Hepatic Dysfunction or Pharmacogenetic Considerations
5-FU	Inhibition of the enzyme thymidylate synthase, the rate-limiting step in thymidine formation	*Dose limiting:* Myelosuppression and mucositis with bolus administration Diarrhea and hand–foot syndrome with continuous infusion *Additional toxicities:* Skin discoloration, nail changes, photosensitivity, and neurologic toxicity	Do not give if bilirubin greater than 5 mg/dL (86 µmol/L) DPD deficiency may result in increased toxicity. Testing not routine but may be considered in those with excessive toxicity
Capecitabine (Xeloda)	Orally active prodrug of 5-FU. Once activated, the mechanism of action is the same	Similar to continuous infusion 5-FU	CrCl 30–50 mL/min (0.50–0.83 mL/s) decrease starting dose to 75% of the original dose Do not give if CrCl< 30 mL/min (0.50 mL/s)
Irinotecan (Camptosar)	Topoisomerase inhibitor that forms a complex with the covalently bound DNA topoisomerase enzyme and interferes with the DNA breakage–resealing process	*Dose limiting:* Early and late diarrhea *Additional toxicities:* Neutropenia, nausea, and vomiting	Decrease dose one level in patients with a homozygous UGT1A1*28 allele. Having this allele decreases the hepatic metabolism of irinotecan and increases the toxicity
Oxaliplatin (Eloxatin)	Similar to other platinum analogues (cisplatin) in that it binds to the N-7 position of guanine, which results in cross-linking of DNA and double-stranded DNA breaks	*Dose limiting:* Acute (within first 2 days) and persistent (> 14 days) neuropathies *Additional toxicities:* Anaphylactic-like reactions, dyspnea, nausea, vomiting	No formal dose adjustment, though use with caution in patients with mild-to-moderate renal dysfunction
Bevacizumab (Avastin)	Monoclonal antibody that binds to VEGF and inhibits angiogenesis	*Dose limiting:* Hypertension, bleeding episodes, thrombotic events *Additional toxicities:* Rare perforation of the bowel, proteinuria	None
Ziv-aflibercept (Zaltrap)	Recombinant fusion protein that binds to VEGF and inhibits angiogenesis	*Dose limiting:* Hypertension, bleeding episodes, thrombotic events, infection, diarrhea *Additional toxicities:* Rare perforation of the bowel, proteinuria	None
Ramucirumab (Cyramza)	Monoclonal antibody that binds to VEGF-2 and inhibits angiogenesis	*Dose limiting:* Hypertension, bleeding, thrombosis *Additional toxicities:* Gastrointestinal perforation, proteinuria, delayed wound healing	None
Regorafenib (Stivarga)	Multiple protein kinase inhibitor, including VEGF KIT, PDGFR, RET, FGFR, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, SAPK2, PTK5, and Abl	*Dose limiting:* Hypertension, hand–foot skin reaction *Additional toxicities:* GI perforation, impaired wound healing, hemorrhage, RPLS, fatigue, electrolyte imbalance, hepatotoxicity	Do not use if Child-Pugh class C hepatic impairment Specific recommendations exist for hepatotoxicity developing while on therapy
Cetuximab (Erbitux)	Binds to the cell surface EGFR, preventing EGF and TGF-α binding. This decreased cell proliferation of cancer cells	*Dose limiting:* Infusion-related reactions, acneiform skin rash *Additional toxicities:* Diarrhea, hypomagnesemia, hypocalcemia, interstitial lung disease	*KRAS* WT only
Panitumumab (Vectibix)	Similar to cetuximab	*Dose limiting:* Acneiform skin rash *Additional toxicities:* Infusion-related reactions, diarrhea, hypomagnesemia, hypocalcemia, interstitial lung disease	*KRAS* WT only

(Continued)

Table 91–6

FDA-Approved Drugs Used in Colon Cancer (*Continued*)

Generic Name (Trade Name)	Mechanism of Action	Common Toxicities	Dosing Adjustments for Renal or Hepatic Dysfunction or Pharmacogenetic Considerations
Trifluridine/ tipiracil (Lonsurf)	Thymidine analog, inhibits DNA synthesis	*Dose limiting:* Myelosuppression *Additional toxicities:* Nausea, diarrhea, stomatitis	Do not initiate therapy in moderate or severe hepatic impairment
Pembrolizumab (Keytruda)	Monoclonal antibody that inhibits PD-1 receptor and prevents PD-1 pathway activation	*Toxicities:* Immune-mediated colitis, dermatitis, hepatitis, etc	Indicated for MSI-H

5-FU, 5-fluorouracil; CrCl, creatinine clearance; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; PD, programmed death; RPLS, reversible posterior leukoencephalopathy syndrome; TGF, transforming growth factor; VEGF, vascular endothelial growth factor; WT, wild type.

call their healthcare provider immediately. Late-onset diarrhea may require hospitalization or discontinuation of therapy, and fatalities have been reported. Additional toxicities with irinotecan include leukopenia (including neutropenic fever) and moderate nausea and vomiting. Toxicities of irinotecan appear to be greater when the drug is given weekly compared with other administration schedules.

Similar to 5-FU, a pharmacogenomic abnormality is associated with irinotecan toxicity. UDP-glucuronosyltransferase (UGT1A1) is an enzyme that is responsible for the glucuronidation of SN-38 to inactive metabolites, and reduced or deficient levels of this enzyme correlate with irinotecan-induced diarrhea and neutropenia.[15,50] The FDA approved a blood test that detects variations in this gene. This test may assist healthcare providers in predicting which patients may develop severe toxicities from "normal" doses of irinotecan and can be ordered before patients receive irinotecan.[15] The package insert recommends dose reductions of one level in patients who are UGT1A1 homozygous variants. Irinotecan is administered as an IV bolus over 60 to 90 minutes in a variety of dosing schedules.

Oxaliplatin

Oxaliplatin (Eloxatin) is similar to other platinum analogues (cisplatin) in that it binds to the N-7 position of guanine that results in cross-linking of DNA and double-stranded DNA breaks.[50] Oxaliplatin differs from cisplatin in that the DNA damage induced by oxaliplatin may not be as easily recognized by DNA repair genes often seen in colorectal cancer. Oxaliplatin, in combination with 5-FU–based regimens, is indicated for the first- and second-line treatment of metastatic colorectal cancer as well as the adjuvant treatment of colorectal cancer.

The dose-limiting toxicity of oxaliplatin is acute and chronic neuropathy.[16] Acute neuropathies occur within 1 to 2 days of dosing, resolve within 2 weeks, and usually occur peripherally. These acute neuropathies occur in almost all patients to some degree and are exacerbated by exposure to cold temperature or cold objects. Healthcare providers should instruct patients to avoid cold drinks, avoid use of ice, and cover skin before exposure to cold or cold objects. In addition, carbamazepine, gabapentin, amifostine, and calcium and magnesium infusions have been used to both prevent and treat oxaliplatin-induced neuropathies, although the use of these agents is not widely accepted.[16] Persistent neuropathies generally occur after eight cycles of oxaliplatin and are characterized by defects that can interfere with daily activities (eg, writing, buttoning, swallowing, and walking). Patients may receive predefined breaks from oxaliplatin to decrease the onset of these toxicities with reinitiation of therapy.[26] This strategy varies among protocols but involves administering a certain number of predefined oxaliplatin cycles and then stopping. Maintenance therapy with another agent is usually administered and then the oxaliplatin-based regimen is restarted based on the protocol. These neuropathies occur in up to half of patients receiving oxaliplatin but usually resolve with dosage reductions or after oxaliplatin is stopped.[16] Oxaliplatin has minimal renal, myelosuppressive effects, and nausea and vomiting when compared with other platinum drugs. Oxaliplatin is given IV in a variety of dosing schedules with a typical dose of 85 mg/m^2 IV every 2 weeks.

Bevacizumab

Bevacizumab (Avastin) is a recombinant, humanized monoclonal antibody that inhibits VEGF. VEGF is a proangiogenic growth factor found in many cancers, including colorectal, and is thought to promote blood vessel formation and metastasis of the tumor by binding to VEGF receptors on tumors. Bevacizumab inhibits circulating VEGF, preventing it from binding to receptors and decreasing the formation of new blood vessels.[15,16] Additionally, bevacizumab may allow for increased concentrations of traditional chemotherapy such as irinotecan to reach the tumor to exert its pharmacologic effect. Bevacizumab is not effective alone and must be used in combination with other agents effective in colorectal cancer. It is indicated for first- and second-line treatment of patients with metastatic colorectal cancer in combination with IV 5-FU–based regimens. Bevacizumab is also approved for use in combination with 5-FU-irinotecan or 5-FU-oxaliplatin–based chemotherapy for treatment of patients with metastatic colorectal cancer whose disease has progressed on a first-line bevacizumab-containing regimen.

Adverse effects associated with bevacizumab include hypertension, which is common but easily managed with oral antihypertensive agents. Thrombotic events (including myocardial infarctions, pulmonary embolisms, and deep vein thrombosis) occur more frequently in the elderly patients with cardiovascular risk factors and need to be monitored carefully. Because bevacizumab interferes with normal wound healing, it should not be given shortly before or after surgical procedures.[15] Initiation within 28 days of surgery is not recommended to allow for proper wound healing and decrease the risk of bleeding. The amount of time needed after bevacizumab discontinuation to perform elective surgical procedures is less clear, but healthcare providers should take into consideration bevacizumab's half-life of approximately 20 days when making clinical decisions.[33] Patients should have their urine checked for protein before each dose of bevacizumab to check for potential kidney damage. Patients who have developed 2+

protein on the urinalysis require additional testing before receiving therapy. These patients will have their 24-hour urine collected and assessed for protein. Therapy is interrupted if urine protein excretion exceeds 2 g/24 hours or more and resumed when urine protein excretion decreases to less than 2 g/24 hours.

Finally, there is a risk of GI perforation that is rare but potentially fatal. Patients complaining of abdominal pain associated with vomiting or constipation should be counseled to call their physician immediately. Bevacizumab is commonly given at a dose of 5 mg/kg IV every 14 days until disease progression. Once disease progresses and salvage chemotherapy is initiated, the benefit of continuing bevacizumab is unclear.

Ziv-aflibercept

Ziv-aflibercept (Zaltrap) is a soluble recombinant fusion protein developed by fusing sections of the VEGFR-1 and VEGFR-2 immunoglobulin domains to the F_c portion of human IgG1 antibody. This results in trapping the VEGF-A, VEGF-B, and PIGF ligands before they get to the native transmembrane receptors, and, therefore, inhibiting the angiogenic process.[15,45] It is FDA approved for the treatment of metastatic colorectal cancer in combination with FOLFIRI after progression on an oxaliplatin-based regimen. The dose is 4 mg/kg as an IV infusion over 1 hour every 2 weeks in combination with FOLFIRI.

Toxicities include severe and potentially fatal hemorrhage, GI perforation, and compromised wound healing for which the FDA has given ziv-aflibercept a black-box warning. Other adverse effects common to VEGF inhibition (thromboembolic events, hypertension, and proteinuria) are seen. As a result, ziv-aflibercept shares similar monitoring parameters and warnings to those mentioned in the bevacizumab section. Finally, additional warnings for neutropenia, diarrhea and dehydration, and reversible posterior leukoencephalopathy syndrome (RPLS) require monitoring patients for signs and symptoms of these toxicities.

Ramucirumab

Ramucirumab (Cyramza) is a fully human IgG-1 monoclonal antibody that targets and binds to the VEGFR-2, inhibiting ligand activation of the receptor and subsequent vascular tumor growth.[46] For the treatment of colorectal cancer, ramucirumab is FDA-approved at a dose of 8 mg/kg IV in combination with FOLFIRI in patients who have progressed on or after therapy with 5-FU, oxaliplatin, and bevacizumab.

Ramucirumab shares an adverse effect profile similar to that of the previously discussed VEGF inhibitors bevacizumab and ziv-aflibercept, including black-box warnings for risk of hemorrhage, GI perforation, and impaired wound healing.

Regorafenib

Regorafenib (Stivarga) is an oral medication that inhibits multiple protein kinases. Its main mechanism of action in colorectal cancer appears to be related to the inhibition of vascular endothelial receptors involved in angiogenesis. The importance of additional protein kinase inhibited by regorafenib is unknown in colorectal cancer. Regorafenib is FDA approved as a single agent for metastatic colorectal cancer in the third- or fourth-line setting.[47] The dose of regorafenib is 160 mg orally, once daily for the first 21 days of each 28-day cycle and it must be taken with a low-fat breakfast to improve absorption.

Adverse effects for regorafenib include those typical for VEGF inhibition (hemorrhage, hypertension, wound healing complications, and GI perforation) mentioned with bevacizumab and ziv-aflibercept. Regorafenib has a black-box warning for hepatotoxicity that requires baseline liver function tests (ALT, AST, and bilirubin), then every 2 weeks during the first 2 months of therapy, and then monthly. In patients with elevated liver function tests holding doses, dose reductions, or permanent discontinuation of regorafenib may be necessary. Also, asthenia, fatigue, decreased appetite, hand–foot syndrome, diarrhea, mucositis, weight loss, infection, and dysphonia occurred in over 30% of patients. Refer to Chapter 99 on supportive care for management. Finally, regorafenib is a substrate of CYP3A4 and patients should be screened for potential drug interactions.

Cetuximab and Panitumumab

Cetuximab (Erbitux) and panitumumab (Vectibix) are monoclonal antibodies directed against the EGFR. Cetuximab is a chimeric antibody, whereas panitumumab is a fully human monoclonal antibody. EGFR is overexpressed in colorectal cancers and leads to an increase in tumor proliferation and growth. Cetuximab received FDA approval for use in *RAS* WT, EGFR-expressing metastatic colorectal cancer in irinotecan-relapsed or irinotecan-refractory patients. Cetuximab should be administered in combination with irinotecan but can be used as a single agent in patients who cannot tolerate irinotecan-based chemotherapy. Panitumumab is approved as monotherapy agent and as first-line therapy in combination with FOLFOX in *RAS* WT metastatic colorectal cancer.

Both agents are well tolerated with infusion-related reactions being the dose-limiting toxicity of cetuximab and rash most commonly seen with panitumumab. Patients receiving cetuximab require premedication with diphenhydramine and may require modifications to their administration schedule or permanent discontinuation if they develop severe allergic toxicity. A skin rash and diarrhea are also commonly seen with both agents, and healthcare practitioners should provide counseling to patients about these adverse effects. Treatment options include common medications used to treat acne (doxycycline), topical and systemic steroids, and general skin care. Patients may be offered these agents prophylactically, upon initiation of therapy, to decrease the potential impact the rash has on their quality of life. Development of rash may be a surrogate marker of response, and clinicians should attempt to minimize the complications of the rash before discontinuing therapy.[15] Other toxicities common to both agents include low magnesium, calcium, and potassium levels that require checking levels and replacement therapy as clinically indicated. A rare adverse effect (< 1%), interstitial lung disease is seen with all agents that inhibit EGFR, and patients should be instructed to report any new-onset shortness of breath. Cetuximab has an initial loading dose of 400 mg/m^2 IV infusion. Weekly doses of 250 mg/m^2 are then administered starting the following week. Panitumumab is given 6 mg/kg IV every 2 weeks.

Trifluridine and Tipiracil

Trifluridine/tipiracil (Lonsurf) is an oral agent that incorporates two components. The active component is trifluridine, a thymidine-based nucleic acid analog which is incorporated into DNA and interferes with DNA synthesis. Tipiracil hydrochloride inhibits TP and thereby prevents degradation of the active trifluridine and allows for adequate plasma concentration of active drug.[48] The FDA-approved dose of 35 mg/m^2 orally is based on the trifluridine component and is administered twice daily on days 1 to 5 and 8 to 12 of a 28-day treatment cycle. It is given as a single-agent in patients who have previously received 5-FU, oxaliplatin, irinotecan, anti-VEGF therapy, and anti-EGFR therapy (if *RAS* WT).

Adverse effects include myelosuppression (particularly neutropenia and anemia), fatigue, stomatitis, diarrhea, and nausea. Trifluridine/tipiracil has moderate emetic potential and pretreatment for nausea is recommended. Each dose should be taken within 1 hour of completion of the morning and evening meals. The unusual dosing schema of this agent may be difficult for some patients and negatively affect compliance, thus careful counseling and written dosing guidelines should be offered to all patients.

Pembrolizumab

Pembrolizumab is a humanized IgG4 monoclonal antibody that inhibits the programmed death 1 (PD-1) receptor to prevent ligand binding and subsequent pathway activation. The PD-1 pathway is an immune pathway that typically serves as a negative feedback system to suppress T-cell response. Many tumors upregulate the PD-1 pathway to encourage immune suppression and prevent host immune activity against tumor cells.[49] Pembrolizumab blocks this negative feedback mechanism to induce T-cell activation and subsequent antitumor immune response. Pembrolizumab is FDA approved in colon cancer patients with dMMR or MSI-H tumors after failure of standard chemotherapies. Patients with dMMR tumors typically have many mutations resulting in production of many abnormal proteins that serve as antigens to the immune system. Reactivation of the immune system by pembrolizumab is often an effective strategy in these patients. Pembrolizumab is given intravenously at a flat dose of 200 mg every 3 weeks for up to 24 months. Adverse effects are mainly related to overactivation of the immune system. Though most patients tolerate it quite well, patients may exhibit immune-mediated toxicity in nearly any organ in their body, particularly dermatitis, colitis, and endocrinopathies.[15,49] These and most other immune-mediated toxicities must be managed by temporary or permanent drug discontinuation and initiation of oral corticosteroids.

RECTAL CANCER

Although often treated similarly to colon cancer, there are some important differences in the treatment of rectal cancer, especially in the adjuvant setting. Rectal cancer involves tumors found in the distal 15 cm of the large bowel and, as such, is very distinct from colon cancer in that it has a propensity for both local and distant recurrence. The higher incidence of local failure and poorer overall prognosis associated with rectal cancer are attributable to limitations in surgical techniques. Therefore, multimodality therapies with a combination of chemotherapy, radiation, and surgery are at the forefront in the treatment of rectal cancer with the main goal of survival and quality of life by preserving the function of the anal sphincter. In addition, because treatment with surgery, radiation, or systemic chemotherapy at the time of the recurrence is often suboptimal, adjuvant therapy after tumor resection is an important aspect of treatment of the primary tumor. Similar to adjuvant therapy for colon cancer, 5-FU provides the basis for chemotherapy regimens for rectal cancer.

KEY CONCEPT Adjuvant therapy consisting of 5-FU–based chemotherapy in combination with radiation therapy should be offered to patients with stage II or III cancer of the rectum.[50] Radiation therapy decreases the rate of local recurrences, but 5-FU decreases the risk of distant tumor recurrence as well as acting as a radiosensitizer. Toxicities from combined modality therapy include severe hematologic toxicity, enteritis, and diarrhea. Additional trials have sought to determine optimal combinations of concurrent radiation and 5-FU. Similar to tumors in the colon, continuous infusions of 5-FU appear to be superior to bolus doses. However, leucovorin does not appear to improve efficacy of adjuvant treatment for rectal cancer. The use of oral alternatives to 5-FU that are also known to enhance radiation effects, such as capecitabine, are under investigation with preliminary data suggesting the combination of capecitabine and radiation is likely to be safe and effective. In addition, based on the efficacy in colon cancer, FOLFOX regimens have moved into clinical trials in the adjuvant setting.

Another unique aspect of rectal cancer is the use of neoadjuvant therapy. Preoperative radiation (with or without chemotherapy) is given to downstage the tumor before surgical resection to improve sphincter preservation.[50]

KEY CONCEPT Metastatic rectal cancer is treated with similar regimens as outlined in the colon cancer section that are used for palliation of symptoms.[50]

Patient Encounter Part 4

Despite completing six cycles of adjuvant chemotherapy, this patient's disease progresses, and a CT scan reveals metastases to his liver. The tumor is sent for pharmacogenomic profiling and is found to have the wild-type *KRAS* gene.

What pharmacologic treatment options are available for the treatment of his metastatic disease?

OUTCOME EVALUATION

The goals of monitoring are to evaluate whether the patient is receiving any benefit from the management of the disease, detect recurrence, and minimize the adverse effects of treatment. During treatment for active disease, patients should undergo monitoring for measurable tumor response, progression, or new metastases; these tests may include chest CT scans or X-rays, abdominal or pelvic CT scans or X-rays, depending on the site of disease being evaluated for response; and carcinoembryonic antigen (CEA) measurements every 3 months if the CEA level is or was previously elevated.[17] A positron emission tomography (PET) scan can be considered to identify localized sites of metastatic disease when a rising CEA level suggests metastatic disease but results of CT scans and other imaging studies are negative. Symptoms of recurrence such as pain, changes in bowel habits, rectal bleeding, pelvic masses, anorexia, and weight loss develop in fewer than 50% of patients. Patients who undergo curative surgical resection, with or without adjuvant therapy, require close follow-up because early detection and treatment of recurrence could still result in patient cures. In addition, early treatment for asymptomatic metastatic colorectal cancer appears superior to delayed therapy. Colorectal cancer surveillance guidelines published by the American Society of Clinical Oncology recommend against routinely monitoring liver function tests, complete blood count (CBC), FOBT, CT scans, annual chest X-rays, or pelvic imaging in asymptomatic patients.

In addition, a CBC should be obtained before each course of chemotherapy administration to ensure that hematologic values are adequate. In particular, white blood cell counts and absolute neutrophil counts can be decreased in patients receiving chemotherapy such as irinotecan and 5-FU. Baseline liver function tests and an assessment of renal function should be evaluated before and periodically during therapy. Other selected laboratory tests include checking for the presence of protein in the urine in patients receiving bevacizumab and monitoring of magnesium, calcium, and potassium in patients receiving cetuximab or panitumumab.

Patients should be evaluated during every treatment visit for the presence of anticipated side effects from their treatment, and healthcare practitioners should anticipate these adverse reactions and aggressively treat and prevent them from occurring. These generally include loose stools or diarrhea from irinotecan, 5-FU, and capecitabine; hand–foot syndrome from 5-FU and capecitabine; nausea or vomiting from irinotecan, 5-FU, and oxaliplatin; mouth sores from 5-FU; neuropathies from oxaliplatin; bleeding and hypertension from bevacizumab; and skin rash associated with cetuximab and panitumumab.

SUMMARY

Recent advances in the treatment of cancer of the colon and rectum now offer the potential to improve patient survival, but for many patients, improved DFS and PFS represent equally important therapeutic outcomes. In the absence of the ability of a specific treatment to demonstrate improved survival, important outcome measures should include the effects of the treatment on patient symptoms, daily activities, PS, and other quality-of-life indicators. Individualized patient care to balance the risks associated with treatment and benefits of a specific treatment regimen is necessary to optimize patient outcomes.

Patient Care Process

Collect Information:

- Perform a medication history for the use of prescription and nonprescription medications and dietary supplements. Identify allergies to medications and other substances.
- Review the medical history and physical assessment findings. Identify the stage of malignancy.
- Review patient-specific factors, tumor-specific factors, and laboratory information that may influence chemotherapy selection and drug dosing.
- Speak with the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.
- Compile a list of appropriate chemotherapy treatment regimens.

Assess the Information:

- Determine the goal of therapy and prognosis based on stage of disease.
- Review the medication history (including prescription and OTC medications) to identify agents that may worsen the patient's symptoms of colon cancer. Identify agents that effect bowel function (resulting in diarrhea or constipation) or agents such as NSAIDs that may cause GI bleeding.
- Determine whether the patient is taking any substance that could potentiate chemotherapy toxicities or interact with prescribed medications.
- Based on the medical history, determine whether the patient has compelling indications or contraindications for specific chemotherapy.
- Review relevant laboratory tests (eg, CBC, electrolytes, complete metabolic panel to determine liver and hepatic function, tumor markers, and tumor genetic profile) which might impact drug selection or dosing.
- Identify a list of the potential appropriate chemotherapy regimens and the related toxicities.
- Determine supportive care needs including nausea and vomiting control, pain management, prevention of infections, electrolyte supplementation, and toxicity management.
- Determine PS of the patient (see Chapter 88).

Develop a Care Plan:

- Review the chemotherapy order and assess efficacy, dosages, drug interactions, and possible adverse effects from the regimen (see Tables 91–3 and 91–5).

Implement the Care Plan:

- Discuss lifestyle modifications that may assist in symptom and disease management.
- Calculate the body surface area (BSA) and determine if doses are optimal and correct for this patient. Evaluate laboratory values to assist in this process.
- Review supportive care options to decrease the impact of adverse effects for this patient (see Chapters 88 and 99).
- Determine whether the patient has insurance coverage or whether recommended agents are included on the institution's formulary.
- Counsel patient on potential adverse effects of the regimen.

Follow-up: Monitor and Evaluate:

- Follow up when the patient is scheduled for their next round of chemotherapy. Assess the patient for adverse effects of the regimen or other supportive care measures that may need to be added (eg, pain management).
- Review medication history, physical examination, laboratory results, and other imaging and diagnostic tests to evaluate if the patient should continue on their current chemotherapy regimen.

Abbreviations Introduced in This Chapter

APC	Adenomatous polyposis coli
CapeOX	Capecitabine and oxaliplatin
CBC	Complete blood count
CEA	Carcinoembryonic antigen
COX-2	Cyclooxygenase-2
CTC	Computed tomographic colonography
dMMR	DNA mismatch repair
DFS	Disease-free survival
DPD	Dihydropyrimidine dehydrogenase
EGFR	Epidermal growth factor receptor
FAP	Familial adenomatous polyposis
FIT	Fecal immunochemical test
FOBT	Fecal occult blood test
FOLFIRI	Folinic acid, fluorouracil, and irinotecan
FOLFOX	Folinic acid, fluorouracil, and oxaliplatin
GI	Gastrointestinal
HNPCC	Hereditary nonpolyposis colorectal cancer
INR	International normalized ratio
MSI	Mircrosatellite instability
NSAID	Nonsteroidal anti-inflammatory drug
PET	Positron emission tomography
PFS	Progression-free survival
PS	Performance status
TNM	Tumor, node, metastasis
TP	Thymidine phosphorylase
UGT	UDP-glucuronosyltransferase
VEGF	Vascular endothelial growth factor

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Prostate Cancer

Amber B. Cipriani and Daniel J. Crona

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Identify risk factors associated with prostate cancer development.
2. Discuss the benefits and risks associated with prostate cancer screening.
3. Appraise the prognostic- and patient-specific data needed to determine appropriate treatment options.
4. Evaluate pharmacotherapeutic treatment options for patients with localized prostate cancer, metastatic **castration-sensitive prostate cancer** (mCSPC), nonmetastatic **castration-resistant prostate cancer** (nmCRPC), and metastatic castration-resistant prostate cancer (mCRPC).
5. Recognize common adverse effects and formulate a monitoring plan for patients receiving androgen deprivation therapy for prostate cancer based on patient-specific factors and the prescribed regimen.
6. Recognize the common adverse effects and formulate a monitoring plan for patients receiving treatment for metastatic prostate cancer.
7. Identify patients who are eligible for targeted treatment with poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors or immune checkpoint inhibitors based on molecular testing results.
8. Provide recommendations for bone health for patients undergoing treatment for prostate cancer.

INTRODUCTION

KEY CONCEPT Prostate cancer is the most frequently diagnosed cancer among men in the United States and represents the second leading cause of cancer-related deaths in all men.[1] The disease course ranges from indolent, asymptomatic tumors that may not require treatment to rapidly progressing, aggressive tumors that result in distant metastases, morbidity, and mortality.

EPIDEMIOLOGY AND ETIOLOGY

In the United States alone, it is estimated that 248,530 new cases of prostate cancer will be diagnosed, and more than 34,130 deaths will occur in 2021. Although prostate cancer incidence increased during the late 1980s and early 1990s due to widespread **prostate-specific antigen (PSA)** screening, prostate cancer–related deaths declined beginning around 2000, but have been stable since 2013.[1]

Prostate cancer risk factors include age, race/ethnicity, and family history of prostate cancer (Table 92–1).[2] Age is the greatest predictor of risk, and while the disease is rare among men under age 40, the incidence sharply increases with each subsequent decade of life.[3] An evaluation of autopsies from men who died of unrelated causes revealed prostate cancer in 2%, 29%, 32%, 55%, and 64% of men in their third, fourth, fifth, sixth, and eighth decades of life, respectively.[4]

Race

The incidence of clinical prostate cancer varies across geographic regions. Scandinavian countries and the United States report the highest incidences of prostate cancer, while it remains relatively rare in Japan and other Asian countries.[2] African American men have the highest rate of prostate cancer in the world, and prostate cancer mortality among African Americans is approximately twice that observed among Caucasian patients. Hormonal, dietary, and genetic differences, as well as differences in access to health care, may contribute to the variability in prostate cancer incidence and mortality among different populations.[2] Testosterone, commonly implicated in the pathogenesis of prostate cancer, is 15% higher in African American men, when compared to Caucasian men. Japanese men demonstrate decreased activity of 5-α-reductase, when compared with African American and Caucasian men.[5,6] In addition, variations in the androgen receptor (*AR*) gene exist. *AR* transcription is inversely correlated with the length of trinucleotide (CAG) repeats in the *AR* transactivation domain. Shorter CAG repeat sequences have been found in African Americans, and thus a combination of increased testosterone and *AR* activation may account for the increased prostate cancer risk among African Americans.[5]

Family History

Men with a brother or father with prostate cancer have twice the risk of prostate cancer compared to the rest of the population, and 5% to 10% of all prostate cancers are thought to be inherited.[7] Carriers of germline mutations in one of 16 DNA repair genes (eg, *BRCA1*, *BRCA2*, and *CHEK2*) are known to have an increased risk of developing prostate cancer and now eligible for the treatment with poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors.[8] **KEY CONCEPT** Germline genetic testing is now recommended for all men with metastatic, regional, or high to very high risk localized prostate cancer.[9]

Table 92–1

Risk Factors Associated With Prostate Cancer

Factor	Possible Relationship
Probable Risk Factors	
Age	> 70% of cases are diagnosed in men older than 65 years
Race	African Americans have a higher incidence and death rate
Genetic	Familial prostate cancer inherited in an autosomal dominant manner Germline mutations in 1 of 16 DNA repair genes (eg, *BRCA1, BRCA2, ATM,* and *CHEK2*) are associated with increased prostate cancer risk and severity
Possible Risk Factors	
Environmental	Clinical carcinoma incidence varies worldwide Latent carcinoma similar between regions Nationalized men adopt intermediate incidence rates between that of the United States and their native country
Occupational	Increased risk associated with cadmium exposure
Dietary	Mediterranean diet associated with reduced risk of prostate cancer Increased risk associated with high-meat and high-fat diets Decreased intake of 1,25-dihydroxyvitamin D, lycopene, and β-carotene increases risk
Hormonal	Does not occur in castrated men Low incidence in cirrhotic patients Up to 80% are hormonally dependent African Americans have 15% increased testosterone Japanese have decreased 5-α-reductase activity Polymorphic expression of the androgen receptor gene

Other Factors

Benign prostatic hyperplasia (BPH) is common among elderly men, affecting more than 40% of men older than 70 years. BPH results in urinary symptoms (eg, hesitancy and frequency). Because prostate cancer affects a similar age-group and often has similar presenting symptoms, the presence of BPH often complicates the diagnosis of prostate cancer, although it does not appear to increase the risk of prostate cancer.[6] Smoking has not conclusively been associated with an increased risk of prostate cancer, but smokers with prostate cancer have an increased mortality from the disease, when compared with nonsmokers with prostate cancer.[6]

PATHOPHYSIOLOGY

The prostate gland is a solid, walnut-shaped organ positioned between the neck of the bladder and the urogenital diaphragm (Figure 92–1). More than 95% of prostate cancer cases are adenocarcinomas.[10] Rarer tumor types include small cell neuroendocrine cancers, sarcomas, and transitional cell carcinomas.

Prostate cancer can be graded systematically according to the histologic appearance of the malignant cell and then categorized into well-, moderately, or poorly differentiated grades.[10,11] Gland architecture is examined and then rated on the Gleason scale of 1 (well-differentiated) to 5 (poorly differentiated). At least two different specimens are examined, and the score for each specimen is added together. Groupings for total Gleason score are 2 to 4 for well-differentiated, 5 to 6 for moderately differentiated, and 7 to 10 for poorly differentiated tumors. Poorly differentiated tumors grow rapidly (poor prognosis), while well-differentiated tumors grow slowly (better prognosis).

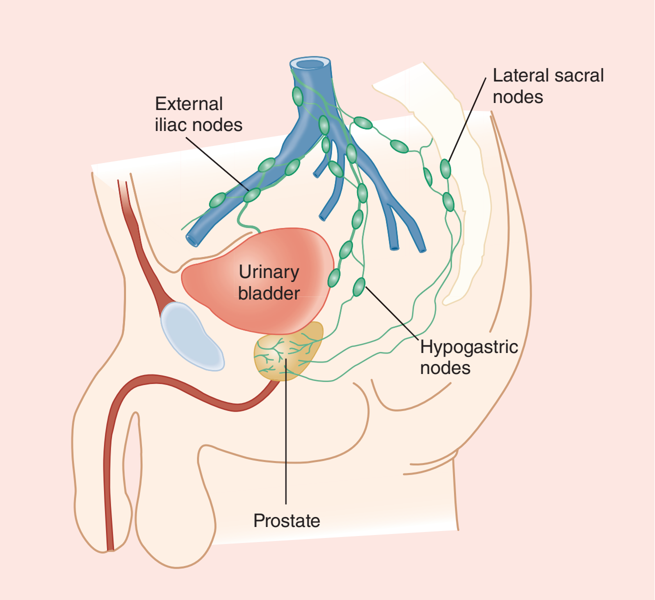

FIGURE 92–1. The prostate gland. (From DiPiro JT, Yee GC, Posey M, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill, 2020:2304.)

Metastatic spread can occur by local extension, lymphatic drainage, or hematogenous dissemination.[10,11] Lymph node metastases are more common in patients with large, undifferentiated tumors that invade the seminal vesicles. Pelvic and abdominal lymph nodes are the most common sites of lymph node involvement (see Figure 92–1). Osseous skeletal metastases from hematogenous spread are the most common sites of distant spread. The most common site of bone involvement is the lumbar spine. The lung, liver, brain, and adrenal glands are the most common sites of visceral involvement; however, initial metastatic invasion does not occur in visceral organs, and the prostate is rarely a site for the metastatic spread of other solid tumors.

Normal growth and differentiation of the prostate depends on the presence of androgens, specifically dihydrotestosterone (DHT).[11,12] The testes and the adrenal glands are the major sources of circulating androgens. Hormonal regulation of androgen synthesis is mediated through a series of biochemical interactions among the hypothalamus, pituitary, adrenal glands, and testes (Figure 92–2).

Testosterone, the major androgenic hormone, accounts for 95% of the androgen concentration.[12] The primary source of testosterone is the testes; however, 3% to 5% of testosterone is derived from direct adrenal cortical secretion of testosterone or C19 steroids such as androstenedione.[11] In the prostate, 5-α-reductase converts testosterone to a more active form, DHT, and DHT is the active ligand that binds and activates the AR.

In early-stage prostate cancers, aberrant tumor cell proliferation is promoted by DHT-induced activation of the AR signaling axis. Blockade and reduction of circulating androgens can induce tumor regression in most patients. Hormonal manipulations to reduce circulating androgens can occur through several mechanisms (Table 92–2).[13,14] The testes can be removed surgically

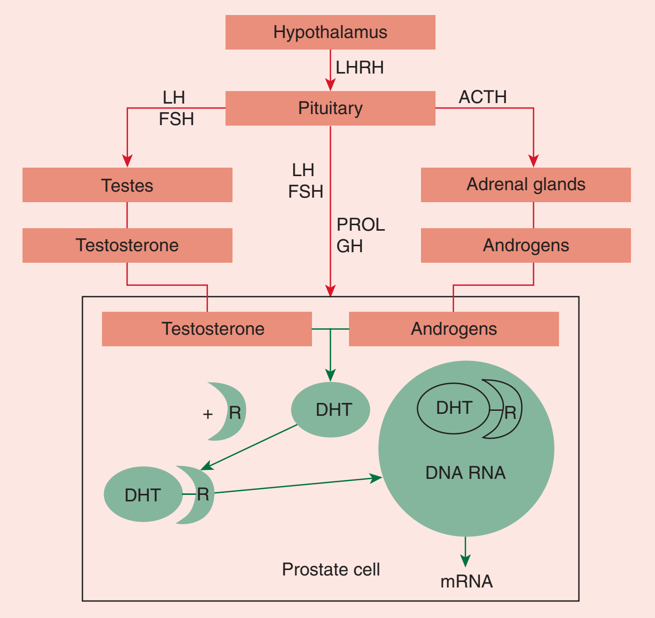

FIGURE 92–2. Hormonal regulation of the prostate gland. (ACTH, adrenocorticotropic hormone; DHT, dihydrotestosterone; DNA, deoxyribonucleic acid; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; LHRH, luteinizing hormone–releasing hormone; PROL, prolactin; R, receptor; RNA, ribonucleic acid.) (From DiPiro JT, Yee GC, Posey M, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill, 2020:2304.)

(orchiectomy) to limit androgen production, or chemical interference of hormonal pathways that modulate prostatic growth can be accomplished at several steps using androgen deprivation therapy (ADT) (see Figure 92–2). Reduction in the release of luteinizing hormone (LH) and LH-releasing hormone (LHRH) (also known as gonadotropin-releasing hormone [GnRH]) by estrogens, LHRH agonists, direct GnRH antagonists, progesterones, and cyproterone acetate can also reduce testosterone secretion from the testes.[11,14]

Table 92–2

Hormonal Manipulations in Prostate Cancer

- Androgen Source Ablation
    - Orchiectomy
    - Adrenalectomy
    - Hypophysectomy
- LHRH or LH inhibition
    - Estrogens
    - LHRH agonists
    - Progesterones[a]
    - Cyproterone acetate[b]
- Androgen synthesis inhibition
    - Abiraterone
    - Aminoglutethimide
    - Ketoconazole
    - Progesterones[a]
- Antiandrogens
    - Flutamide
    - Bicalutamide
    - Nilutamide
    - Enzalutamide
    - Cyproterone acetate[b]
    - Progesterones
- 5-α-Reductase inhibition
    - Finasteride[b]
    - Dutasteride[b]
- GnRH antagonists
    - Degarelix
    - Relugolix

[a] Minor mechanisms of action.

[b] Investigational compounds or use.

GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; LHRH, luteinizing hormone–releasing hormone.

The physiologic response to LHRH depends on both the dose and the mode of administration. Intermittent pulsed LHRH administration, which mimics the endogenous release pattern, results in sustained release of both LH and follicle-stimulating hormone (FSH); however, high dose or continuous infusions of LHRH inhibit gonadotropin release via receptor downregulation. Structural modification of the naturally occurring LHRH, combined with innovative delivery methods, has produced a series of LHRH agonists that cause a similar downregulation of pituitary receptors, and a decrease in testosterone production.[15] Androgen synthesis can also be inhibited in the testes or adrenal gland. Pregnenolone is the precursor substrate for all adrenal-derived steroids, including androgens, glucocorticoids, and mineralocorticoids. Abiraterone is a specific and potent inhibitor of CYP17A1, decreasing the conversion of pregnenolone to dehydroepiandrosterone (DHEA), a required precursor for testosterone. Ketoconazole, an imidazole antifungal agent, causes a dose-related reversible reduction in serum cortisol and testosterone concentration through a similar mechanism. Megestrol is a synthetic derivative of progesterone that also inhibits the synthesis of androgens. This inhibition appears to occur at the adrenal level, but circulating levels of testosterone are also reduced, suggesting that inhibition at the testicular level may also occur.[15]

The conversion of testosterone to DHT may be inhibited by 5-α-reductase inhibitors. However, antiandrogens inhibit the formation of the DHT–receptor complex and thereby interfere with androgen-mediated action at the cellular level. Antiandrogens, and not 5-α-reductase inhibitors, have demonstrated the most therapeutic utility in the treatment of prostate cancer.[15]

In advanced stages of the disease, prostate cancer cells may be able to survive and proliferate without the growth signals normally provided by circulating androgens. When this occurs, these tumors are referred to as castration-resistant prostate cancer (CRPC) (previously described as "hormone refractory" or "androgen independent"). Because tumors remain amenable to secondary hormonal manipulations, and because the reintroduction of androgens can continue to promote tumor growth, the term castration resistant more accurately reflects the clinical picture.

PREVENTION AND EARLY DETECTION

Screening

Early detection of potentially curable cancers is the goal of prostate cancer screening. For cancer screening to be beneficial, it must reliably detect cancer at an early stage and identify those cancers that would benefit from an early intervention to decrease

Patient Encounter 1: Prevention and Screening

A 62-year-old African American man with a medical history significant for BPH presents to the pharmacy for a refill of his finasteride. He wants to know what he can do to reduce his risk of prostate cancer. He has a family history of prostate cancer (paternal father died of prostate cancer at 84 years old) and breast cancer (his paternal grandmother died of breast cancer at 72 years old), but he has never been screened for prostate cancer.

What do you recommend for prostate cancer screening?

Do you recommend genetic testing for this patient?

mortality. Whether prostate cancer screening fits these criteria has generated considerable controversy.[16,17] Digital rectal examination (DRE) has been a recommended prostate cancer screening method since the early 1900s. Primary advantages of DRE include specificity for detecting prostate cancer (> 85%), low cost, safety, and ease of performance. However, DRE has only moderate sensitivity (approximately 60%), and is subject to interclinician variability.

KEY CONCEPT PSA is a useful marker for detecting prostate cancer at early stages, predicting outcome for localized disease, monitoring disease-free status, and monitoring response to treatment of advanced-stage disease. PSA is a member of the human kallikrein gene family of serine proteases. PSA is produced by columnar secretory cells in the prostate and plays a role in the liquefaction of seminal fluid. PSA levels are detected via a blood test, and levels greater than 10 ng/mL (10 mcg/L) are associated with prostate cancer. While the relative ease and noninvasive nature of the PSA test make it the preferred method for screening, the low specificity for prostate cancer detection is a significant limitation.[18,19] In addition to patients with prostate cancer, PSA may also be elevated in men who are smokers, cases of acute urinary retention, acute prostatitis, and prostatic ischemia or infarction, as well as in patients with BPH (an extremely common condition in men at risk of prostate cancer). PSA elevations between 4.1 and 10 ng/mL (4.1-10 mcg/L) cannot distinguish between BPH and prostate cancer, which limits the utility of PSA alone for the early detection of prostate cancer. Additionally, not all men with clinically significant prostate cancer have a serum PSA outside of the reference range.[16] Specific recommendations for screening vary amongst different professional organizations, ranging from recommendations against PSA screening all together to recommendations to initiate screening in high-risk men (eg, men as young as 45 years old) who have had a balanced discussion with their provider.

Chemoprevention

The use of 5-α-reductase inhibitors, such as finasteride and dutasteride, as chemopreventive strategies for prostate cancer has been debated for many years.[20,21] Both finasteride and dutasteride can falsely lower PSA by approximately 50%, which should be a consideration for clinicians initiating these medications. Although no prospective studies have validated PSA monitoring thresholds in patients receiving 5-α-reductase inhibitors, the PSA threshold can be lowered by 50% (eg, a PSA of 4 ng/mL [4 mcg/L] for a patient receiving dutasteride that would be equivalent to a PSA of 8 ng/mL [8 mcg/L] for a patient not prescribed 5-α-reductase inhibitor).

Data regarding the effectiveness of finasteride and dutasteride on reducing the risk of prostate cancer were assessed in individual studies, and then later evaluated in a comprehensive Cochrane Review of 41,638 patients.[20] The use of 5-α-reductase inhibitors reduced the risk of prostate cancer by 25% when compared to placebo; however, patients who were diagnosed with prostate cancer presented with higher-grade (Gleason 7–10) prostate tumors, when compared to those diagnosed from the placebo arm. Adverse effects observed more commonly in the 5-α-reductase inhibitor treatment arms included decreased libido, erectile dysfunction, and gynecomastia.

Based on the risk of development of more aggressive prostate tumors, combined with a lack of overall survival benefit and increased risk of adverse effects, the use of 5-α-reductase inhibitors for prostate cancer prevention is not recommended. The American Society of Clinical Oncology and the American Urological Association (AUA) guidelines recommend that asymptomatic men who have a PSA of 3 ng/mL or less, and continue to be screened with regular PSA levels, may benefit from a discussion of both the benefits (eg, possible reduced risk of prostate cancer) and potential risks (eg, adverse effects and the possibility of high-grade tumors) of 5-α-reductase inhibitor therapy.[22] Patients who are prescribed 5-α-reductase inhibitors for benign conditions (eg, lower urinary tract symptoms) may benefit from a similar discussion.

Table 92–3

Diagnostic and Staging and Classification Systems Workup for Prostate Cancer

Initial tests	DRE PSA TRUS (if either DRE is positive or PSA is elevated) Biopsy
Staging tests	Gleason score on biopsy specimen CBC Liver function tests Serum phosphatases (acid/alkaline) Excretory urography
Additional staging tests (dependent on tumor classification, PSA, and Gleason score)	Bone Scan Multiparametric MRI Lymph node evaluation Pelvic/abdominal CT ^{111}In labeled capromab pendetide scan Bipedal lymphangiogram Transrectal MRI

CBC, complete blood count; CT, computed tomography; DRE, digital rectal examination; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; TRUS, transrectal ultrasonography.

CLINICAL PRESENTATION AND DIAGNOSIS (TABLE 92–3)

KEY CONCEPT The prognosis for patients with prostate cancer depends on the histologic grade and stage of the prostate cancer. Details of staging are discussed in Chapter 88 and can also be

Clinical Presentation of Prostate Cancer

Localized Disease

Asymptomatic

Locally Invasive Disease

Ureteral dysfunction, frequency, hesitancy, and dribbling

Impotence

Advanced Disease

Back pain

Cord compression

Lower extremity edema

Pathologic fractures

Anemia

Weight loss

found in seminal guidelines.[9] One of the most important prognostic criteria appears to be the histologic grade, assessed by Gleason score, because poorly differentiated tumors ultimately impact disease staging. Poorly differentiated tumors are highly associated with both regional lymph node involvement and distant metastases.[10] Once the tumor has spread into regional lymph nodes, there is a significantly increased risk of disease recurrence after curative intent therapy. In order to complete a full diagnostic workup, patients should have a DRE, receive relevant imaging studies, undergo a biopsy for tissue diagnosis, obtain baseline PSA and testosterone levels, and participate in an interview to determine both relevant comorbidities (to determine life expectancy) and family history (to inform the need for germline genetic testing).[9]

TREATMENT

Desired Outcome

The desired outcome in early-stage prostate cancer is to minimize morbidity and mortality from prostate cancer, with an acceptance that some degree of morbidity may occur as a result of treatment.[9] Early-stage disease may be treated with surgery, radiation, or observation/active surveillance. Although surgery and radiation can be curative, they are associated with significant morbidity. Because the overall goal is to minimize morbidity and mortality associated with the disease, observation/active surveillance are appropriate in selected individuals who wish to avoid morbidity, or for whom aggressive interventions may not be clinically appropriate (eg, comorbid conditions). Advanced prostate cancer, where there is evidence of metastatic spread, is not curable. Treatment of advanced disease should focus on providing symptom relief and maintaining the quality of life. The cornerstone treatment for advanced prostate cancer is ADT, with the goal of reducing testosterone to castration levels through surgical or pharmacological treatment modalities.

General Approach to Treatment

The initial treatment for prostate cancer depends on the disease stage, Gleason score, presence of symptoms, and life expectancy of the patient.[9] Table 92–4 provides details of the recurrence risk stratification and recommended treatment options based on prognosis and life expectancy for patients who present with localized prostate cancer. The backbone of treatment for patients, at low-to-intermediate risk of prostate cancer recurrence, is local therapy with radiation and/or surgery, rather than systemic treatment with medication. Given the indolent nature of many prostate cancers, monitoring patients with low-risk disease and limited life expectancy with observation is an option. For these patients, noncurative treatment would be considered at progression. In contrast to monitoring patients through observation, active surveillance implies that curative therapies with some expected morbidity would be pursued upon progression of disease. In patients who are of sufficient risk to warrant invasive procedures, radiation therapy (external beam or brachytherapy), or radical prostatectomy (with or without a pelvic lymph node dissection [PLND]) can be considered.[9] Because patients with asymptomatic, early-stage disease generally have an excellent 10-year survival rate, the immediate morbidities associated with prostatectomy or radiation must be balanced with the lower likelihood of dying from prostate cancer. In general, more aggressive treatments for early-stage prostate cancer are reserved for younger men, although patient preference is a major consideration in all treatment decisions.

Radical prostatectomy and radiation therapy are generally considered therapeutically equivalent for localized prostate cancer.[9] Complications from radical prostatectomy include blood loss, stricture formation, incontinence, lymphocele, fistula formation, anesthetic risk, and impotence. Nerve-sparing radical prostatectomy can be performed in many patients, and 50% to 80% regain sexual potency within the first year. Acute complications from radiation therapy include cystitis, proctitis, hematuria, urinary retention, penoscrotal edema, and impotence (30% incidence).[9,10] Chronic complications include proctitis, diarrhea, cystitis, enteritis, impotence, urethral stricture, and incontinence.[10] Because radiation and prostatectomy have significant and immediate morbidity compared with observation alone, some patients may elect to postpone therapy until they become symptomatic.

Systemic therapy with ADT can be considered in patients with unfavorable intermediate risk and can be combined with radiation treatment depending on the presence of lymph node metastases.

The management of patients with a high and very high risk of localized prostate cancer recurrence includes the use of systemic treatments, including ADT and other drugs, in addition to local therapy with radiation/surgery (Table 92–4). Choice of initial management of these patients should include consideration of patient symptom burden as well as life expectancy. Radiation tends to be most common in this patient population, although selected individuals with a low tumor volume may receive a radical prostatectomy, with or without PLND. The duration of treatment with ADT in patients with higher risk disease is longer than in those with low intermediate–risk disease. **KEY CONCEPT** Androgen deprivation with an LHRH agonist should be used in combination with radiation therapy for patients with high or very high risk, locally advanced prostate cancer to improve outcomes over radiation therapy alone.[28]

In patients who are found to have regional lymph node involvement of their prostate cancer, and who have a life expectancy of more than 5 years, ADT is the backbone of therapy and may be combined with radiation and/or abiraterone + prednisone. Secondary hormonal manipulations, therapies that target the AR signaling axis, cytotoxic chemotherapy, immunotherapy, radiopharmaceutical therapy, or best supportive care are used for patients who progress after initial therapy.[9]

Patient Encounter 2: Early-Stage Disease

A 70-year-old man was found to have an abnormal DRE. His PSA was found to be elevated at 22 ng/mL. A prostate biopsy was performed by TRUS, which revealed an adenocarcinoma with a Gleason score of 9 (4 + 5). His tumor was staged as T_{3a} (evidence of tumor extension outside the prostate). He has a medical history of hypertension but is otherwise healthy. He expresses a wish to pursue aggressive therapy.

How would you stratify this patient's risk of developing progressive or metastatic prostate cancer?

What testing would you recommend for this patient?

What treatment options would you consider for a patient with this level of risk of developing progressive or metastatic prostate cancer?

Table 92–4

Initial Management of Localized Prostate Cancer[9 a,b]

Recurrence Risk	Disease Features		Expected Survival (years)	Initial Therapy
Very Low	T_{1c} and Gleason ≤ 6 and PSA < 10 ng/mL (mcg/L) and < 3 biopsy cores positive with ≤ 50% cancer in each core and PSA density < 0.15 ng/mL/g		< 10 10–20 >20	Observation AS AS *or* RP *or* RT
Low	T_1–T_{2a} and Gleason ≤ 6 and PSA < 10 ng/mL (mcg/L)		< 10 >10	Observation AS *or* RP ± PLND *or* RT
Intermediate	Has one or more intermediate risk factors (IRF): • T_{2b}–T_{2c} • Gleason 7 • PSA 10–20 ng/mL (mcg/L)	**Favorable intermediate:** • 1 IRF • Gleason 3 + 4 • < 50% of biopsy cores positive	< 10 >10	Observation *or* RT AS *or* RT *or* RP ± PTLD
		Unfavorable intermediate: • 2–3 IRFs • Gleason 4 + 3 • ≥ 50% biopsy cores positive	< 10 >10	Observation *or* RT + 4–6 months of ADT *or* intensive RT ± 4–6 months of ADT RP ± PLND (with addition of RT and/*or* ADT depending on lymph node involvement) *or* RT + 4–6 months of ADT *or* intensive RT ± 4–6 months of ADT
High	T_{3a} or Gleason 8–10 or PSA > 20 ng/mL (mcg/L)		< 5 AND asymptomatic	Observation *or* ADT *or* RT
Very High **Locally Advanced**	$T_{3b–T4}$ or primary Gleason pattern 5 or > 4 cores with Gleason 8–10		≥ 5 OR with symptoms	RT + ADT (x1–3 years) *or* RP + PLND with addition of RT and/or ADT depending on lymph node involvement
Regional	Any T, N1, M0		< 5 AND asymptomatic ≥ 5 OR with symptoms	Observation *or* ADT ADT + RT *or* ADT + RT + abiraterone + steroid

[a] ADT = serum testosterone levels < 50 ng/dL (1.74 nmol/L).

[b] Medical, or surgical ADT are equivalent.

AS, active surveillance; ADT, androgen deprivation therapy; PLND, pelvic lymph node dissection; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy.

Data from National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology—Prostate Cancer Version 02.2020. 2020. Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf (accessed August 16, 2020).

Nonpharmacologic Therapy

▶ *Observation/Active Surveillance*

Observation involves monitoring the course of the disease and initiating palliative treatment if cancer progresses or the patient becomes symptomatic. PSA and DRE testing are performed every 6 to 12 months, but invasive biopsies are not performed if progression is suspected. The goal of observation is to maintain quality of life in the setting of a prostate cancer diagnosis and is most appropriate in elderly, frail men with limited life expectancy. In subtle contrast, patients treated with active surveillance have the intent of initiating curative treatment approaches should the cancer appear to progress. PSA and DRE testing are performed every 6 to 12 months, and prompt biopsies are indicated if progression is expected. Active surveillance is employed in younger patients with long-life expectancies who want to delay the morbidity associated with curative treatments, such as surgery, radiation, or ADT.

▶ *Orchiectomy*

Bilateral orchiectomy, or surgical removal of the testes, is a form of ADT that rapidly reduces circulating androgens to castration levels (ie, serum testosterone levels < 50 ng/dL [1.7 nmol/L]).[9] However, many patients find this procedure psychologically unacceptable, while others are simply not surgical candidates because of age. Orchiectomy may be the preferred initial treatment for patients with impending spinal cord compression or ureteral obstruction.

▶ *Radiation*

The two commonly used methods for radiation therapy are external beam radiotherapy (EBRT) and brachytherapy.[27-29] In EBRT, doses of 75 to 79 Gray (Gy) are delivered in 35 to 41 fractions in patients with low-grade prostate cancer and up to 81 Gy for those with intermediate- or high-grade prostate cancer. Brachytherapy involves the permanent implantation of radioactive beads of 145 Gy of ^{125}iodine or 125 Gy of ^{103}palladium and is generally reserved for individuals with low-risk cancers. Radiation therapy may be used to treat local, or locally advanced prostate cancer with curative intent. In later stages of disease, short courses of EBRT can be used to palliate symptoms.[9,23]

▶ *Radical Prostatectomy*

Radical prostatectomy is performed in patients with resectable disease who are surgical candidates, and who require definitive therapy based on both risk factors and patient preference.

Complications from radical prostatectomy include blood loss, stricture formation, incontinence, lymphocele, fistula formation, anesthetic risk, and impotence. The procedure can be combined with a regional lymph node dissection to ensure that the disease has not extended to the local lymph nodes.

Pharmacologic Therapy for Early-Stage Disease

▶ *Luteinizing Hormone–Releasing Hormone Agonists*

LHRH agonists are a reversible method of ADT and as effective as orchiectomy in treating prostate cancer.[9,24] Currently, the list of approved LHRH agonists include leuprolide, leuprolide depot, leuprolide implant, triptorelin depot, triptorelin implant, histrelin LA, and goserelin acetate implant. Leuprolide can be administered every 4, 12, 16, or 24 weeks; goserelin every 4 or 12 weeks; triptorelin every 4, 12, or 24 weeks; and histrelin every 12 months. The leuprolide depot formulation contains leuprolide acetate in coated pellets. The dose is administered intramuscularly, and the coating dissolves at different rates to allow sustained leuprolide levels throughout the dosing interval. The goserelin implant contains goserelin acetate dispersed in a plastic matrix of D,L-lactic and glycolic acid copolymer and is administered subcutaneously. Hydrolysis of the copolymer material provides continuous release of goserelin over the dosing period. Triptorelin LA is administered as an intramuscular injection (11.25 mg) every 84 days. Triptorelin depot is a 3.75 mg formulation injected every 28 days. Histrelin LA is surgically implanted every 12 months.

Several randomized trials have demonstrated that leuprolide, goserelin, histrelin, and triptorelin are effective agents when used alone in patients with advanced prostate cancer.[14] Response rates of approximately 80% have been reported. The choice between the four LHRH agonists is usually made on the basis of cost, as well as patient and prescriber administration schedule preferences.

The most common adverse effects reported with LHRH agonist therapy include vasomotor symptoms, such as hot flashes, erectile dysfunction, decreased libido, and injection-site reactions. Long-term adverse effects include decreased bone mineral density and metabolic syndrome.[14] Disease flare within the first week of therapy can be caused by an initial induction of LH and FSH that is induced by the LHRH agonist, leading to an initial period of increased testosterone production. Tumor flare manifests clinically as an exacerbation of disease-related symptoms, primarily increased bone pain or urinary symptoms.[9] The reaction usually resolves after 2 weeks and has a similar onset and duration pattern for the various depot LHRH agonist formulations. Initiating an antiandrogen (see Table 92–2) prior to LHRH agonist administration, and continuing for 2 to 4 weeks, is a frequently used strategy to minimize initial tumor flare.

LHRH agonist monotherapy can be used as initial therapy for advanced prostate cancer, with response rates similar to orchiectomy.[9] A lower incidence of cardiovascular-related adverse effects associated with LHRH agonist therapy has been observed, when compared to estrogens. Patients should be advised that a tumor flare could occur in the first week but could be mitigated by the addition of an antiandrogen during that period. Caution should be exercised if initiating LHRH agonists in patients with the potential for ureteral obstruction or spinal cord impingement because irreversible complications may occur.

Another potentially serious complication of ADT is decreased bone mineral density, leading to an increased risk of osteoporosis, osteopenia, and skeletal fractures.[25] Men initiated on long-term ADT should generally have a baseline bone mineral density test and be initiated on calcium and vitamin D supplementation.[9]

▶ *Gonadotropin-Releasing Hormone Antagonists*

An alternative to LHRH agonists are GnRH antagonists, degarelix or relugolix.[26] These agents reversibly bind to GnRH receptors on cells in the pituitary gland, reducing the production of testosterone to castration levels. The major advantage of direct GnRH antagonists over LHRH agonists is the speed at which they can achieve the drop in testosterone levels; castration levels are achieved in 7 days or less (compared to 28 days with leuprolide), which eliminates the risk of tumor flare and the need to initiate a concomitant antiandrogen. Degarelix is equivalent to leuprolide in lowering testosterone levels for up to 1 year and is approved for the treatment of advanced prostate cancer. Degarelix is available as 40 and 20 mg/mL (mcg/L) vials for subcutaneous injection, and the starting dose is 240 mg followed by 80 mg every 28 days. The starting dose should be split into two 120 mg injections. Relugolix is an oral tablet that is superior to leuprolide in lowering testosterone levels over 100 days and approved in advanced prostate cancer. The first dose of relugolix is 360 mg on day 1, followed by 120 mg daily thereafter.

The most frequently reported adverse effects include injection-site reactions (degarelix only), including pain, erythema, swelling, induration, and nodules. Most adverse effects are transient and mild to moderate, leading to discontinuation in less than 1% of patients. Other adverse effects include liver function test (LFT) elevations and osteoporosis. Because of the risk of developing osteoporosis, calcium and vitamin D supplementation should be considered. Degarelix not approved in combination with antiandrogens.

▶ *Antiandrogens*

Antiandrogens bind cytosolic AR, thereby decreasing available binding sites for endogenous androgens to activate the AR. First-generation nonsteroidal antiandrogens are flutamide, bicalutamide, and nilutamide (Table 92–5). Monotherapy with first-generation antiandrogens is less effective than LHRH agonist therapy. Therefore, for advanced prostate cancer, all currently available antiandrogens are indicated only in combination with ADT: flutamide and bicalutamide are indicated in combination with an LHRH agonist, while nilutamide is indicated after **orchiectomy**.

The most common antiandrogen-related adverse effects are listed in Table 92–5. Diarrhea is reported more frequently with flutamide than bicalutamide. Few clinical trials have been conducted to directly compare the first-generation antiandrogens.[9]

▶ *Combined Androgen Blockade*

Although up to 80% of patients with advanced prostate cancer respond to initial hormonal manipulation, almost all patients progress within 2 to 4 years after initiating therapy. Two main mechanisms of androgen reactivation have been proposed: (1) the tumor could be heterogeneously composed of cells that are hormone dependent and hormone independent, or (2) the tumor could be stimulated by extratesticular androgens (including intratumoral synthesis of androgens) that are converted intracellularly to DHT. Combined androgen blockade (CAB), which is the combination of LHRH agonists or orchiectomy with first-generation antiandrogens, aims to interfere with multiple hormonal pathways to more completely ablate androgens.

Table 92–5

First-Generation Antiandrogens

Antiandrogen	Usual Dose	Adverse Effects
Flutamide	750 mg/day	Gynecomastia Hot flushes Gastrointestinal disturbances (diarrhea) Liver function test abnormalities Breast tenderness Methemoglobinemia
Bicalutamide	50 mg/day	Gynecomastia Hot flushes Gastrointestinal disturbances (diarrhea) Liver function test abnormalities Breast tenderness
Nilutamide	300 mg/day for first month; then 150 mg/day	Gynecomastia Hot flushes Gastrointestinal disturbances (nausea or constipation) Liver function test abnormalities Breast tenderness Visual disturbances (impaired dark adaptation) Alcohol intolerance Interstitial pneumonitis

Many studies have been performed comparing CAB with conventional medical or surgical castration. A meta-analysis of 27 trials revealed a small (3.2%), but statistically significant, improvement in 5-year survival for patients treated with CAB, when compared to ADT alone.[27] However, adverse effects are far more common in patients who receive CAB and include diarrhea, LFT elevations, and anemia. Because the benefits of CAB are relatively small, and the increased adverse effects are not insignificant, it is appropriate to use either LHRH agonist monotherapy or CAB as initial therapy for metastatic prostate cancer. CAB may be most beneficial for improving survival in patients with minimal disease and preventing tumor flare.[9] All other patients may be started on LHRH agonist monotherapy, and an antiandrogen may be added after several months if androgen ablation is incomplete, or if disease progression occurs despite a castration level of testosterone.[28]

There is a considerable debate about when to start ADT in advanced prostate cancer patients.[14] The original recommendation to start therapy when symptoms appeared was based on trials that revealed no overall survival difference between patients who started diethylstilbestrol (DES) initially versus those who crossed over to DES treatment when symptoms arose. More recent data demonstrate that early intervention, before symptoms appear, may be appropriate; however, this continues to be balanced by patient goals and quality of life considerations.[29]

Given the morbidity of ADT, intermittent dosing strategies that allow for a break in therapy to restore the quality of life (and some suggest possibly resensitize cancer cells to hormonal blockade) have been investigated. A meta-analysis of 15 separate studies representing over 6000 patients found intermittent ADT noninferior for the overall survival and revealed some improvements in quality of life scores, when compared to continuous ADT dosing.[30] Intermittent ADT should be considered in men who experience significant adverse effects from ADT, and who are willing to undergo more frequent PSA and testosterone monitoring during off-treatment periods.

Patient Encounter 3: Progressive disease

A 66-year-old man was initially diagnosed with localized prostate cancer 2 years ago. At that time, he was classified as high risk and chose to undergo EBRT with the addition of ADT. He was initiated on ADT (leuprolide). His PSA had been stable for some time but has begun to rise over the last 6 months. His PSA 2 months ago was 12 ng/mL, 1 month ago was 27 ng/mL, and today is 45 ng/mL. Imaging studies do not reveal any sites of metastatic disease. His testosterone level today is 10 ng/dL.

How would you characterize the patient's disease?

What pharmacotherapeutic options are available to the patient?

Pharmacologic Therapies in Recurrent and Metastatic Disease

Men who present with or develop metastatic disease while not actively receiving ADT are considered to have metastatic castration-sensitive prostate cancer (mCSPC). This population is treated differently than those who develop metastatic disease despite the use of ADT, known as CRPC. Treatment of men who present with highly aggressive or metastatic disease may involve combinations of ADT with second-generation antiandrogens or cytotoxic chemotherapy. Secondary (or salvage) therapies for patients who progress after their initial treatments depend on the treatment modalities initially employed. For patients diagnosed with localized prostate cancer recurrence, radiotherapy may be used for local disease recurrence after radical prostatectomy. Alternatively, ADT can be used in patients who progress after either radiation therapy or radical prostatectomy.[9,28] Table 92–6 describes the medications used to treat advanced/metastatic prostate cancer.

ADT in Recurrent and Metastatic Prostate Cancer

There is debate about when to initiate ADT in patients who receive local therapy (surgery or radiation) and experience rising PSA levels without radiographic evidence of progression, also known as biochemical recurrence. In these patients, clinicians are encouraged to consider PSA doubling time (eg, how quickly the PSA level is rising), patient life expectancy, the toxicity of ADT, and patient wishes while determining when to initiate ADT.[9]

In patients who progress after initial treatment with ADT alone, secondary hormonal manipulations may be considered. This may include adding an antiandrogen for a patient who either incompletely suppresses testosterone secretion with an LHRH agonist. In patients who progress during CAB, withdrawing antiandrogens, or using agents that inhibit the AR signaling axis, may be considered.[28]

KEY CONCEPT Antiandrogen withdrawal can provide additional symptomatic relief for patients who progress while receiving combined hormonal blockade with an LHRH agonist and an antiandrogen. For patients who receive CAB with an LHRH agonist

Table 92–6

Agents Used in the Treatment of Advanced Prostate Cancer

Drug	Usual Dose	Adverse Effects	Dose Adjustments
Androgen Synthesis Inhibitor			
Abiraterone + Prednisone	500 mg twice daily (1 hour before or 2 hours after a meal) 5 mg once or twice daily	Gastrointestinal disturbances (diarrhea), edema, hypokalemia, hypophosphatemia, hypertension, LFT abnormalities, hypertriglyceridemia	Hepatic Reduce starting dose to 250 mg/day for moderate hepatic impairment Child–Pugh class B), and avoid Child–Pugh class C; withhold treatment if AST/ALT > 5 × ULN or bilirubin > 3 × ULN; DDI Use cautiously with concomitant CYP3A4 inhibitors and inducers
Second-Generation Antiandrogens			
Apalutamide	240 mg PO once daily	Fatigue, hypertension, rash, hypothyroidism, fracture, risk of seizure	*No renal or hepatic dose adjustments* DDI Strong CYP3A4 and CYP2C19 inducer Weak CYP2C9, PGP, BCRP, and OATP1B1 inducer Substrate of CYP2C8 (major) and CYP3A4 (minor)
Darolutamide	600 mg twice daily with food	Fatigue, rash, pain in extremities, decrease in neutrophil count, increase in AST, increase in bilirubin	Renal Reduce dose to 300 mg twice daily for eGFR 15–29 mL/min, not studied in eGFR < 15 mL/min Hepatic Reduce dose to 300 mg twice daily for moderate impairment; not studied in severe impairment DDI Weak CYP3A4 inducer Weak BCRP, OATP1B1 inhibitor Substrate of CYP3A4 (minor), PGP,(minor), UGT1A1, UGT1A9
Enzalutamide	160 mg PO once daily	Gastrointestinal disturbances (diarrhea), musculoskeletal issues (eg, arthralgias and myalgias), asthenia, fatigue, peripheral edema, LFT abnormalities, seizures, PRES	*No renal or hepatic dose adjustments* DDI Strong CYP3A4 inducer Moderate CYP2C9 and CYP2C19 inducer Avoid CYP3A4, CYP2C9, and CYP2C19 sensitive substrates Avoid strong inducers and inhibitors of CYP2C8
Cytotoxic Chemotherapy			
Cabazitaxel	20 mg/m^2 IV every 3 weeks	Fluid retention, constipation, mucositis, myelosuppression, hypersensitivity	Hepatic Discontinue if patient ALT > 2 × ULN, or if patient develops jaundice DDI Avoid concomitant use of CYP3A4 inhibitors and inducers Hematologic Ensure CBC recovery prior to administration
Docetaxel	75 mg/m^2 IV every 3 weeks	Fluid retention, alopecia, mucositis, myelosuppression, hypersensitivity	Hepatic Do not administer if AST/ALT > 1.5 × ULN and ALP > 2.5 ULN DDI Avoid concomitant use of CYP3A4 inhibitors Hematologic Ensure CBC recovery prior to administration
Immunotherapy			
Pembrolizumab	200 mg IV every 3 weeks OR 400 mg IV every 6 weeks	Fatigue, muscle pain, pyrexia, pruritus, autoimmune toxicities (dermatitis, colitis, hepatitis, hypophysitis, hypothyroidism)	*No renal or hepatic dose adjustments* DDI The use of immunosuppressants may lessen the therapeutic effects
Sipuleucel-T	> 50 million autologous CD54+ cells obtained from leukapheresis. CD54+ cells are activated with PAP-GM-CSF. three total doses given	Hypersensitivity, chills, fever, fatigue, headache, and myalgias	*No renal or hepatic dose adjustments* DDI The use of immunosuppressants may lessen the therapeutic effects

(Continued)

Table 92–6

Agents Used in the Treatment of Advanced Prostate Cancer (*Continued*)

Drug	Usual Dose	Adverse Effects	Dose Adjustments
PARP Inhibitors			
Olaparib	300 mg PO twice daily	Fatigue, nausea, myelosuppression, nausea, secondary malignancy	Renal Reduce dose to 300 mg twice daily for eGFR 15–30 mL/min, not studied in eGFR < 15 mL/min DDI Avoid use with concomitant strong and moderate CYP3A4 inhibitors (if cannot be avoided then reduce olaparib dose). Avoid use with concomitant strong CYP3A4 inducers
Rucaparib	600 mg PO twice daily	Fatigue, nausea, myelosuppression, nausea, AST/ALT elevation, increased SCr, secondary malignancy	*No renal or hepatic dose adjustments* DDI Use cautiously with concomitant drugs that are also CYP1A2, CYP2C9, CYP2C19, and CYP3A4 substrates

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BRCP, breast cancer resistance protein transporter; CBC, complete blood count; CD, cluster of differentiation; CYP, cytochrome P450; DDI, drug–drug interaction; eGFR, estimated glomerular filtration rate; GM-CSF, granulocyte-macrophage colony-stimulating factor; IV, intravenous; LFT, liver function test; OATP, organic anion transporting polypeptide transporter; PARP, poly (ADP-ribose) polymerase; PGP, P-glycoprotein transporter; PO, oral; PRES, posterior reversible encephalopathy syndrome; SCr, serum creatinine; UGT, uridine 5′-diphospho-glucuronosyltransferase; ULN, upper limit of normal.

and an antiandrogen, antiandrogen withdrawal can be the first salvage manipulation.[9,28] Somatic genetic mutations in *AR* arise in patients treated with antiandrogens and cause these agents to exhibit receptor agonist properties. Objective and subjective responses have been reported in patients following antiandrogen discontinuation from their CAB regimen. Patient responses to antiandrogen withdrawal manifest as significant PSA reductions and improved clinical symptoms. Antiandrogen withdrawal responses lasting 3 to 14 months have been reported in up to 35% of patients, and patient responses seem to closely correlate with longer antiandrogen exposure times.[28]

KEY CONCEPT When advanced prostate cancer progresses, despite castration levels of testosterone, it is known as CRPC. For patients who initially received an LHRH agonist alone, castration testosterone levels should be documented. Patients with inadequate testosterone suppression (eg, levels > 20 ng/dL [0.7 nmol/L]) can be treated by adding an antiandrogen, or performing an orchiectomy. If castration testosterone levels have been achieved, but symptoms of progression are evident or a PSA rise is observed, the patient's disease is considered to have progressed to CRPC. Because androgens remain a growth signal for the cancer, ADT is continued throughout the treatment course of CRPC, and the cancer may continue to respond to treatments that target the AR signaling axis (eg, enzalutamide or abiraterone).

KEY CONCEPT Second-generation therapies that target the AR signaling axis, such as abiraterone and enzalutamide, improve survival in patients with mCSPC, nonmetastatic CRPC (nmCRPC), and mCRPC (see Table 92–7).

▶ *Second-Generation Antiandrogens*

Despite initial responses to ADT and first-generation antiandrogens, disease progression eventually occurs. Second-generation antiandrogens not only inhibit the AR from binding its ligand, but they also prevent the AR from translocating into the cell nucleus, further inhibiting androgen signaling. Of note, second-generation antiandrogens are still combined with ADT (either a GnRH agonist/antagonist or orchiectomy) to obtain castration levels of testosterone in all treatment settings discussed below.

Apalutamide

Apalutamide is a second-generation antiandrogen that binds directly to the ligand-binding domain of the AR, inhibits nuclear

Table 92–7

First-Line Treatment Options for Advanced and Metastatic Prostate Cancer

	Locally Advanced/ Nonmetastatic	Metastatic
Castration Naïve (ADT *initiated* to achieve testosterone < 50ng/mL in all cases)	• ADT	• ADT • ADT + apalutamide • ADT + enzalutamide • ADT + abiraterone + prednisone • ADT + docetaxel
Castration Resistant (ADT *continued* to maintain testosterone < 50 ng/mL in all cases)	• Apalutamide • Darolutamide • Enzalutamide	• Enzalutamide • Abiraterone + prednisone • Docetaxel + prednisone • Sipuleucel-T • Radium-223 (if symptomatic bone mets) • Mitoxantrone (if symptomatic with visceral mets and cannot tolerate other treatments)

ADT, androgen deprivation therapy; mets, metastases.

translocation of AR, inhibits DNA binding of the AR, and prevents AR-mediated transcription. Apalutamide was compared to placebo in 1052 men with mCSPC in the TITAN trial. All men in the trial received either medical or surgical castration. In this patient population, apalutamide demonstrated improved progression free survival (PFS) and overall survival (OS) at 24 months.[31]

In men with nonmetastatic CRPC, apalutamide + ADT demonstrated an improvement in metastasis-free survival compared to placebo in the SPARTAN trial. Notably, the rate of adverse events leading to discontinuation in this study was 10.6% in the apalutamide group versus 7.0% in the placebo group, underscoring the relatively good tolerability of the agent.[32] Apalutamide is associated with rash, fatigue, hypertension, and a risk of fracture and seizure. Compared to the other antiandrogens, apalutamide has an increased risk of hypothyroidism. Care should be taken to screen patients for drug–drug interactions (DDIs) (see Table 92–6), as apalutamide is a strong inducer of CYP3A4 and CYP2C19. Common drug interactions include statins, DOACs, PPIs, clopidogrel, and citalopram.

Darolutamide

Darolutamide is another second-generation antiandrogen that competitively inhibits ligand binding to the AR while also inhibiting nuclear translocation and AR-mediated transcription. Compared to other second-generation antiandrogens, daralutamide has fewer effects on CYP enzymes, resulting in fewer drug interactions (see Table 92–6). The drug also has lower central nervous system penetrance compared to enzalutamide and apalutamide, resulting in a lower risk of fatigue and seizures. Darolutamide + ADT was compared to placebo + ADT in men with nmCRPC in the ARAMIS trial and demonstrated an improved metastasis-free survival.[33]

Enzalutamide

Enzalutamide was the first second-generation antiandrogen to obtain Food and Drug Administration (FDA) approval and has demonstrated efficacy in men with both CSPC and CRPC (see Table 92–6**).** In mCSPC, enzalutamide demonstrated improved metastasis-free survival compared to placebo in the ARCHES trial.[34] Enzalutamide has also demonstrated approved OS in nmCRPC in the PROSPER study.[35] In those with mCRPC, enzalutamide is an effective first-line treatment option in chemotherapy-naive patients, as well as a viable second-line option in patients who have failed prior to docetaxel chemotherapy.[36,37] Primary adverse effects include fatigue, diarrhea, hot flashes, musculoskeletal pain, and hepatotoxicity (ie, LFT elevations).[36,37] Seizures and posterior reversible encephalopathy syndrome are rare but serious adverse effects. Enzalutamide is a strong inducer and inhibitor of CYP3A4, as well as a moderate inducer and inhibitor of both CYP2C9 and CYP2C19, so DDIs are a consideration.

Patient Encounter 4: Metastatic disease at presentation

A 63-year-old man presents to clinic with severe abdominal and back pain. After a complete workup, he is diagnosed with metastatic prostate cancer, with evidence of metastatic disease in his lungs, liver, and bones (femur and spine). He has a PMH significant for hypertension (controlled on lisinopril and metoprolol), atrial fibrillation (currently on rivaroxaban), and restless leg syndrome (untreated, but currently controlled).

How would you characterize this patient's prostate cancer?

Which available pharmacotherapeutic options would be preferable for this patient?

▶ *Androgen Synthesis Inhibitors*

Despite ADT, androgen synthesis can continue to occur in the periphery (eg, adrenal glands) or via intratumoral synthesis. Androgen synthesis inhibitors, such as aminoglutethimide 250 mg orally every 6 hours or ketoconazole 400 mg orally three times daily, can provide symptomatic relief for a short time in approximately 50% of patients with progressive disease despite previous ADT.[38] With the advent of newer agents, their role in therapy has diminished substantially.

Abiraterone

Cytochrome P450 enzymes play a critical role in androgen synthesis. CYP17A1 inhibition prevents the conversion of pregnenolone to DHEA, a requisite precursor for testosterone. Abiraterone acetate is a potent and specific inhibitor of CYP17A1, resulting in further testosterone reductions, when combined with continued ADT. Abiraterone has demonstrated benefit in combination with ADT in CSPC as initial treatment in the LATITUDE study, as well as in mCRPC both before and after receipt of docetaxel chemotherapy.[9,39] Inhibition of CYP17A1 can result in mineralocorticoid excess, which underlies many of the adverse effects associated with abiraterone, and is the reason why it is always prescribed concomitantly with daily prednisone (given once daily in CSPC and twice daily in CRPC). Prednisone serves to prevent activation of a response to perceived cortisol deficit via negative feedback. Symptoms of mineralocorticoid excess include fluid retention, hypokalemia, and hypertension. Hepatotoxicity (eg, LFT abnormalities) is a less common but sometimes severe adverse effect. Abiraterone should be administered on an empty stomach (1 hour before or 2 hours after a meal), as food significantly increases absorption. As a CYP3A4 substrate, abiraterone should be used cautiously with concomitant CYP3A4 inhibitors and inducers (Table 92–6).

The need to take abiraterone twice daily on an empty stomach to avoid variation in drug exposure can lead to issues with adherence. A novel fine-particle formulation of abiraterone was developed that allows for once daily dosing of 500 mg with similar extent of abiraterone absorption and demonstrated clinical equivalence with regard to serum testosterone levels.[40] Fine-particle abiraterone must be administered with methylprednisolone once daily to prevent mineralocorticoid excess. The lack of long-term safety and efficacy data with this alternative formulation makes it an option mainly in patients who are not able to properly administer abiraterone.[9]

▶ *Chemotherapy*

KEY CONCEPT Chemotherapy with docetaxel improves survival in patients with mCSPC and mCRPC, particularly in patients with high disease burden. Chemotherapy with cabazitaxel improves survival in patients with mCRPC who have either progressed on or are intolerant to docetaxel.

Docetaxel

Docetaxel is an antimicrotubule taxane, which has been shown to improve survival in mCRSC patients when administered at 75 mg/m^2 every 3 weeks for six cycles in combination with ADT in the CHAARTED trial. Of note, the clinical benefit of docetaxel was more pronounced in patients with a higher burden of disease in this trial.[41] In men with mCRPC, docetaxel with prednisone 5 mg twice daily (to further inhibit adrenal steroid production in castration-resistant disease) demonstrated improved overall survival when compared to mitozantrone plus daily prednisone.[41] The most common adverse effects of docetaxel include nausea, alopecia, bone marrow suppression, fluid retention, and peripheral neuropathy. Premedication with dexamethasone is recommended to prevent fluid retention associated with docetaxel. Docetaxel undergoes extensive hepatic metabolism; patients with hepatic impairment may not be eligible for the treatment with docetaxel due to an increased risk of adverse effects (Table 92–6).

Cabazitaxel

Cabazitaxel is also an antimicrotubule taxane with demonstrated activity in docetaxel-resistant cell lines and animal models of human cancer. Low affinity for the P-glycoprotein efflux transporter, when compared to docetaxel, could conceivably be the reason why cabazitaxel remains effective in the setting of docetaxel resistance. In docetaxel-pretreated patients, cabazitaxel (25 mg/m^2 every 3 weeks with prednisone 10 mg/daily) significantly improved progression-free and overall survival compared with mitoxantrone and prednisone.[42] Later, the FDA approved a reduced cabazitaxel dose of 20 mg/m^2 every 3 weeks based on evidence of similar efficacy but better tolerability, when compared to 25 mg/m^2.[43] The most significant adverse effects associated with cabazitaxel include neutropenia, neuropathy, and diarrhea. Hypersensitivity reactions can occur with cabazitaxel, so premedication with an antihistamine, corticosteroid, and H$_2$ antagonist is recommended. Cabazitaxel undergoes extensive hepatic metabolism and should be avoided in patients with hepatic dysfunction. Cabazitaxel is a CYP3A4 substrate, so concomitant use of CYP3A4 inhibitors and inducers should be avoided as well (see Table 92–6).

▸ *Immunotherapy*

Sipuleucel-T is an autologous immunotherapy that was approved for patients with asymptomatic or minimally symptomatic mCRPC.[45] Eligible patients first undergo leukapheresis to collect peripheral blood mononuclear cells (the cellular fraction that contains dendritic cells), which are sent to a central processing laboratory. These are stimulated with a fusion protein of prostatic acid phosphatase (PAP) and granulocyte-macrophage colony-stimulating factor (GM-CSF). PAP is a specific tumor antigen, while GM-CSF is an immune cell activator. The cultured cells are then returned and infused into the patient. This procedure is performed every 2 weeks for a total of three treatments. Adverse effects associated with sipuleucel-T are generally mild to moderate and include transient chills, fever, and headache (see Table 92–6). Sipuleucel-T was shown to improve overall survival, when compared to placebo in men with mCRPC, but the trial excluded patients with visceral metastases.[44] Despite a modest improvement in survival, sipuleucel-T did not decrease the time to disease progression and thus does not offer significant relief from disease-related symptoms. It is not appropriate in symptomatic patients with rapidly progressing disease for whom treatments that delay tumor progression are feasible.

Immune checkpoint inhibitors are now being used broadly in a variety of cancers. Immune checkpoint inhibitors (PD1, PDL1, and CTLA4 inhibitors) work by inhibiting signals that lead to T-cell senescence and thus increase the immune response to cancer. Pembrolizumab, a PD1 inhibitor, is FDA approved for patients with metastatic solid tumors who have a high tumor mutation burden, defined as 10 or more mutation/megabase of DNA, or microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) that are documented by molecular testing, who have progressed on prior treatment, and who have no alternative treatment options. Mismatch repair is deficient in tumor cells of 5% to 12% of men with mCRPC.[45] Molecular testing assays that can detect these abnormalities should be used to properly identify advanced and metastatic prostate cancer patients who may benefit from pembrolizumab.[9]

▸ *Poly(Adenosine Diphosphate-Ribose) Polymerase (PARP) Inhibitors*

Somatic and germline mutations that result in deficiencies of DNA repair genes are common in men with mCRPC.[45] PARP enzymes are involved in normal DNA repair. When PARP enzymes are inhibited in the setting of additional deficiencies in DNA repair by homologous recombination, genetic instability results in cell death. Olaparib has demonstrated efficacy in the treatment of mCRPC in patients who harbor deleterious germline or somatic mutations in DNA damage repair genes (*ATM*, *BRCA1*, *BRCA2*, *BARD*, *BRIP1*, *CDK12*, *CHEK1/2*, *FANCL*, *PALB2*, and *RAD51*). Patients treated with olaparib had progressed on enzalutamide or abiraterone (none had failed chemotherapy with docetaxel).

Table 92–8

Second-Line Treatment Options for mCRPC

	If Patient Received First-Line Abiraterone or Enzalutamide	If Patient Received First-Line Docetaxel:
Preferred regimens	• Docetaxel + prednisone	• Abiraterone + prednisone • Cabazitaxel + prednisone • Enzalutamide
Useful in certain patients	• Sipuleucel-T (if no visceral mets) • Olaparib (based on genetic testing) • Pembrolizumab (based on molecular testing) • Radium-223 (if symptomatic bone mets)	• Mitoxantrone (palliation in symptomatic patients) • Rucaparib (based on *BRCA* status) • Pembrolizumab (based on molecular testing) • Radium-223 (if symptomatic bone mets)
Other regimens	• Abiraterone + prednisone (if enzalutamide used previously) • Cabazitaxel + prednisone • Enzalutamide (if abiraterone used previously) • Fine-particle abiraterone + methylprednisolone • Rucaparib (based on *BRCA* status)	• Docetaxel + prednisone rechallenge • Fine-particle abiraterone + methylprednisolone • Sipuleucel-T (if no visceral mets) • Olaparib (based on genetic testing)

BRCA, breast cancer susceptibility gene; mCRPC, metastatic castration-resistant prostate cancer; mets, metastases.

Patient Encounter 5: Treatment of mCRPC

A 69-year-old man was diagnosed with localized prostate cancer 4 years ago. He initially underwent a radical prostatectomy. He experienced rising PSA on three separate clinic visits 1 year ago and was found to have metastatic disease in the lumbar spine. He was initiated on ADT + enzalutamide for the treatment of his mCSPC 1 year ago. He presents to clinic today with a rising PSA and evidence of new bone metastases on imaging. He complains of severe back and hip pain. His laboratory values today suggest normal organ function, a PSA of 102 ng/dL, and a testosterone of 4 ng/mL. A sample of his tumor was sent for next-generation sequencing, and he is found to have a microsatellite stable disease and no evidence of alterations in DNA mismatch repair genes. He did receive germline genetic testing that did not reveal any mutations in BRCA1/2.

What treatment options should be considered for this patient?

Radiological PFS was improved in the olaparib arm; however, this response appears to be driven by patients with *BRCA2* mutations.[46] A second PARP inhibitor, rucaparib, obtained FDA approval in patients with mCRPC who harbor germline or somatic DNA damage repair mutations (specifically in *BRCA1/2*) and have progressed after both ADT and taxane-based chemotherapy. Further characterization of favorable disease characteristics to predict response to PARP inhibitors is needed, and studies evaluating combination therapies are underway.[9]

▶ *Bone Protective Therapies*

Radium-223 is an alpha particle emitter and calcium-mimetic radiopharmaceutical that provides significant palliation to mCRPC patients with bone metastases.[47] Radium-223, infused every 4 weeks for six total treatments, has been shown to significantly improve the overall survival, as well as skeletal pain and patient quality of life. Common adverse effects are nausea, vomiting, peripheral edema, and moderate myelosuppression. Radium-223 has been associated with lower rates of myelosuppression compared to other alpha-emitting radiopharmaceuticals. Radium-223 is appropriate for first-, second-, or third-line treatment of patients with mCRPC and symptomatic bone pain.

Given the risk of fractures associated with ADT, bone health is an important aspect of prostate cancer management at all stages. All patients on ADT without metastatic disease should receive calcium and vitamin D supplementation, along with bone density studies based on patient Fracture Risk Assessment Tool (FRAX) risk score. Patients with elevated fracture risk scores may receive treatment with denosumab (60 mg subcutaneously every 6 months), zoledronic acid (5 mg intravenous [IV] every 12 months),

Patient Care Process

Collect Information:

- Obtain complete medical history, family history (including family cancer history), and social history.
- Obtain complete list of any concomitant prescription and over-the-counter medications; be sure to include herbal, vitamin, and mineral supplements.
- Verify completion of prostate cancer workup and staging, including PSA level, pathology results, and staging scans, if indicated.
- Discuss symptom burden with the patient to identify bothersome symptoms that should be addressed by treatment plan.
- Obtain labs to evaluate organ function in order to appropriately choose therapy plan.

Assess the Information:

- Identify prognostic factors that influence the development of metastatic prostate cancer.
- Stratify the patient of the risk with regard to the stage of disease, Gleason score, PSA level, comorbid conditions, and life expectancy.
- Assess laboratory values and organ function with regard to treatment options.
- Identify treatment-related morbidity that would be a barrier to adherence based on the patient's current symptoms and goals of care.

Develop a Care plan:

- Using cancer stage, risk level, and patient-directed goals of therapy, determine if drug therapy is indicated.
- Identify appropriate pharmacotherapy that maximizes efficacy while minimizing toxicity based on patient-specific comorbidities, organ function, and care goals.
- Assess cost of proposed therapies and ensure that they are affordable and reasonable for the patient.

Implement the Care Plan:

- Discuss the benefits and risks of appropriate treatment options with the healthcare team and patient.
- If drug therapy is selected, review patient medical history for drug–drug and drug–herbal interactions.
- Discuss clear goals of care with the patient.
- Initiate therapy.

Follow-up: Monitor and Evaluate:

- If patient is asymptomatic, monitor PSA and circulating androgens for castration level of testosterone. If patient is symptomatic, monitor symptoms for improvement or worsening. Obtain imaging studies to evaluate the response of distant metastases.
- Monitor for any new signs or symptoms of progression, and adverse effects from therapy. Evaluate adherence to ADT. Consider intermittent ADT if patient reports intolerance or significant decrease in the quality of life.
- Consider removal of antiandrogen if CAB approach is chosen and patient demonstrates progression.
- Consider PSA velocity and symptom burden when assessing for the need for treatment changes.

or alendronate (70 mg PO weekly) with the intention of increasing bone mineral density.[9]

Skeletal metastases from hematogenous spread are the most common sites of distant spread of prostate cancer. In men with CRPC who have bone metastases, both zoledronic acid (4 mg IV every 4 weeks or every 12 weeks) and denosumab (120 mg subcutaneously every 4 weeks) have been shown to decrease the incidence of skeletal-related events (fracture, spinal cord compression, or the need to surgery or radiation to the bone). While denosumab has demonstrated superiority over zoledronic acid in the prevention of skeletal-related events, denosumab also has an increased risk of hypocalcemia and thus may not be appropriate in all patients.[48] Both denosumab and zoledronic acid are associated with osteonecrosis of the jaw. Dental procedures should be avoided while receiving these agents, and dental screening prior to initiation is recommended.[9]

OUTCOME EVALUATION

Prostate cancer monitoring depends on the grade and stage of the cancer. When definitive, curative therapy is attempted, check objective parameters (eg, imaging studies, DRE) to assess tumor response and monitor PSA to assess for recurrence or progression. Following definitive therapy, PSA is checked every 6 months for the first 5 years and annually thereafter.[27,28] Local recurrence in the absence of a rising PSA may occur, so annual DRE and radiologic studies based on patient-reported symptoms are also performed. In the metastatic setting, treatments that target AR signaling and traditional chemotherapies have been shown to increase survival. Clinical efficacy is measured using imaging studies, symptom scores, weight changes, analgesic requirements, and PSA response. When using PSA as a surrogate for disease progression, it is important to consider not only the degree of elevation, but also the velocity at which the marker changes. A rapid PSA velocity has been associated with an increased risk of all-cause mortality and should warrant consideration of therapeutic intervention. Monitoring for adverse effects is different for each treatment modality but is similarly important.[50] For oral agents, medication adherence is also an important monitoring parameter at each clinic visit.

Abbreviations Introduced in This Chapter

ADT	Androgen deprivation therapy
AR	Androgen receptor
BPH	Benign prostatic hyperplasia
CAB	Combined androgen blockade
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CYP	Cytochrome P450
DES	Diethylstilbestrol
DHT	Dihydrotestosterone
DRE	Digital rectal examination
EBRT	External beam radiation therapy
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
Gy	Gray
LFT	Liver function test
LH	Luteinizing hormone
LHRH	Luteinizing hormone–releasing hormone
mCRPC	Metastatic castration-resistant prostate cancer
mCSPC	Metastatic castration-sensitive prostate cancer
nmCRPC	Nonmetastatic castration-resistant prostate cancer
PAP-GM-CSF	Prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor
PARP	Poly(ADP-ribose) polymerase
PLND	Pelvic lymph node dissection
PSA	Prostate-specific antigen
RANK	Receptor activator of nuclear factor kappa-B
SNP	Single-nucleotide polymorphism
TRUS	Transrectal ultrasound

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93

Melanoma

Chung-Shien Lee

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Identify the risk factors associated with skin cancer.
2. Devise a plan of lifestyle modifications for the prevention of skin cancer.
3. Discuss the importance of mutation testing in the therapy selection for melanoma treatment.
4. Explain the goals of therapy for the treatment of different nonmelanoma and melanoma stages.
5. Compare and contrast the available pharmacologic treatment options for nonmelanoma and melanoma skin cancer.
6. Suggest management strategies for patients experiencing adverse effects of pharmacologic therapy.

INTRODUCTION

Skin cancer is the most common malignancy in the United States with over 5 million new diagnoses reported in roughly 3 million individuals. Of these, more than 95% are diagnosed with nonmelanoma skin cancer (NMSC), while the rest of skin cancer diagnoses are accounted for by malignant melanoma (MM).[1,2] NMSC incidence increased 300% since 1994 and continues to rise due to increasing high-risk populations, such as organ transplant and photosensitizing medication users. NMSC consists of basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs), which originate in the basal cell layer and the hair follicle stem cells, respectively.[3] MM differs substantially from NMSC with regard to its metastatic potential, prognosis, and treatment options.

MALIGNANT MELANOMA

EPIDEMIOLOGY AND ETIOLOGY

MM is the most diagnosed malignancy in young adults and the fifth most frequently diagnosed cancer overall in the United States, representing approximately 5% of all cancer cases. Although accounting for less than 3% of the skin cancer diagnoses, MM is responsible for the majority of skin cancer deaths (75%).[1,4] With a median age at diagnosis of 65, approximately half of MM cases are diagnosed between ages 55 and 74. An estimated 106,110 new cases are predicted to occur in 2021.[5] However, these figures may underestimate MM, since many superficial and in situ melanomas are treated in outpatient settings and thus not included in the Surveillance, Epidemiology, and End Results (SEER) registry.

RISK FACTORS

MM risk factors include environmental and host factors. **KEY CONCEPT** Sun exposure and ultraviolet (UV)-based artificial tanning are the main environmental triggers for melanoma occurrence. Residing in sunnier climates closer to the equator with potential for chronic sun exposure also increases the risk of melanoma. While MM can occur in any ethnic group and also on less exposed areas of the body, individuals of fair complexion (fair hair and light-colored eyes) have an increased risk.[5] Furthermore, individuals with genetic susceptibility may develop exacerbated skin reactions to the sun or UV radiation (UVR), particularly UVB. While UVB exposure is a well-known risk factor, the most common genetic lesions induced by UVB are C to T conversions, while the most common melanoma associated mutations are BRAF V600E and NRAS Q61L, which are unlikely to be caused by UVB.[6] Recent evidence does supports a UVR-induced mutation mechanism for melanoma occurrence: the hot-spot mutations in *RAC1*, *STK19*, and *PPP6C*.[7]

Furthermore, well-documented UVR-induced *TP53* tumor suppressor gene mutations are responsible for ineffective DNA repair, resulting in apoptosis dysregulation, modified keratinocyte expansion, and initiation of skin cancer. Today, it is estimated that over two-thirds of MMs are attributable to UVR. Moreover, childhood severe sunburns were associated with twice the risk of developing melanoma.

Epidermal melanin acts as a sun protection factor in individuals with darker skin tones, providing an skin protection factor (SPF) of up to 13.4 in Black people.[8] Family history of MM in a first-degree relative is associated with twice the risk of MM. Benign melanocytic nevi (benign moles) are also consistently identified as a risk factor for MM development. The risk of developing MM is also higher in patients with a personal history of MM, NMSC, or dysplastic nevus syndrome.[9] Having five or more dysplastic nevi increases the risk of MM up to six times. A similarly increased risk was noted in cases with congenital melanocytic nevi (bigger than 20 cm diameter).[9] A set of host-related risk factors used in the assessment of MM risk is provided in Table 93–1.

PRIMARY PREVENTION OF SKIN CANCER

Educating patients to avoid excessive exposure to the sun is strongly supported by the American Academy of Dermatology, American Cancer Society, Environmental Protection Agency, and Centers for Disease Control and Prevention. These programs aim at increasing public awareness about the mutagenic effect of

Table 93–1

Host-Related Risk Factors for Melanoma Development

Demographics
- Gender: male
- Age: > 60 years

Skin Phenotype
- Fitzpatrick skin type: pale white skin, blue or green eyes, blond or red hair
- Tanning ability: tendency to sunburn
- Moles: increased count and size with atypical features and pattern

Medical History
- Sunburns: multiple with or without blistering
- Cancer: benign or malign skin cancer or childhood cancers
- Impaired immune system: hematopoietic or solid organ transplant, HIV/AIDS
- Genodermatoses: Xeroderma pigmentosum

Genotype
- First-degree family history
- Susceptibility genes (*CDKN2A, CDK4, MC1R, BRCA2, BAP1*)

Data from Refs. [4,7].

UVR exposure and changing social norms related to sun protection and tanning, with an ultimate goal to decrease skin cancer incidence and deaths related to MM. The following strategies are recommended to minimize UVR exposure:

- Seek shade when outdoors, especially between 10 AM and 2 PM
- Wear hats that provide shade for the face, ears, and neck
- Wear protective clothing made of tightly woven fabric that covers the arms, legs, and torso. Clothing with a UV protection factor (UPF) can provide additional protection.
- Avoid sunbathing and indoor tanning
- Take extra caution when located near water, sand, and snow
- Use UV (radiation) A/B (UVA/B) waterproof sunscreen with a minimum SPF of 15; reapply every 2 hours if sweating or swimming
- If wearing makeup, use one with SPF

Patient Encounter 1, Part 1

A 70-year-old Black man presents to his dermatologist with complaints of pain surrounding a mole located on his right arm.

History: He has been getting his moles checked regularly since it was recommended by his primary doctor 20 years ago. He has four prominent moles located on his chest, neck, and face, but eight larger, notable nevi on his back and arms. Over the last month, he noted a new discolored mole appearing on his right arm with increasing pain.

The man reports that he loves hiking and the outdoors and hikes usually from 10 AM to 4 PM at least three times weekly for the last 40 years. He does not use sunscreen stating he does not like the way it feels.

What risk factors does this patient have for the development of melanoma?

Are any of his risk factors modifiable?

What concerns exist with the development of a new mole at his age?

Sunscreen should not be the sole means of skin cancer prevention. While sunscreen reduces risk of actinic keratosis (AK) and SCC, there is limited evidence to support efficacy in preventing BCC and MM. In addition, sun protection options can lead to or increase the risk of vitamin D deficiency or insufficiency.[10] Therefore, vitamin D level should be closely monitored, and appropriate supplementation is recommended for blood levels lower than 30 ng/dL.

SECONDARY PREVENTION OF SKIN CANCER

Secondary prevention of skin cancer involves detection of premalignant cancers for early intervention to increase the likelihood of cure. Regular screening by skin self-examination or total skin examination performed by healthcare providers consistently identifies smaller and thinner lesions in high-risk patients.[11] To date, the recommendations for melanoma screening are conflicting because there are no randomized, controlled, prospective melanoma trials demonstrating that routine screening reduces mortality. However, evidence exists that clinical whole-body skin examination reduces the incidence of thick melanomas, a pathological feature known to be directly associated with MM mortality.

PATHOPHYSIOLOGY

Although the vast majority of MMs originate from the skin, few may arise from various other epithelial tissues, including the conjunctiva, oral mucosa, penis, urethra, and others. The malignant process originates in abnormal melanocyte proliferation as a consequence of genetic susceptibility and/or exposure to a mutagenic agent, such as UVB. Interestingly, in individuals with high genetic susceptibility, MM may develop on body sites only exposed intermittently, such as the trunk or thighs, while it requires significant chronic UVB exposure of areas such as face and neck, in individuals with low genetic susceptibility.[12] Thus, location alone may be an indication regarding the occurrence mechanism.

Genetic Basis of Melanoma Development

MM has the highest prevalence among the cancers caused by chronic mutagenic exposure.[6] Approximately half of MM cases carry *BRAF V600* mutations and are expected to derive a clinical benefit from BRAF inhibitors.[7] BRAF is a serine/threonine protein kinase that is a member of the RAF kinase family, which is a part of the RAF/MEK/ERK serine threonine cascade (also known as ERK/MAP kinase pathway or "classical" mitogen-activated protein kinase [MAPK] pathway).[12] Mutations in *BRAF* activate the ERK/MAP pathway and thus trigger melanocyte proliferation and clonal expansion. *BRAF*-mutant melanomas tend to occur in individuals younger than 55 years with Fitzpatrick skin types I or II, lower cumulative UV exposure, and on skin areas intermittently exposed to the sun. Out of more than 50 *BRAF* mutations described, the valine to glutamic acid (*BRAF V600E*) substitution accounts for over 75% of all *BRAF* mutations.[13] BRAF and MEK kinase inhibitors are the mainstay treatment for *BRAF* mutation–positive metastatic melanoma.

Since melanocytes' differentiation, proliferation, and survival regulation is controlled by a microphthalmia-associated transcription factor (MITF), its alteration impacts antiapoptotic proteins leading to uncontrolled growth and tumor development. Other relevant MM mutations include *CDKN2A* and *PTEN* deletions, as well as *RAC1*, *NRAS*, *PPP6C*, and *STK19*.

Table 93–2

Characteristics of Different Types of Skin Cancer

	Malignant Melanoma				Nonmelanoma Skin Cancer	
	Superficial Spreading	Nodular	Lentigo Maligna	Acral Lentiginous	Basal Cell Carcinoma	Squamous Cell Carcinoma
Frequency	70%	10%–15%	10%	< 10%	75%	20%
Location	Female: Head, neck, legs Male: Trunk	Trunk, head, neck	Face, head, neck	Palms, soles, nail beds	Head and neck	Face, hands, forearms
Age	Fifth decade	Seventh decade	Eighth decade	Sixth decade	> 40 years	> 40 years
Ethnicity	White	White	White	Ethnic groups of color	Nonspecific	African Americans
Prognosis	Good	Very poor	Good	Very poor	Good	Poor
Clinical features	Long horizontal growth phase (5–7 years)	Very aggressive, deeply invasive, no identifiable horizontal growth phase	Long horizontal growth phase (10 years) In situ, only 5% are malignant	Aggressive, rapid progression from horizontal to vertical growth	Rarely metastasizes Several subtypes	Metastasizes Premalignant and in situ variants

Data from Refs. 8 and 10.

Clinical Presentation and Diagnosis

There are four major subtypes of cutaneous MM: superficial spreading, nodular, lentigo maligna melanoma, and acral lentiginous (Table 93–2). They each vary in clinical and growth characteristics.[14]

SEER data show that 83% of diagnosed MM are locally confined, 9% are diagnosed after the cancer has spread regionally, 4% are diagnosed with distant metastasis, and the remaining 4% cannot be staged.[5] KEY CONCEPT Once skin cancer is diagnosed, the disease is staged to determine confinement to the original location or any spread to other sites, such as the lymph nodes, liver, brain, lungs, or bone. The purpose of staging is to determine prognosis and aid in clinical decision-making. As with most solid tumors, the tumor, node, metastasis (TNM) classification is used to stage MM. Staging of solid tumors is described in Chapter 88.

Determination of lymph node involvement is an independent prognostic factor, and it provides therapy selection guidance. MM patients whose peripheral and deep margin status after biopsy indicate a risk for disease spread to the lymph nodes also receive a sentinel lymph node (SLN) biopsy. An SLN is the nearest lymph node to receive lymph draining directly from the biopsied tumor.

Other prognostic factors considered for assessment include primary tumor thickness (Figure 93–1), the presence of ulceration at the primary site, local mitotic activity, the presence of tumor-infiltrating lymphocytes (TIL), and gender.[15,16] Male sex is associated with poor prognosis and adverse outcome in MM.[17]

Skin Examination

The ABCDE acronym is a helpful mnemonic for recognizing the signs and symptoms of early MM (Figure 93–2).[9] Not all MMs, including nodular melanoma, have all ABCDE characteristics; thus, ABCDE is not meant to provide a comprehensive evaluation of all MM features. The characteristics for each of the letters are described in Figure 93–2. It should be noted that the evolution of a lesion is one of the most important warning signs in the assessment for MM.

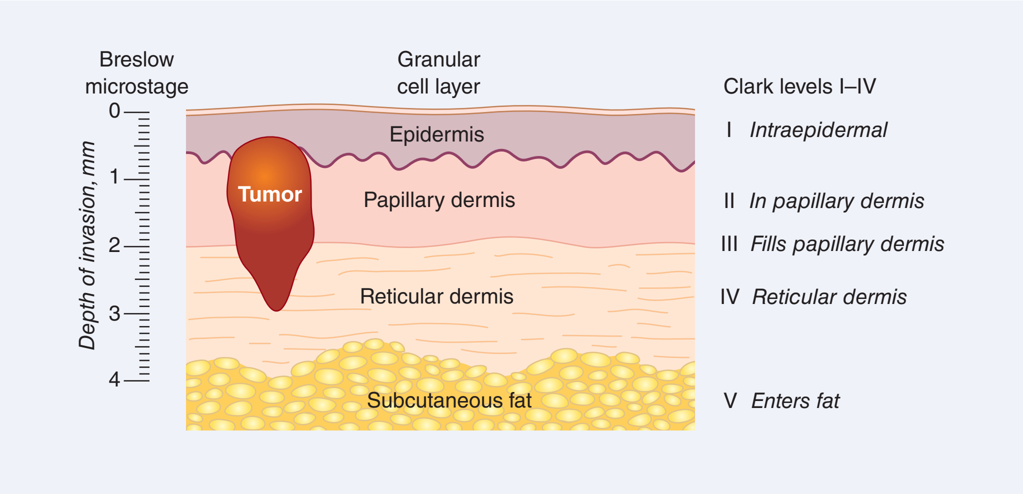

FIGURE 93–1. Skin anatomy: Breslow microstaging and Clark levels. Clark level refers to the level of penetration into the dermis. Breslow classification measures tumor thickness in millimeters from the epidermis to the deepest depth of penetration into the dermis. (From Langley RGB, Barnhill RL, Mihm Jr, MC, et al. Neoplasms: cutaneous melanoma. In: Freedberg IM, Eisen AZ, Wolff K, et al., eds. Fitzpatrick's Dermatology in General Medicine, 6th ed. New York, NY: McGraw-Hill; 2003:938.)

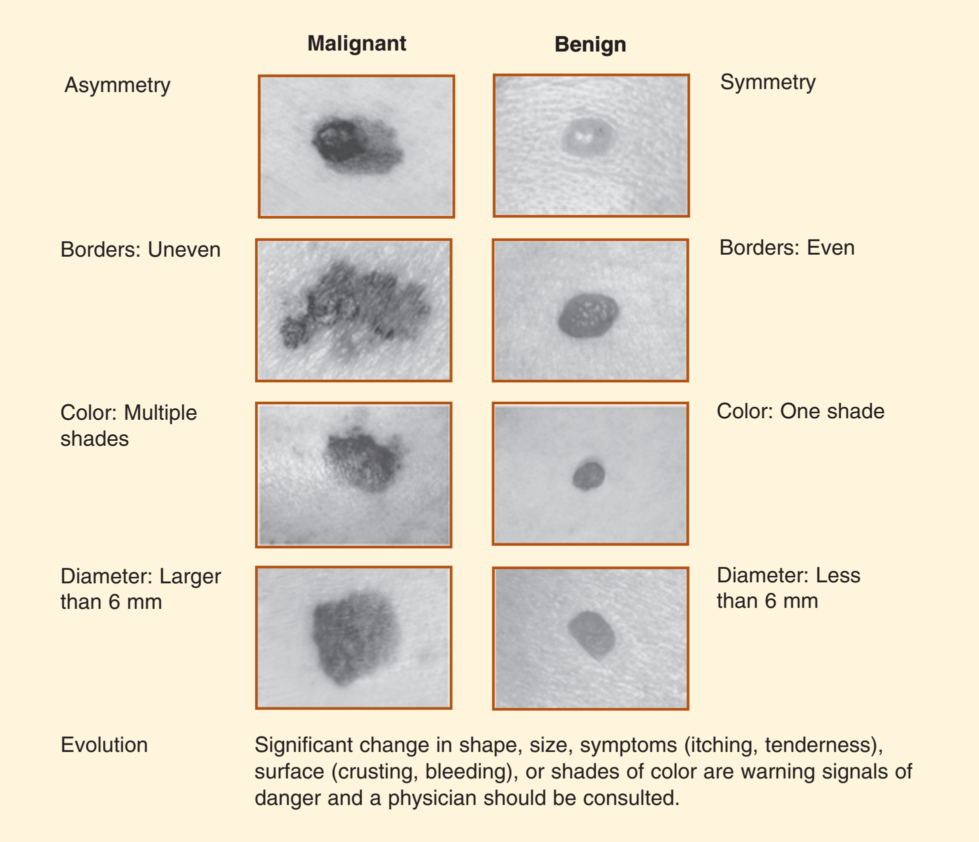
Malignant
Benign
Asymmetry
Symmetry
Borders: Uneven
Borders: Even
Color: Multiple shades
Color: One shade
Diameter: Larger than 6 mm
Diameter: Less than 6 mm
Evolution
Significant change in shape, size, symptoms (itching, tenderness), surface (crusting, bleeding), or shades of color are warning signals of danger and a physician should be consulted.

FIGURE 93–2. ABCDE features of early melanoma. (Images courtesy of the Skin Cancer Foundation, New York, www.skincancer.org.)

Clinical Presentation of MM

MM lesions may occur anywhere on the body. The most common sites are the head, neck, trunk, and extremities. MM appearance such as thickness, the presence, or the absence of ulceration, as well as any lesion characteristic change, are important risk indicators. Abnormal presentations of a mole or lesion indicate the need for further assessment.

- **Asymmetry:** Half the lesion does not mirror the other half
- **Border:** Sharp, ragged, uneven, and irregular borders
- **Color:** Multiple shades of brown, black, red, blue, or gray
- **Diameter:** Larger than 6 mm or the size of a pencil head eraser
- **Evolving:** Significant change in shape, size, symptoms, surface, or shades of color

Other signs and symptoms to monitor for in a lesion, in addition to ABCDE, include the following:

- Sudden or continuous lesion enlargement or elevation
- Changes in the skin surrounding the nevus
- Presence of redness, swelling, itching, tenderness, or pain
- Friability of the lesion with bleeding or oozing (ie, ulceration) is an indicator of poor outcomes

Less Common Sites and Manifestations of MM

It is important to examine these sites for "hidden" MM.

- Nail bed
- Mucosal tissue
- Scalp
- Eye

In the nail bed, a black streak or wide variegated brown streak, elevation of nail bed, darker skin surrounding the nail, deformed or destroyed nail, or an increasing nail streak size over time are all possible manifestations of MM.

Diagnostic Tests

- Dermoscopy
- Biopsy

Staging Tests (Depending on Patient's Presentation)

- Baseline chest radiography
- Tumor cell mitotic rate
- LDH level
- CT of chest, abdomen, pelvis
- SLN biopsy: **KEY CONCEPT** The status of the SLN involvement is one of the most powerful independent prognostic factors predicting survival. It also provides the clinician with guidance for therapy decisions and accurate staging.
- PET
- MRI

TREATMENT

Early diagnosis of MM is a key to improved prognosis. New-onset melanoma cases usually present with a recent history of unusual melanocyte growth or an area of irritation around a patch of melanocyte cells. Alternately, the melanoma may have gone undetected for years. In either of the two possibilities, a definitive diagnosis of any suspected cutaneous malignancy should be confirmed by a biopsy before treatment is initiated. MM treatment options depend on the tumor size, location, pathological features, and stage. The age of the patient and medical history, including the results of genotyping studies, all play a role in the clinical decision-making. The considered options include surgery, radiation, **immunotherapy**, **targeted therapy**, biochemotherapy, a combination of immunotherapy and chemotherapy, and a combination of immunotherapy and targeted therapy.

Desired Outcomes

The primary goal in MM treatment is the eradication of the tumor, lowering the risk of recurrence and metastasis. Secondary goals of MM therapy include preserving skin tissue integrity, appearance, and function while providing optimal cosmetic outcomes. For localized MM (stages I and IIA), surgical resection of the tumor is curative. Thus, probability of cure may be considerably improved with early diagnosis. Patients with regional disease, however—stages IIB, IIC, and III—have a poorer prognosis, characterized by a higher chance for recurrence. In cases with regional disease, the goal of therapy is relapse prevention and maintenance of the quality of life. Finally, in melanoma patients with disseminated disease, cure or prevention of relapse have become somewhat achievable outcomes as a result of immune checkpoint inhibitors. Supportive care is essential for patients undergoing systemic treatment to optimize the quality of life.

Patient Encounter 1, Part 2

PMH: HTN since 20 years ago, type II diabetes since 15 years ago, and hypercholesterolemia since 15 years ago dysplastic nevus syndrome. Patient is currently being treated with azithromycin for an upper respiratory tract infection.

FH: Father had type II diabetes, hypercholesterolemia, gout, and hypertension. Mother had dysplastic nevus syndrome, but no melanoma and breast cancer.

SH: Patient is a retired office worker. Married with three adult children.

Examination: Reveals an asymmetrical new nevus of approximately 6 mm with irregular discolored borders and a lighter center on the right arm with no lesions noted.

Biopsy: Excisional biopsy of the right arm nevus reveals melanoma.

CT Scan: No distant metastases.

Laboratory Data: Normal.

He underwent wide surgical excision of the lesion with a 3-mm margin resection after lymphatic mapping with sentinel lymph node biopsy. Pathology revealed negative margins and two of three nodes positive for melanoma. His melanoma is diagnosed as a stage IIIB. Testing for BRAF mutation comes back negative. Lymphadenectomy of the right axilla has been performed as well.

Would surgical excision of the lesion be curative in this patient?

Could medications typically used to treat his current disease states increase his risk of developing melanoma?

Considering the patient has stage IIIB melanoma, what pharmacologic treatment would you recommend?

MM treatment outcomes largely depend on the clinical disease stage at the time of diagnosis. Based on the data published in the SEER Cancer Statistics Review, the 5-year survival rate for patients with localized MM is 99%, the rate decreases to 66% in cases with regional disease, and it drops below 27% in individuals diagnosed with distant disease. There has been tremendous improvement with distant disease. The 5-year survival rate was never greater than 20% prior to 2010 but is projected to top 40% in the near future.[5]

Nonpharmacologic Therapy

▶ *Surgery*

KEY CONCEPT The primary treatment modality for local/regional disease (stages I to III) is surgical excision of the tumor with lymphadenectomy in patients with positive SLN. The goals of surgical excision are to gain local control and achieve potential cure while minimizing morbidity. Achieving adequate surgical margins for the primary tumor is important in preventing local recurrence and improving the overall survival. The extent of the surgical margin is, generally, dictated by the tumor thickness, but also by the result of the SLN.[18] The most common first site of recurrence in primary melanoma after tumor excision is the lymph nodes. In patients with regional or distant melanoma, surgical excision provides temporary symptomatic relief. Individuals with regional disease presenting with a good performance status and less aggressive tumor biology may observe longer disease-free intervals after surgery; however, this is only possible if disease can be successfully contained within the anatomical region. By contrast, in patients with stage IV melanoma median 5-year survival rates range from 5% to 19% depending on the location and number of metastases.[19] Surgical resection of symptomatic or life-threatening brain lesions may be an option to reduce neurologic deficits, seizures, and intracranial hypertension in patients with MM disseminated to the brain.[18]

▶ *Radiation*

Radiation is rarely indicated for the treatment of primary melanoma. An exception is when surgical excision cannot be performed. Radiation treatment may be administered as adjuvant therapy in areas where complete excision of the tumor is difficult, such as the face, or may be employed in lymphatic areas when complete lymphadenectomy is not feasible. In cases with bone metastasis, radiation may be indicated as palliative therapy to decrease fracture risk, control spinal cord compression, and improve pain management.[20] Radiation may also be used for symptom control of central nervous system (CNS) metastases.[20]

Brain metastases, presenting as headaches and seizures, are common in advanced melanoma, between 10% and 40% of patients presenting with CNS disease and more than 50% developing CNS disease.[18,21] Historically, life expectancy ranged from 3 to 5 months after the development of brain metastasis, however, new treatment modalities have improved this to approximately 1 year.

Table 93–3

Systemic and Regional Therapy for Primary Melanoma and Metastatic Disease

	Stage II_B/II_C	Stage III (SLN+)	Stage III (Clinical Node+)	Stage III with Local Disease	Metastatic or Recurrent Disease
Ipilimumab[a]		X	X	X	X
Intralesional therapy T-VEC, BCG				X	X[b]
Isolated limb infusion/perfusion Melphalan				X	
Topical therapy Imiquimod				X	
Nivolumab		X	X	X	X
Pembrolizumab		X	X	X	X
Dabrafenib/trametinib (if BRAF V600 positive)		X	X	X	X
Vemurafenib/cobimetinib (if BRAF V600 positive)					X
Encorafenib/binimetinib (if BRAF V600 positive)					X

[a] If prior exposure to anti-PD-1 therapy.

[b] T-VEC.

BCG, Bacille Calmette–Guerin; SLN+, sentinel lymph node positive; T-VEC, talimogene laherparepvec.

Data from NCCN Melanoma Treatment Guidelines 2020; www.nccn.org. Last accessed August 18, 2020.

Pharmacologic Therapy

Historical approaches to the management of melanoma included cytotoxic chemotherapy, immunotherapy with interleukin-2 (IL-2) or interferon-α-2b, and combinations of these therapies. However, BRAF inhibitors and immunotherapy with checkpoint inhibitors and ipilimumab have replaced these earlier strategies.[22-28]

▶ *Intralesional Therapy*

Intralesional therapies have been evaluated in melanomas since the 1960s and are generally associated with high response rates locally, but a lack of systemic activity.

Talimogene Laherparepvec (T-VEC)

Talimogene laherparepvec (T-VEC) is the first FDA-approved intralesional therapy for the treatment of unresectable, recurrent melanoma. It is a genetically modified herpes simplex oncolytic virus therapy administered directly into the cutaneous or subcutaneous melanoma lesions or into the visible or palpable nodal lesions.[24] The virus is designed to selectively multiply in the tumor cells. Its mechanism of action is still being investigated; however, the therapeutic benefit likely occurs via the involvement of the tumor antigens that are thought to serve as an autologous vaccine. The drug is delivered by injection using a "fanning" technique (one needle entry with multiple directions of administration), starting with the largest tumor. Grade 3 or 4 treatment-related adverse events were reported in 7.3% of the treated patients and included nausea and vomiting, abdominal pain, fever and chills, and wound infection.[24] Of the treated patients, 12.2% achieved a complete response. T-VEC use is usually limited to patients with unresectable disease with limited visceral involvement.

Patient Encounter 1, Part 3

This patient presents 3 weeks later after the initiation of nivolumab, 1 week prior to the next dose with diarrhea. He reports having three bowel movements a day for the last several days.

What, if any, changes would be appropriate to this patient's stage IIIB melanoma treatment?

What additional laboratory tests are appropriate to request at this time?

Bacille Calmette–Guerin

An attenuated strain of *Mycobacterium bovis* originally developed as a vaccine against tuberculosis, the Bacille Calmette–Guerin is sometimes used for intralesional administration to stimulate an immune response toward the injected site; however, adverse effects, including anaphylaxis, preclude its routine use.[29]

▶ *Immune Checkpoint Inhibitors*

T-cell activation involves two different signals that enhance the host immune response:[30]

- T-cell receptor binding to the major histocompatibility complex presented peptide located on the antigen-presenting cell (APC)
- T-cell costimulatory receptor (CD28) interaction with a costimulatory ligand (B7) on the APC surface

The cytotoxic T lymphocyte (CTL)–associated protein 4 (CTLA-4) is expressed in CD4+ and CD8+ T cells and regulatory T cells. CTLA-4 is a member of the immunoglobulin (Ig) superfamily that migrates to the T-cell surface upon its activation allowing binding with a higher affinity to the B7 ligand than CD28. This results in a downregulation on the immune response; in other words, CTLA-4 acts as a "brake" on the activation of the immune system.[30]

Ipilimumab As a human monoclonal CTLA-4-specific antibody, ipilimumab has a high affinity for CTLA-4 and prevents CTLA-4 from binding to B7, an action that inhibits the downregulation of the immune response.[30] Ipilimumab increases proliferation of activated T cells and increases the interactions between T cells and cancer cells. Ipilimumab is FDA approved for unresectable metastatic melanoma, either as a single agent or in combination with nivolumab, as well as the adjuvant treatment of stage III melanoma.[31,32] T-cell activation can lead to severe adverse events, such as enterocolitis, hepatitis, dermatitis, including toxic epidermal necrolysis, neuropathy, and endocrinopathy. Corticosteroids are the treatment of choice for ipilimumab-induced adverse events. The administration of steroids to treat the side effects does not affect ipilimumab's effectiveness. Interestingly, there may be a correlation between immune-related adverse events and treatment success.[33]

Nivolumab Many tumor cells express programmed death-ligand 1 (PD-L1), a surface marker that can interact with programmed death-1 (PD-1) receptor on T cells and B cells, thus diminishing the body's immune response. Nivolumab is an IgG4 human antibody that targets PD-1, hence preventing the PD-L1 binding to PD-1. As a result, T cells remain active to mount an immune response against the tumor. Nivolumab is indicated for both unresectable and metastatic MM as a single agent or in combination with ipilimumab, after progression on ipilimumab or a BRAF and MEK inhibitor (if *BRAF V600* mutation positive). It is also indicated in the adjuvant setting for stage III, resected melanoma. Patients with confirmed unresectable, previously treated, stage III or IV melanoma without *BRAF* mutation receiving nivolumab had a 72.9% overall survival rate at 1 year, as compared to 42.1% in the dacarbazine group.[34] Common side effects may include rash, pruritus, peripheral edema, fatigue, diarrhea, and cough. Rare but serious adverse events may include ventricular arrhythmia, infection, colitis, hepatotoxicity, and neuropathy.

Pembrolizumab This checkpoint inhibitor is an anti-PD-1 humanized antibody. The FDA-approved indication includes unresectable and metastatic MM following ipilimumab and, if *BRAF* V600 mutation positive, a BRAF and MEK inhibitor. Pembrolizumab is also indicated in the adjuvant setting for stage III completely resected melanoma. In patients with unresectable stage III or IV melanoma who received up to one previous therapy, 2-year survival rates were 55%.[35] Common side effects may include arthralgia and constipation/diarrhea, while rare but serious adverse events may include colitis, hepatitis, pancreatitis, pneumonitis, and hypophysitis. According to a study comparing the incidence of immune-related adverse events associated with ipilimumab versus pembrolizumab, significantly fewer gastrointestinal and dermatological adverse events were reported with pembrolizumab use; however, a higher incidence of thyroiditis and pneumonitis was noted.[36]

Atezolizumab Atezolizumab is a humanized anti-PD-L1 antibody that was FDA-approved for BRAF V600 mutation–positive unresectable or metastatic melanoma in combination with cobimetinib and vemurafenib. This is the first approved checkpoint inhibitor and targeted therapy combination. The addition of atezolizumab to a BRAF and MEK inhibitor compared to a BRAF and MEK inhibitor demonstrated a 22% reduction in the risk of progression. Common side effects, when given in combination with a BRAF and MEK inhibitor, may include rash, musculoskeletal pain, fatigue, hepatotoxicity, pyrexia, nausea, pruritus, edema, stomatitis, hypothyroidism, and photosensitivity reaction. Rare but serious adverse events may include colitis, hepatitis, pneumonitis, and hypophysitis.

▶ *RAF-MEK-ERK Pathway Targeted Therapy for BRAF-Mutant MM*

KEY CONCEPT BRAF/MEK combined regimens provide a considerable therapeutic advantage against occurrence of melanoma resistance in patients with metastatic melanoma.

Vemurafenib/Cobimetinib The serine/threonine kinase B-Raf (BRAF) is an intermediary in the signal transduction through the RAF-MEK-ERK MAPK pathway. BRAF activation is followed downstream by the activation of ERK with increase in the cyclin D1 levels, and enhanced cellular proliferation.[37] The proto-oncogene B-Raf *(BRAF)* is mutated in approximately 50% of melanomas, and over 75% of these mutations are *BRAF V600E.*[13] Vemurafenib is an oral serine/threonine kinase inhibitor that binds to the adenosine triphosphate binding domain of *BRAF* mutant; hence, the presence of the mutation is required for treatment effect.[38] Vemurafenib selectively targets the *BRAF V600E* isoform and has an indication for the treatment of unresectable stage IIIC or metastatic melanoma that is *BRAF V600* mutation positive. **KEY CONCEPT** Although vemurafenib was initially approved as a single agent, resistance develops rapidly via activation of MEK, and the combination of vemurafenib and the MEK inhibitor cobimetinib demonstrates improved progression-free survival compared to vemurafenib alone in patients with *BRAF-mutant* metastatic melanoma[39] (see Figure 93–3 and Table 93–4 for dosing recommendations).

Common side effects associated with vemurafenib may include photosensitivity, rash, arthralgia, and alopecia. Rare but serious side effects may include QT interval prolongation, hand–foot syndrome, vision changes, and SCC, although the latter can be excised without discontinuation of the agent.[37] Vemurafenib is metabolized by CYP3A4 and thus may interact with its inducers or inhibitors. It may increase the serum concentration of substrates of CYP1A2 and 2D6. It may decrease the serum concentration of substrates of CYP3A4.

Cobimetinib commonly causes photosensitivity, diarrhea, nausea, pyrexia, elevations in liver function tests (LFTs), as well as electrolyte abnormalities. Decreases in ejection fraction and hypertension can occur in up to 20% of the patients. Rare but serious adverse effects include bleeding and secondary neoplasms, including squamous and basal cell skin cancer and melanoma. Cobimetinib is metabolized by CYP3A4 and thus may interact with its inducers or inhibitors.

Dabrafenib/Trametinib Similar to vemurafenib, dabrafenib is a selective inhibitor of BRAF V600E kinase. While it is approved as both monotherapy for unresectable and metastatic MM with *BRAF V600E* mutation and combination therapy with trametinib for unresectable and metastatic MM with *BRAF V600E* or *V600K* mutation, the drugs are used almost exclusively in combination, as the combination has demonstrated superior efficacy than either drug administered as a single agent. The combination also significantly reduces the risk of recurrence of melanoma in completely resected patients with stage III melanoma when compared to placebo.[40, 41] Common side effects with dabrafenib include hypoglycemia, arthralgia, hand–foot syndrome, pyrexia, and neutropenia, while rare but serious adverse events may include QT prolongation, serious febrile reactions, uveitis, iritis, and SCC. Similar to vemurafenib, SCC can be excised without discontinuing dabrafenib. Dabrafenib is metabolized by CYP3A4 and 2C8 and thus may interact with its inducers or inhibitors. It may decrease the serum concentration of substrates of CYP3A4 and 2C9.

Trametinib is a MEK-1 and MEK-2 kinase inhibitor targeting MAPK pathway downstream of BRAF. The drug is approved as

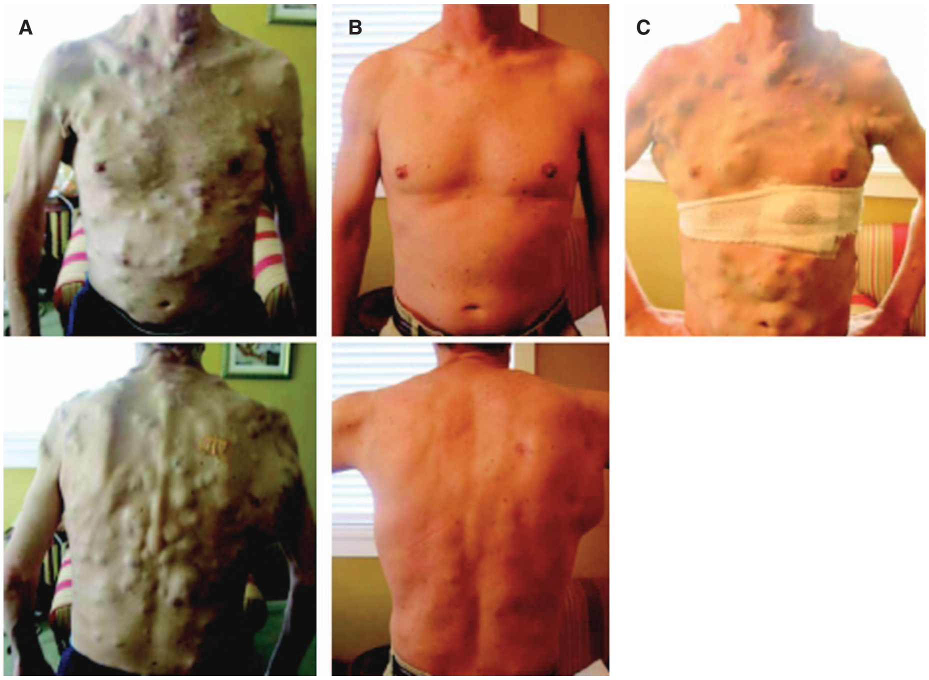

FIGURE 93–3. RAF inhibition resistance in melanoma. A 38-year-old man with BRAF-mutant melanoma. **A:** Before initiation of RAF inhibitor. **B:** After 15 weeks of therapy with an RAF inhibitor. **C:** After relapse, after 23 weeks of therapy. (Reproduced with permission from the Journal of Clinical Oncology. Wagle N, Emery E, Berger MF, et al. Dissecting therapeutic resistance to RAF inhibition in melanoma by tumor genomic profiling. J Clin Oncol. 2011;29(22):3085–3096.)

monotherapy or in combination with dabrafenib for *BRAF V600E* or V600K mutation–positive unresectable and metastatic melanoma, although currently only used in combination. Common side effects with trametinib include dry skin, diarrhea, and nail changes, while rare but serious adverse events may include vision changes and rhabdomyolysis.

Encorafenib/Binimetinib Encorafenib is a selective inhibitor of BRAF V600E kinase approved for unresectable and metastatic MM with *BRAF V600E* or *V600K* mutation only in combination with binimetinib. Similar to cobimetinib and trametinib, binimetinib is a MEK-1 and MEK-2 kinase inhibitor. The combination has prolonged survival compared to single-agent BRAF inhibitors. Common side effects with encorafenib and binimetinib include fatigue, nausea, vomiting, abdominal pain, and arthralgia, while rare but serious adverse events may include vision changes and QT prolongation.

The combination of a BRAF and MEK inhibitor has shown to be superior to monotherapy but has demonstrated a different side-effect profile. Combination treatments were associated with higher rates of flu-like symptoms, such as pyrexia and chills, and reduced ejection fraction. BRAF inhibitor monotherapy was associated with higher rates of musculoskeletal complaints, alopecia, hand–foot syndrome and skin toxicities, particularly keratoacanthoma, and cutaneous SCC. Severe toxicity was similar with combination treatment compared to the BRAF inhibitor monotherapy treatment.

OUTCOME EVALUATION

When evaluating MM therapy outcomes, refer to the primary and secondary goals of the respective MM stage, treatment selection, and case-related particularities, such as cosmetic considerations. Always evaluate the awareness and approach to avoid sun or UVR exposure, including compliance with regular total-body skin self-examination, regardless of disease stage and implemented treatment. Advise for appropriate changes if needed.

For localized disease:

- Evaluate skin integrity after tumor resection, appearance, and function.
- Assess the quality of life after surgery and whether any skin graft–related complication has been reported.
- Verify patient and family understanding regarding recurrence prevention.

For regional disease:

- Assess skin appearance and recovery after radiation therapy, as well as the quality of life and motor function recovery after lymphadenectomy.
- Evaluate effectiveness of any anticancer treatment.
- Review the relevant labs and make necessary treatment changes.
- Review treatment adverse events and the appropriateness of their management.
- Discuss treatment alternatives and options for recurrence prevention.

For disseminated disease:

- Identify patients' and their family goals and their compatibility with the observed treatment outcomes.
- Review the relevant labs and evaluate the effectiveness of palliative treatment.
- Assess chronic therapy side effects and evaluate the appropriateness of adverse event reporting and management.
- Assess patients' psychological, physical, and social functioning.

- Evaluate the use of current resources, such as the hospital's social service department or the American Cancer Society for assistance in dealing with the disease emotionally. Recommend attending support group meetings or talking to a counselor if or before they become overwhelmed with the diagnosis.

Table 93–4

Melanoma Treatment Dosing Recommendations[a]

Intralesional Therapy

Talimogene laherparepvec: 4 × 10^6 PFUs in ≤ 4 mL injected by intralesional fanning; inject 4 × 10^8 PFUs in ≤ 4 mL injected by intralesional fanning after 3 weeks, and biweekly thereafter for up to 24 doses

Immune Checkpoint Inhibitors

Ipilimumab: 3 mg/kg IV (over 90 minutes) every 3 weeks ×4 doses; permanently discontinue if not completed within 16 weeks[e]

Nivolumab: 240 mg IV (over 30 minutes) every 2 weeks or 480 mg IV (30 minutes) every 4 weeks until[c,d,e]

1 mg/kg IV (over 30 minutes) every 3 weeks × 4 doses (in combination with ipillmumab), then 240 mg every 2 weeks or 480 mg every 4 weeks[c,d,e]

Pembrolizumab: 200 mg IV (over 30 minutes) every 3 weeks or 400 mg IV (over 30 minutes) every 6 weeks[c,d,e]

Atezolizumab: 240 mg IV (over 1 hour) every 2 weeks until[c,d,e,f]

RAF-MEK-ERK Pathway Inhibitors

Vemurafenib: 960 mg orally every 12 hours[b,d]
Dabrafenib: 150 mg orally every 12 hours[d,g]
Trametinib: 2 mg orally once daily[d,g]
Cobimetinib: 60 mg orally once daily, days 1–21 of each 28-day cycle
Encorafenib: 450 mg orally once daily[d]
Binimetinib: 45 mg orally every 12 hours[d]

Chemotherapy

Dacarbazine: 250 mg/m^2/day IV, days 1–5, every 21 days[h]
Temozolomide: 150–200 mg/m^2 orally × 5 days, every 4 weeks
Vinblastine: 2 mg/m^2 days 1–4 and 22–25 of 6-week cycle
Cisplatin: 75 mg/m^2 IV day 1 with temozolomide 200 mg/m^2 orally × 5 days, cycled every 4 weeks
Carboplatin: target AUC 6 days, 1 of a 21-day cycle
Carmustine: 150 mg/m^2 IV day 1 with cisplatin 25 mg/m^2 IV days 1–3; repeat cycle with dacarbazine and cisplatin every 21 days; repeat cycle of carmustine every 42 days

[a] Refer to clinical trials to determine the specific dose based on the regimen the patient is receiving.

[b] Caution in severe renal or hepatic impairment; no dose adjustment needed for mild-to-moderate impairment.

[c] Baseline renal, liver, and thyroid function required; monitor periodically during treatment.

[d] Continue regimen until disease progression or unacceptable toxicity occurs.

[e] No formal studies have been done to assess cytochrome P450 interactions.[32]

[f] If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

[g] Take on empty stomach.

[h] Inactive until metabolized by the liver; it requires reasonably good liver function.

IV, intravenous; SC, subcutaneous.

Data from U.S. Food and Drug Administration. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Last accessed August 18, 2020.

PATIENT CARE PROCESS

Refer to the section at the end of the chapter for the patient care process recommended for both MM and NMSC care.

KERATINOCYTE CARCINOMA

EPIDEMIOLOGY AND ETIOLOGY

Also known as NMSC, keratinocyte carcinoma[42] accounts for the vast majority of all newly diagnosed cancers each year. BCC is the most common form of keratinocyte carcinoma followed by the SCC as the second most common in the United States (see Table 93–2).

The true prevalence of keratinocyte carcinoma may be underestimated due to its treatment in outpatient settings, without formal reporting to cancer registries. Yet, understanding its incidence is critical to designing treatment strategies and providing proper resource allocation for its prevention.[43] The number of individuals with at least one NMSC procedure in the Medicare fee-for-service database increased by over 14% between 2006 and 2012. Although, BCC was previously reported as the most common form of NMSC, comprising 75% of the NMSC, the most recent study indicates a 50:50 ratio of BCC to SCC diagnosed in a Medicare population.[43] The majority of NMSCs are curable, and the mortality rate is low, however not negligible; cure rates approach 98%, and the overall 5-year survival rate is considerably greater than 95%. Metastasis occurs in less than 0.1% of BCCs compared to 3.6% of SCCs. Roughly 75% of all keratinocyte carcinoma deaths are attributed to SCC.[44] Keratinocyte carcinoma is associated with considerable morbidity related to functional and cosmetic deformity. In addition, it is an economic burden; the associated costs for NMSC treatment reaching $4.8 billion between 2007 and 2011, nearly double as compared to NMSC expenditure between 2002 and 2006. Importantly, both these figures exceed the costs of MM expenditure for the corresponding time frame.[45]

RISK FACTORS

The risk of developing keratinocyte carcinoma is multifactorial. Skin phenotype plays a similar role as in the MM development; individuals with pale skin, blue or green eyes, and blond or red hair are at risk of developing NMSC as well. A tendency to sunburn or an increased cumulative lifetime UVR exposure, particularly UVB due to its penetrability and higher energy, leads to biologically damaging effects, including direct DNA damage, signaling receptor-mediated pathways activation, and reactive oxygen species (ROS) formation.[3] Greater cumulative lifetime sun exposure is associated with a higher risk of developing SCC, but intermittent and childhood sun exposure correlates more with BCC. Individuals with a keratinocyte carcinoma have a 10-fold increased risk of developing subsequent skin cancer as compared to the general population.[46]

The vast majority of BCC cases are sporadic, although a small number occur in patients with Gorlin syndrome, an autosomal dominant disorder caused by mutations in the *PTCH1* gene. Additionally, up to 70% of patients with sporadic BCC have a mutation in the *PTCH1* gene.[46] By contrast, individuals with previous SCC are more likely to acquire additional SCC and, potentially, melanoma.[3] SCC has been reported to occur 100 folds more often in organ transplant recipients as compared to the general public, possibly due to the immunosuppressive therapy requirements in transplant patients.

Although responsible for a smaller number of keratinocyte carcinomas, arsenic has been shown to promote the expression of

Table 93–5

Photosensitizing Drugs

Antidepressants: citalopram, bupropion, fluoxetine
Glucose-lowering meds: glimepiride, glyburide, glipizide
Immunosuppressants: methotrexate, cyclosporine
Antibiotics: azithromycin, doxycycline, sulfonamides, ketoconazole, voriconazole, griseofulvin, trimethoprim
Insomnia/seizure/anxiety meds: alprazolam, quetiapine, zolpidem, valproic acid, gabapentin
Antiarrhythmics: amiodarone
Other: estrogens, cholesterol-lowering meds, NSAIDs, isotretinoin, vitamin A, St. John's wort
Antihypertensives: lisinopril, labetalol, hydralazine, diuretics

SCC-related keratins possibly by epigenetic modifications. Other reported offenders linked to the occurrence of NMSCs include photosensitizing drugs (Table 93–5), human papilloma virus and smoking, with the latter being reported rather in association with SCC than BCC.[47]

PATHOPHYSIOLOGY

NMSCs arise from epidermal keratinocytes and involve primarily squamous cells and basal cells of the epidermis and dermis skin layers. BCCs arise from interfollicular basal cells or keratinocytes in hair follicles or sebaceous glands.[47] Among them, AKs are the most common premalignant lesions. Incidence of AKs is primarily driven by increased cumulative UVR exposure. It is estimated that up to 16% of the AKs will progress to SCC, while approximately a quarter will undergo regression within a year.[47]

CLINICAL PRESENTATION AND DIAGNOSIS

BCC is characterized as *circumscribed* or *diffuse*, and within these two groups, it is further classified according to the type, degree of differentiation, and depth of invasion. The circumscribed types include nodular BCC, adenoid BCC, fibroepithelioma, and basosquamous or metatypical carcinoma. The diffuse BCC types are plaque-like with horizontal spread and poorly differentiated margins and include the superficial BCC, the morpheaform BCC, and the micronodular BCC.

Nodular BCC is the most common type of BCC followed by superficial BCC. The morpheaform BCC is the most aggressive subtype, while superficial BCC is the least.[13] BCC has indolent growth characteristics with a very low metastatic and mortality rate.[48] Paradoxically, BCCs can cause extensive local destruction and significant disfigurement. Approximately 80% of BCCs occur on the head and neck. Superficial BCC occurs predominantly on the trunk. Early-stage BCC is usually small, translucent, or pearly with raised telangiectatic edges.[48] BCC may also appear as raised, yellowish-reddish lesions with a border resembling a string of pearls and telangiectasia. Dermatoscopy may distinguish between a benign and malignant lesion; however, clinical examination is usually sufficient for the diagnosis of BCC. Depending on the size of the tumor, subtype, and treatment planned, a biopsy may be needed.

SCC usually presents on sun-exposed sites because of UVR damage to the skin. Unlike BCC, SCCs are preceded by premalignant lesions such as dysplastic leukoplakia (DL), AK, or SCC in situ (Bowen disease).[48] DL appears as a thickened skin formed in response to trauma or benign human papilloma virus infections. Its occurrence in other locations, such as the oral mucosa, may be due to chronic exposure to chewing tobacco. AK presents as a small papule on areas of sun damage to the skin. The rate of AK progression to SCC is 1% to 10% in 10 years and may be higher if a patient has more than five AKs.[48] Patients with a Bowen lesion present with slowly enlarging erythematous scaly or crusted plaques and have a 3% to 5% risk of progressing to SCC. A typical SCC lesion has an adherent crust and ill-defined edges; the first sign of malignant SCC is the induration of the lesion. The rate of metastasis for SCC is 2% to 6% and may be as high as 10% to 14% in high-risk sites such as the ear and lip and 30% in the genital area.[49] If progressing to metastasis, this may occur 1 to 2 years after the diagnosis of the primary SCC with 80% of metastasis involving the regional lymph nodes.

Keratinocyte carcinoma staging follows the TNM staging system recommended by the American Joint Committee on Cancer, based on tumor size, lymph node involvement, and dissemination. It is seldom done for patients with BCC because nodal

Patient Encounter 2, Part 1

A 43-year-old woman presents to her dermatologist with a raised lesion located in front of her right ear. She states that it got enlarged over the last few months.

History: The lesion began as a "reddish spot" nearly 2 years ago, then has raised, becoming gradually enlarged and more noticeable over the last 4 months.

The woman reports being a frequent tanning bed user due to her pale complexion but uses sunscreen regularly while outside, especially when vacationing on the beach. However, she does not typically reapply sunscreen on her face due to her makeup.

What are some characteristics that differentiate BCC from SCC?

What counseling points can be provided concerning the use of sunscreen or UV protective sprays on the head and face?

Patient Encounter 2, Part 2

PMH: The patient is 3 years status post renal transplantation.

FH: Father has HTN, diabetes, and atherosclerosis. Mother has osteoporosis and breast cancer.

Examination: Reveals a round, flesh-colored, waxy papule 0.4 cm in diameter positioned 1 cm from the tragus of the right ear with a pearly appearance and slight pigmentation in the center. Two irregular blood vessels are visible.

Which type of NMSC is most likely present on this patient?

What risk factors, if any, does this patient have for recurrence of the disease or progression to metastases?

What is the most appropriate initial treatment option for this patient?

and visceral metastases are rare for this type of keratinocyte carcinoma.[48] Dermatoscopy may be employed for such instances, a technique involving the use of epiluminescence or surface microscopy. This test is usually performed by the dermatologist and may improve early detection.

TREATMENT

KEY CONCEPT In patients diagnosed with BCC and SCC, the primary goal of therapy is cure and prevention of recurrence. Despite the low mortality rate, the tissue destruction, functional impairment, and disfigurement associated with keratinocyte carcinoma diagnosis and treatment are very significant issues. Therefore, secondary goals of therapy for NMSC are preservation of function and restoration of cosmesis. The treatment options for NMSC involve surgery, pharmacologic therapy, or a combination thereof. Treatment selection depends on factors such as tumor size, the site of the lesion, patient comorbidities, histologic particularities, and clinical nature of the cancer.

Nonpharmacologic Therapy

▶ *Surgery*

Surgery is the primary treatment modality for all patients diagnosed with keratinocyte carcinomas. Full-thickness ablative procedure in the form of surgical excision of the tumor along with a margin of normal tissue surrounding the tumor is the preferred method for high-risk tumors. Obtaining negative surgical margins is critical for cure and decreasing the risk of tumor recurrence. A margin of 4 to 5 mm in the case of well-defined keratinocyte carcinomas ensures peripheral clearance in 95% of cases. Depending on the tumor size, degree of differentiation, and invasion of surrounding structures, larger margins of resection may be necessary.[48] The two most common surgical techniques used are electrodessication and curettage (ED&C) and Mohs micrographic surgery (MMS). The indications of each of these procedures are described below.

Low-risk tumors defined as small, well differentiated, and slow growing can be treated with superficial ablative techniques, including ED&C and cryotherapy.[48] ED&C is a simple, cost-effective technique that uses repeated cycles of using a curette to cut through malignant tissue followed by the application of high voltage low current to the skin causing drying or desiccation of the tissue. ED&C is indicated for well-defined superficial lesions that are not located in areas with increased risk for metastasis. The disadvantage of this technique is that histologic confirmation of complete tumor removal is not possible.[44] This procedure is not recommended for the treatment of recurrent disease, tumors of the face, and high-risk tumors.[44]

For high-risk NMSC or tumors located in cosmetically or anatomically sensitive areas, MMS is the procedure of choice. The goal of this therapy is complete removal of the cancer with preservation of as much surrounding normal tissue as possible. MMS involves careful dissection, staining of frozen sections, and anatomic mapping of the tumor specimen. Sections are assessed immediately under the microscope by the surgeon, and the process is repeated until a tumor-free margin is attained. MMS cures 93% of primary NMSC and 90% to 94% of recurrent disease compared with 92% and 77% cure rate with standard excision for primary and recurrent disease, respectively.[50] Cure rates for all modalities decrease with the presence of high-risk features but are still superior to MMS.[50]

Cryotherapy is a procedure used primarily for smaller, low-risk keratinocyte carcinomas with clearly defined margins. It involves delivering liquid nitrogen at subzero temperatures as a spray or with a supercooled metal probe to destroy the malignant tissue in a single cycle or multiple cycles.[44] This technique can achieve comparable results to conventional surgery for well-differentiated, not too large, superficial tumors in older patients with BCC.[44] The procedure is contraindicated in the hair-bearing scalp, upper lip, and distal portion of lower leg because of delayed healing and high rates of recurrence.[44]

▶ *Radiation*

Radiation is not standard therapy for the treatment of keratinocyte carcinomas; however, there are circumstances in which radiation may be preferred. It may be offered to patients in whom surgery is not possible because the tumor is inoperable or surgery would lead to unacceptable cosmetic or functional impairment.[50] Radiation to the lip, ear, and nasal entrance for SCC may provide the best cosmetic and functional result. On the other hand, some patients may develop dyspigmentation, radio-dystrophy, or telangiectasia at the irradiated site, resulting in poorer cosmetic outcomes. It should be used with caution in patients younger than 65 years because latent NMSC can develop after 15 to 20 years of radiation exposure.[48]

▶ *Photodynamic Therapy*

Photodynamic therapy (PDT) involves the topical application of a photosensitizing light-activated agent that causes tumor cell damage and death. The photosensitizer is converted to protoporphyrin IX after it is preferentially taken up by active tumor cells. Damage to cell membranes, organelles, and surrounding vasculature occurs when protoporphyrin IX is activated after exposure to a light source. Protoporphyrin IX has absorption bands at 408, 510, 543, 583, and 633 nm; therefore, blue light (corresponding to 408-nm band) and red light (corresponding to 633-nm band) are the most commonly used light wavelengths.[47] Blue light is used for superficial lesions because of its shorter wavelength and it does not penetrate the skin as well as red light.[44]

δ-Aminolevulinic acid (ALA) and methyl aminolevulinate (MAL) are two photosensitizing agents that have FDA approval for the treatment of AK, but MAL is no longer produced in the United States (Table 93–6 for dosing).[28] PDT has also been shown to be effective in the treatment of SCC in situ, but it is not indicated for SCC because of its extensive invasiveness and metastatic potential.[28]

Pharmacologic Therapy

▶ *Fluorouracil*

Nonsurgical treatment is used frequently for superficial keratinocyte carcinomas. Topical 5-fluorouracil has been used for the treatment of dermatologic disorders for approximately 45 years, and it has FDA approval for the treatment of AK and superficial BCC. Fluorouracil is available as both solution and cream with strengths ranging from 1% to 5%. There is also a microsphere-encapsulated 0.5% cream that has reduced systemic absorption with enhanced skin retention to reduce systemic side effects. The microsphere formulation is applied only once a day, providing patient preference and convenience over the twice daily application with the other formulations. The FDA has approved 2% to 5% cream or solution and 0.5% microsphere formulation for AK. For superficial BCC, only the 5% strength is FDA approved for this indication. The most common side effects with topical fluorouracil are expected to occur within the initial 5 to 10 days of treatment and include possible erythema, irritation, burning sensation, pruritus, and pain along with hypo- or hyperpigmentation. Patients may also experience inflammatory reactions that include crusting, edema, and oozing. The fluorouracil strength or frequency of application may be reduced if severe reactions occur. Topical steroids may be used concurrently with fluorouracil cream and for 1 to 2 weeks after treatment.[28] Caution should be used in administering fluorouracil to patients with dihydropyrimidine dehydrogenase deficiency, an enzyme critical in the metabolism of fluorouracil, because increased toxicity may occur.

Table 93–6

Topical Therapy for Actinic Keratosis

Methyl Aminolevulinate Hydrochloride
Apply maximum 1 g topically on lesion(s) for one PDT session, followed by occlusive dressing for 2.5–4 hours, then red light illumination for 7–10 minutes. Two PDT sessions 1 week apart are required.

Aminolevulinic Acid
Apply topically to lesion(s) and let dry, then repeat once; rinse and pat dry after 14–18 hours, then expose to blue light photodynamic therapy illuminator; may repeat after 8 weeks. Cover and protect lesions with light-opaque material for 40 hours; sunscreen is ineffective.

Topical Fluorouracil
Apply 2% or 5% solution or cream topically twice daily over lesions for 2–6 weeks or apply 0.5% microsphere formulation once daily for up to 4 weeks.

Imiquimod
Apply topical formulation at bedtime daily 5 × per week for 6 weeks; leave on skin for 8 hours

The doses presented here are general. Clinicians should refer to reference materials to determine the specific dose based on the regimen the patient is receiving.

PDT, photodynamic therapy.

► *Imiquimod*

This therapy option works by stimulating innate and cell-mediated immune responses. It is FDA approved for the treatment of AK and superficial BCC of the trunk, neck, or extremities when surgery may not be employed and follow-up is assured. Imiquimod has been shown to have complete clearing of AK in 50% of patients and partial clearing in 75% of patients with AK compared with 5% for those treated with placebo. Cure rates for imiquimod 5% in patients with superficial BCC are greater than 90%. The response rate is much lower for nodular BCC at 75%; therefore, it should be used in these patients only if they are not able to undergo surgery, radiation, or cryotherapy, and the tumor is small and in a low-risk area. Imiquimod is not recommended for the treatment of invasive SCC, but data for SCC in situ showed a 93% cure rate; thus, it may be considered for this patient population.

Imiquimod is available in 3.75% strength, which may be applied daily on larger areas of skin, the balding scalp, or the full face, and 5% strength, which may be used on areas of skin that are 25 cm^2 or smaller (see **Table 93–6**). Imiquimod should be applied before bedtime and left on the skin for 6 to 10 hours. The most common side effects with imiquimod involve the area of application and present as erythema, pruritus, a burning or stinging sensation, and tenderness. Less commonly, hypopigmentation, fever, diarrhea, and fatigue may also occur. Temporary discontinuation of imiquimod and application of topical steroids may be necessary to alleviate the irritation symptoms. Imiquimod may be resumed at a decreased frequency after the symptoms have resolved.[28]

► *Vismodegib*

Genetic alterations in the Hedgehog signaling pathway cause loss of function of *PTCH1*, which normally inhibits the signaling activity of Smoothened (SMO), a transmembrane protein involved in Hedgehog signal transduction. This first-in-class oral inhibitor of the Hedgehog signaling pathway is a small molecule that binds to and inhibits SMO. Vismodegib is approved by the FDA for the treatment of adult locally advanced or metastatic BCC that has recurred following surgery or has not been a candidate for surgery or radiation at a dose of 150 mg by mouth daily. Common side effects with vismodegib include muscle spasms, dysgeusia, hair loss, fatigue, nausea, and vomiting, while rare but serious adverse events may include severe cutaneous reactions and embryo–fetal toxicity. Patients should not donate blood or blood products while receiving vismodegib and for 24 months after the final dose of vismodegib.

► *Sonidegib*

Sonidegib is also an inhibitor of the Hedgehog signaling pathway. It is FDA approved for the treatment of adult patients with locally advanced (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy at a dose of 200 mg by mouth daily on an empty stomach. Common side effects with sonidegib include muscle spasms, dysgeusia, hair loss, fatigue, nausea, vomiting, and elevated serum creatinine, while rare but serious adverse events may include rhabdomyolysis and embryo–fetal toxicity. Patients should not donate blood or blood products while receiving sonidegib and for 20 months after the final dose of sonidegib.

OUTCOME EVALUATION

- Evaluate awareness and approach to avoid sun exposure and perform total-body skin self-examination.
- Assess treatment tolerance at every visit and ensure proper administration technique with topical treatments, such as fluorouracil or imiquimod: cleaning of treatment area before application, lesion area coverage with a 1-cm margin, and use of gloves, as well as handwashing after application.
- Assess side effects' management such as pain, itching, and inflammation and reinforce the need for dermatologist, consult if worsening.
- Verify the presence of the *PTCH1* mutation before initiation of oral SMO inhibitor treatment and assess compliance.

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Patient Care Process

Collect Information:

- Review current diagnosis with emphasis on skin cancer clinical signs (ABCDE)
- Obtain demographic information, family history, geographical location, and any specific lifestyle habit that may constitute risk factors
- Document medical and treatment history with emphasis on immune conditions, immunodeficiencies and immunosuppressive therapies, and medications associated with increased sun-related sensitivity (see Table 93–8)
- Any allergy or history of intolerance to biologics
- Understand cosmetic expectations and identify socioeconomic factors that may interfere with access to treatment and regular follow-ups

Assess the Information:

- Assess the possible causes of tumor occurrence (medical history, lifestyle, treatment, etc)
- Evaluate current performance status and assess other medications compliance
- Evaluate any treatment history that may (have) cause(d) photosensitivity
- Determine eligibility for immunotherapy and other current pharmacotherapy options
- Assess BRAF genotype status
- Review relevant laboratory tests (eg, electrolytes, liver panel, renal panel)
- Identify any predisposition to expected adverse events

Develop a Care Plan:

- Identify any contraindication for specific treatment options and select the best therapy
- Identify counseling points relevant to the patient and family
- Design a medication administration plan
- Design an adverse event monitoring and management plan

Implement the Care Plan:

- Educate the patient about the current options, explain the therapy selection, medication administration, common adverse events, and reporting and management
- Review the patient's practices for skin cancer prevention
- Discuss the importance of medication adherence and lifestyle modifications to reduce skin cancer risk
- Address any patient concern about treatment outcomes
- Determine access to healthcare insurance and ensure smooth delivery of the treatment
- Assess patient expectations and verify their understanding regarding the course of treatment

Follow-up: Monitor and Evaluate:

- Evaluate how tumor resection affected the skin integrity, appearance, function, and the quality of life postoperative
- Assess skin recovery after radiation
- Verify patient and family understanding regarding subsequent prevention and systematic skin self-examination
- Review reported adverse events and appropriateness of their management
- Discuss treatment alternatives and options for recurrence prevention
- Review the appropriateness of lab monitoring for the ongoing treatment plan
- Address any palliative care symptom and assess patients' psychological, physical, and social functioning

Abbreviations Introduced in This Chapter

AK	Actinic keratosis
ALA	δ-Aminolevulinic acid
APC	Antigen-presenting cell
BCC	Basal cell carcinoma
BRAF	Proto-oncogene B-Raf
CDKN2A	Cyclin-dependent kinase inhibitor-2A
CNS	Central nervous system
CTL	Cytotoxic T lymphocyte
CTLA-4	Cytotoxic T lymphocyte–associated protein 4
CYP	Cytochrome P450
DL	Dysplastic leukoplakia
ED&C	Electrodessication and curettage
ERK	Extracellular signal–regulated kinase
HD	High dose
IFN	Interferon-α-2b
Ig	Immunoglobulin
IL-2	Interleukin-2
LFT	Liver function test
MAL	Methyl aminolevulinate
MAL–PDT	Methyl aminolevulinate–photodynamic therapy
MAP	Microtubule-associated protein
MAPK	Mitogen-activated protein kinase
MEK	MAPK/ERK kinases
MITF	Microphthalmia-associated transcription factor
MM	Malignant melanoma
MMS	Mohs micrographic surgery
NMSC	Nonmelanoma skin cancer
NRAS	Neuroblastoma RAS viral oncogene
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PDT	Photodynamic therapy
PPP6C	Protein phosphatase 6 catalytic subunit
PTCH1	Patch homolog-1
PTEN	Phosphatase and tensin homolog
RAC-1	Ras-related protein C3 botulinum toxin substrate 1 precursor
RAF	Proto-oncogene Raf-1
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	Risk Evaluation and Mitigation Strategy
SCC	Squamous cell carcinoma
SEER	Surveillance, Epidemiology, and End Results
SLN	Sentinel lymph node

SMO	Smoothened
SPF	Skin protection factor
SRS	Stereotactic radiosurgery
STK19	Serine/threonine-protein kinase 19
TIL	Tumor-infiltrating lymphocytes
TNM	Tumor, node, metastasis
UVA/B	Ultraviolet (radiation) A/B
UVR	Ultraviolet radiation
WBRT	Whole-brain radiation therapy
XP	Xeroderma pigmentosum

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Ovarian Cancer

Judith A. Smith

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Demonstrate understanding of the etiology and risk factors associated with the development of ovarian cancer.
2. Justify the risk and benefits of the surgical and chemoprevention options available for decreasing the potential risk of developing ovarian cancer.
3. Interpret and understand the utility of the screening tests and serologic markers for diagnosing ovarian cancer.
4. Distinguish the nonspecific physical signs and symptoms of ovarian cancer.
5. Recommend the appropriate surgical and chemotherapy treatment options for newly diagnosed, persistent, and recurrent ovarian cancer patients.
6. Discuss the role of first-line maintenance treatment for improving overall survival for ovarian cancer patients.
7. Compare and contrast chemotherapy options for women with recurrent platinum-resistant ovarian cancer.

INTRODUCTION

Ovarian cancer is relatively uncommon but is the most incurable of the gynecologic cancers. Ovarian cancer is often denoted as the "silent killer." KEY CONCEPT The primary reason for the high mortality rate associated with ovarian cancer is the nonspecific symptoms and difficulty for early detection or screening that result in patients presenting with advanced disease. The majority of ovarian cancers are of epithelial origin. Each time **ovulation** occurs, the epithelium of the ovary is broken followed by occurrence of cell repair. The incessant ovulation hypothesis proposes that the increasing number of times the ovary epithelium undergoes cell repair is associated with the increasing risk of mutations and ultimately ovarian cancer. Although the majority of patients will achieve a complete response (CR) to primary surgery and chemotherapy, disease recurs in more than 50% of patients in the first 2 years after completion of primary treatment. KEY CONCEPT Ovarian cancers often cause metastasis via the lymphatic and blood systems to the liver and/or lungs. Common complications of advanced and progressive ovarian cancer include **ascites** and small bowel obstruction (SBO), which often are associated with the end of life.

EPIDEMIOLOGY AND ETIOLOGY

In 2021, there were an estimated 21,410 new cases of ovarian cancer diagnosed with an associated 13,770 deaths.[1] Ovarian cancer remains the number one gynecologic killer and the fifth leading cause of cancer-related death in women. Despite great efforts and extensive research, addition of new agents and routes of administration, there has been little change in the mortality rate associated with ovarian cancer over the past six decades. Again, this high mortality rate associated with ovarian cancer can be attributed to its insidious onset of nonspecific symptoms, resulting in the majority of patients not presenting until the cancer has progressed to stages III to IV disease.

As with many other disease states, a significant risk factor associated with ovarian cancer is aging. Risk of ovarian cancer increases from age 40 to 79 years, with the mean age at diagnosis being 63 years and the majority of women being diagnosed between 55 and 64 years.[2]

Ovarian cancer is a sporadic disease; fewer than 10% of ovarian cancers can be attributed to heredity. KEY CONCEPT The majority of cases of ovarian cancer occur sporadically, making it difficult to screen and prevent. Although hereditary cancer accounts for fewer than 10% of all ovarian cancer cases, when there is a family history, it appears to be an important risk factor in the development of ovarian cancer in some patients.[3] If one family member has a diagnosis of ovarian cancer, the associated risk is about 9%, but this risk increases to greater than 50% if there are two or more first-degree relatives (ie, mother and sister) with a diagnosis of ovarian cancer or multiple cases of ovarian and breast cancer.[3] Both breast cancer activator gene 1 (*BRCA1*) and gene 2 (*BRCA2*) mutations have been associated with ovarian cancer. However, *BRCA1* is more prevalent, being associated with 90% of hereditary and 10% of sporadic cases of ovarian cancer.[3] Hereditary breast and ovarian cancer (HBOC) syndrome is one of the two different forms of hereditary ovarian cancer and is associated with germline mutations in *BRCA1* and *BRCA2*.[3-5] The hereditary **nonpolyposis** colorectal cancer (HNPCC) or Lynch syndrome is a familial syndrome with germline mutations causing defects in enzymes involved in DNA mismatch repair, which has been associated with up to 12% of hereditary ovarian cancer cases.[4]

Patient Encounter 1

The patient is a 63-year-old active, nonobese woman, who has been in good health up until recently (last 3 months) when she started to feel frequent reflux, bloating, and fatigue. During a weekly virtual visit with her granddaughter during the corona virus pandemic, she mentioned to her daughter that she had been lots of reflux lately despite use of OTC antacid medications. The following monday she saw her primary care provider who recommended dietary modifications and to complete a 6-week trial of prescription proton pump inhibitor. Six weeks later, her reflux persisted and now she felt more bloated and has started to have difficulty with bowel movements too. Her primary care provider ordered endoscopic exam and an abdominal CT scan that came back positive for bilateral ovarian masses including a 10-cm noncystic mass on left ovary and 6-cm mass on the right ovary, and omentumal thickening. Of note, she has been married for 29 years with only three sexual partners in her lifetime. They have three daughters and a son who are all grown adults. Her first menses was when she was 10 years old and menopause was at age 59 years. She has had infrequent alcohol on social occasions only and denies any tobacco use.

Based on the results from the abdominal CT scan, what laboratory tests are needed and what type of specialist should she be referred to complete her workup?

In the context of this patient, discuss why ovarian cancer is often denoted the "silent killer" and what needs to be done for earlier diagnosis of ovarian cancer.

Discuss the type of surgery recommended and outcome goal for this surgery.

Although it is not clearly defined, hormones and reproductive history are associated with the risk of developing ovarian cancer. **Nulliparity**, infertility, early menarche, or late menopause is associated with an increased risk of ovarian cancer.[6]

Ovarian cancer is associated with certain dietary and environmental factors as well. A diet that is high in galactose and animal fat and meat increases the risk of ovarian cancer, whereas a vegetable-rich diet is suggested to decrease the risk.[6,7]

Screening and Prevention

▶ *Screening*

Currently, there is no standard effective screening tool that is adequately specific or sensitive for early detection.[8]

Pelvic examinations are effective for detecting obvious tumors present with a sensitivity of 67% for detecting all tumors; however, minimal or microscopic disease cannot be detected on physical examination.[9] Pelvic examinations are noninvasive and well accepted, but they do not usually detect ovarian cancer until it is in advanced stage. Transvaginal ultrasound (TVUS) is a component of current screening practices. Typically, it is used in combination with cancer antigen-125 (CA-125) or could be used as a single modality. TVUS releases sonic sound waves that create an image of the ovary to evaluate the size and shape and detect the presence of cystic or solid masses. Limitations of this technique are lack of specificity and an inability to detect peritoneal cancer or cancer in normal size ovaries.[2,9] Most prevention clinics use this multimodality approach to screen high-risk women and recommend yearly ultrasound in combination with CA-125 blood test every 6 months.

Patient Encounter 2

A 45-year-old woman diagnosed with stage IIa adenocarcinoma of the ovary with positive *BRCA1* mutation status post optimal debulking surgery completed six cycles of paclitaxel 175 mg/m^2 IV plus carboplatin AUC 5 IV plus bevacizumab 15 mg/kg that was given once every 21 days. Her CT scan findings suggest no detectable disease and CA-125 within the normal range (13 U/mL [13 kU/L]) upon completion of her chemotherapy. She feels great and has no obvious symptoms of ovarian cancer at this time.

Discuss the advantages and disadvantages of treatment options for maintenance treatment with PARP inhibitor versus bevacizumab versus the combination of both bevacizumab plus PARP inhibitor for this patient. Describe the role of second-look surgery for this patient.

Serum CA-125 is the most extensively evaluated tumor marker for ovarian cancer. **KEY CONCEPT** Because CA-125 is a nonspecific marker, it is not a standard recommendation for routine screening for prevention of ovarian cancer. Unfortunately, since CA-125 is nonspecific, elevated levels can be associated with a number of other gynecologic and GI-related diseases. CA-125 levels in a woman without ovarian cancer are static or tend to decrease over time, but levels associated with malignancy continue to rise.[9,10]

▶ *Prevention*

Ovulation is considered a hostile event to the ovarian epithelium, making it more susceptible to damage and cancer. Interventions or conditions that limit the number of ovulations in a woman's reproductive history, including **multiparity**, have a protective effect.

Chemoprevention Investigational chemoprevention strategies used for ovarian cancer include oral contraceptives (OCs), aspirin, nonsteroidal anti-inflammatory agents, and retinoids, although none of these is currently accepted as standard treatment for the prevention of ovarian cancer. The theory that OCs reduce the number of ovulatory events is a basic explanation of its protective effect. Recent studies have suggested that progestin-induced apoptosis of the ovarian epithelium is responsible for the chemopreventive effect of OCs. The theory is that cells that have genetic damage but are not yet neoplastic have an increased chance of undergoing apoptosis.[10,11] OCs decrease the relative risk to less than 0.4% in women who use OCs for longer than 10 years.[12] However, the maximum protective effect of OC use in women with *BRCA* mutations has been reported to be between 3 and 5 years.[12] At the same time, OC use has been associated with an increased risk of breast cancer.[11,13] Thus, women with a family history of breast cancer are not ideal candidates for this preventive measure.

Nonsteroidal anti-inflammatory agents, aspirin, and acetaminophen have been evaluated for preventing of different cancers, especially hereditary nonpolyposis colon cancer.[13] Although observational studies have linked these to a reduction of ovarian carcinoma risk, evidence is still lacking. Potential mechanisms include effects on normal ovulation shed and inhibition of ovulation.[13] Other pharmacologic interventions that have been suggested but are still being evaluated include vitamin A, lutein,

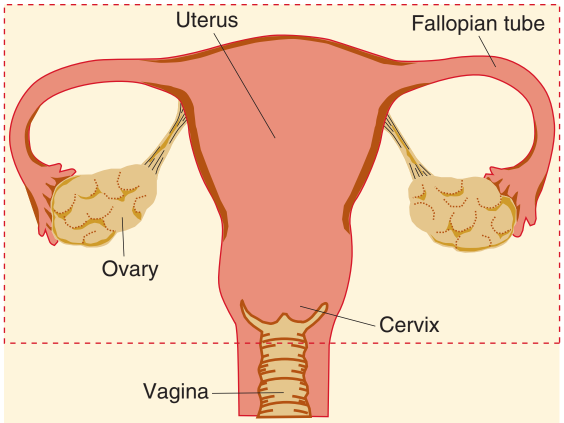

FIGURE 94–1. Diagram of female reproductive tract (uterus, fallopian tubes, ovaries, vagina). The *dashed line box* outlines what is removed during the total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO).

and other carotenoids.[14] The protective effect of these agents is associated with inhibition of cell growth as well as promotion of cellular differentiation.[14]

Prophylactic Surgery Surgical strategies are also used in the prevention of ovarian cancer. The goal is to remove healthy, at-risk organs and ultimately reduce the risk of developing cancer. These surgeries include prophylactic bilateral salpingo-oophorectomy (BSO) or tubal ligation (Figure 94–1).

Prophylactic oophorectomy should be considered in any woman with a high risk of developing ovarian cancer.[15,16] The criteria for defining high risk include any woman with two or more first-degree relatives with epithelial ovarian carcinoma; a family history of multiple occurrences of nonpolyposis colon cancer, endometrial cancer, and ovarian cancer; and a family history of multiple cases of breast and ovarian cancer.[17] Patients undergoing prophylactic oophorectomy need to be made aware that complete protection is not guaranteed.[17-19] Although a 67% reduction in risk has been shown, a potential 2% to 5% risk of peritoneal carcinomatosis remains.[18-20]

Tubal Ligation Tubal ligation is another procedure that has shown potential for risk reduction. However, it is not recommended as a sole procedure in prophylaxis. The protective effect may be attributable to limiting exposure of the ovary to environmental carcinogens. A case–control study conducted by Narod and colleagues[19] found that a history of tubal ligation in *BRCA*-positive women was associated with a statistically significant 63% reduction in risk.

Genetic Screening Genetic screening is recommended for all patients with new ovarian cancer diagnosis. Ovarian cancer has been associated with high prevalence of actionable pathogenic genetic variants.[4] Patients should be screened for genes such as *BRCA1* and *BRCA2* as well as other genes such as those associated with HNPCC or the HBOC syndrome.[3,21] Patient and family counseling and genetic counseling should be available for the patient and family to prepare and deal with the health and psychosocial implications of the genetic test results. Before performing genetic testing, the potential preventive options should be discussed, such as prophylactic BSO and/or total hysterectomy. Cancer risk and patient's health need to be balanced, but typically surgery can be held off until after the childbearing years.[20-22]

PATHOPHYSIOLOGY

The three current theories are the incessant ovulation hypothesis, the pituitary gonadotropin hypothesis, and the chronic inflammatory processes hypothesis.[2] The incessant ovulation hypothesis proposes that the pathogenesis of ovarian cancer is connected to continual ovulation. Ovulation is considered a "hostile" event to the ovaries, perhaps with not enough time for adequate repair. Each time ovulation occurs, the ovary epithelium is disrupted, and cell damage occurs. Thus, repeated ovulations may lead to a greater number of repairs of the ovarian epithelium and increase the possibility of aberrant repairs, mutation, and carcinogenesis.[2] The pituitary gonadotropin hypothesis associates the disease with elevations in gonadotropin and estrogen levels.[2] This leads to an increase in the number of follicles and, therefore, an increased risk of malignant changes. Finally, the chronic inflammatory processes may be involved with various environmental carcinogens to cause cancer.[2,13]

The three major pathologic categories of ovarian tumors include sex-cord stromal, germ cell, and epithelial. About 85% to 90% of ovarian cancers are of epithelial origin. Epithelial ovarian tumors are composed of cells that cover the surface of the ovary such as serous, mucinous, endometrioid, clear cell, and poorly differentiated adenocarcinomas. Germ-cell tumors involve the precursors of ova with the most common type being dysgerminoma, which are most commonly diagnosed in women younger than the age of 40 years and generally have a better prognosis.[2] Sex-cord stromal tumors are not only indolent tumors that produce excess estrogen and androgens but also have a better overall prognosis.[2] Although the histologic type of the tumor is not a significant prognostic factor, it is important to know the histopathologic grade with high-grade being more aggressive and low-grade slower growing. Similar to other solid tumors, clear-cell histology tends to be high grade and often chemotherapy-resistant. Undifferentiated tumors are associated with a poorer prognosis than lesions that are considered to be well or moderately differentiated.

TREATMENT

Desired Outcomes

Healthcare providers use a multimodality approach, including surgery and chemotherapy, in initial treatment of patients with ovarian cancer with a curative intent, or restoring a normal life span. **KEY CONCEPT** Although the majority of patients initially achieve a CR, disease will recur within the first 2 years in more than 50% of patients.[2,23] CR to treatment is defined as no evidence of disease can be detected by physical examination or diagnostic tests and patient has a normalized CA-125.

The stage of disease at the time of diagnosis is the most important prognostic factor affecting overall survival in ovarian cancer patients.[24] The estimated 5-year survival rates of patients with localized, regional, distant, and unstaged ovarian cancer are 92.1%, 73.2%, 28.3%, and 22.8%, respectively.[7] The histology of the disease is another predominant prognostic factor influencing treatment outcomes. Clear-cell and undifferentiated tumors do not respond as well to chemotherapy.[2] The extent of residual disease and tumor grade are also predictive of response to chemotherapy and overall survival.[2] There are other prognostic factors that may predict how well a patient will respond to adjuvant chemotherapy.

The treatment goals shift when a patient presents with recurrent ovarian cancer. The desired outcomes focus on relief of symptoms such as pain or discomfort from ascites, slowing disease progression, and prevention of serious complications such as

Clinical Presentation and Diagnosis of Ovarian Cancer

General

Ovarian cancer typically has delay in diagnosis due to the common nonspecific signs and symptoms often initially suggesting GI-related complications. By the time symptoms become unrelenting and bothersome, patients most likely have advanced stage disease.

Symptoms

Patients may experience episodes or persistent symptoms such as abdominal pain, constipation or diarrhea, flatulence, urinary frequency, or incontinence.

Signs

The degree of abdominal swelling secondary to fluid accumulation may present like "pregnant abdomen" and irregular vaginal bleeding.

Laboratory Test

- CA-125. The normal level is less than 35 U/mL (35 kU/L). Note: This test is associated with a lack of specificity. CA-125 can be elevated in a number of other states such as different phases of the menstrual cycle, endometriosis, and nongynecologic cancers. Therefore, it is important to rule out other cancers associated with the abdominal cavity.
- Carcinoembryonic antigen (CEA). CEA is a marker for colon cancer. A normal value is less than 3 ng/mL (3 mcg/L). However, this can also be elevated in serous papillary carcinomas of ovary.
- CA-19-9 is a marker for many GI tumors such as cholangiocarcinomas.

Chemistries with Liver Function Tests (LFTs)

- LFTs and serum creatinine might be suggestive of extent of disease. The majority of this information is needed to determine if the patient is a surgical candidate. Laboratory study results should be within normal limits.

Complete Blood Count (CBC)

- Abnormalities in CBC are not associated with ovarian cancer; however, this information is needed to determine if the patient is a surgical candidate. Laboratories should be within normal limits.

Other Diagnostic Tests

To characterize local disease, one or both of the following are completed:

- TVUS
- Abdominal ultrasound

To evaluate the extent of disease, only one of the following is completed:

- CT scan
- MRI
- PET scan

Chest X-ray is also often done as part of clearance for surgery.

Ovarian cancer is usually confined to the abdominal cavity, but spread can occur to the lung and liver and less commonly to the bone or brain. Disease is spread by direct extension, peritoneal seeding, lymphatic dissemination, or blood-borne metastasis. Lymphatic seeding is the most common pathway and frequently causes ascites.

SBO. When a patient relapses, the prognostic factors are similar as after initial surgery except that the amount of time that has lapsed since the completion of chemotherapy should be considered to determine if drug resistance is emerging in the tumor. Recurrent platinum-sensitive ovarian cancer patients generally have a better prognosis than platinum-resistant patients.

Nonpharmacologic Therapy

KEY CONCEPT Surgery is the primary treatment intervention for ovarian cancer.[25-27] A total hysterectomy with BSO (TH-BSO) (see Figure 94–1), omentumectomy, and lymphonectomy (or lymph node dissection) is the standard initial surgical treatment of ovarian cancer.[25] The objective of the surgery is to debulk the patient to less than 1 cm of residual disease remains. Residual disease less than 1 cm correlates with better CR rates to chemotherapy and better overall survival compared with patients with bulky residual disease (larger than 1 cm).[22-24] The size of residual tumor masses after primary surgery is found to be another important prognostic factor in patients with advanced ovarian cancer.[27]

A thorough exploratory laparotomy is essential for the accurate staging of the patient.[22-24] **KEY CONCEPT** Ovarian cancer is staged surgically using the International Federation of Gynecology and Obstetrics (FIGO) staging algorithm. For certain patients with limited stage disease, surgery may be curative.

Other surgical procedures have been evaluated to improve overall survival. Debulking surgery is intended to relieve symptoms associated with complications such as SBO and help improve the patient's quality of life but does not have a curative intent. Interval debulking that is completed after two to three cycles of chemotherapy has not translated to an improved survival benefit. Often debated, the benefit of the "second-look laparotomy" to evaluate residual disease after the patient has completed chemotherapy remains controversial because it has been difficult to establish any impact on patients' overall survival. It has questionable benefit because although approximately 40% of patients with advanced disease have a negative second look, 50% still relapse.[2] The role of laparoscopic surgery is somewhat controversial for initial surgery but is more often considered in debulking of recurrent or advanced disease when the intent is palliative rather than curative.[23]

Pharmacologic Therapy

▶ *First-Line Chemotherapy*

KEY CONCEPT After initial surgery, the gold standard of care is six cycles of taxane/platinum-containing regimen for patients with advanced ovarian cancer.[25-27] Patients with limited disease, that is, stage IA, will have observation alone after surgery (Figure 94–2). The majority of patients will receive adjuvant chemotherapy within 3 to 4 weeks after surgery. Most often, paclitaxel is the taxane agent used in combination with carboplatin as the preferred platinum agent.[25-27] Depending on patients' preexisting comorbidities and how well they tolerate chemotherapy regimens, substitution with docetaxel or cisplatin might be considered. The

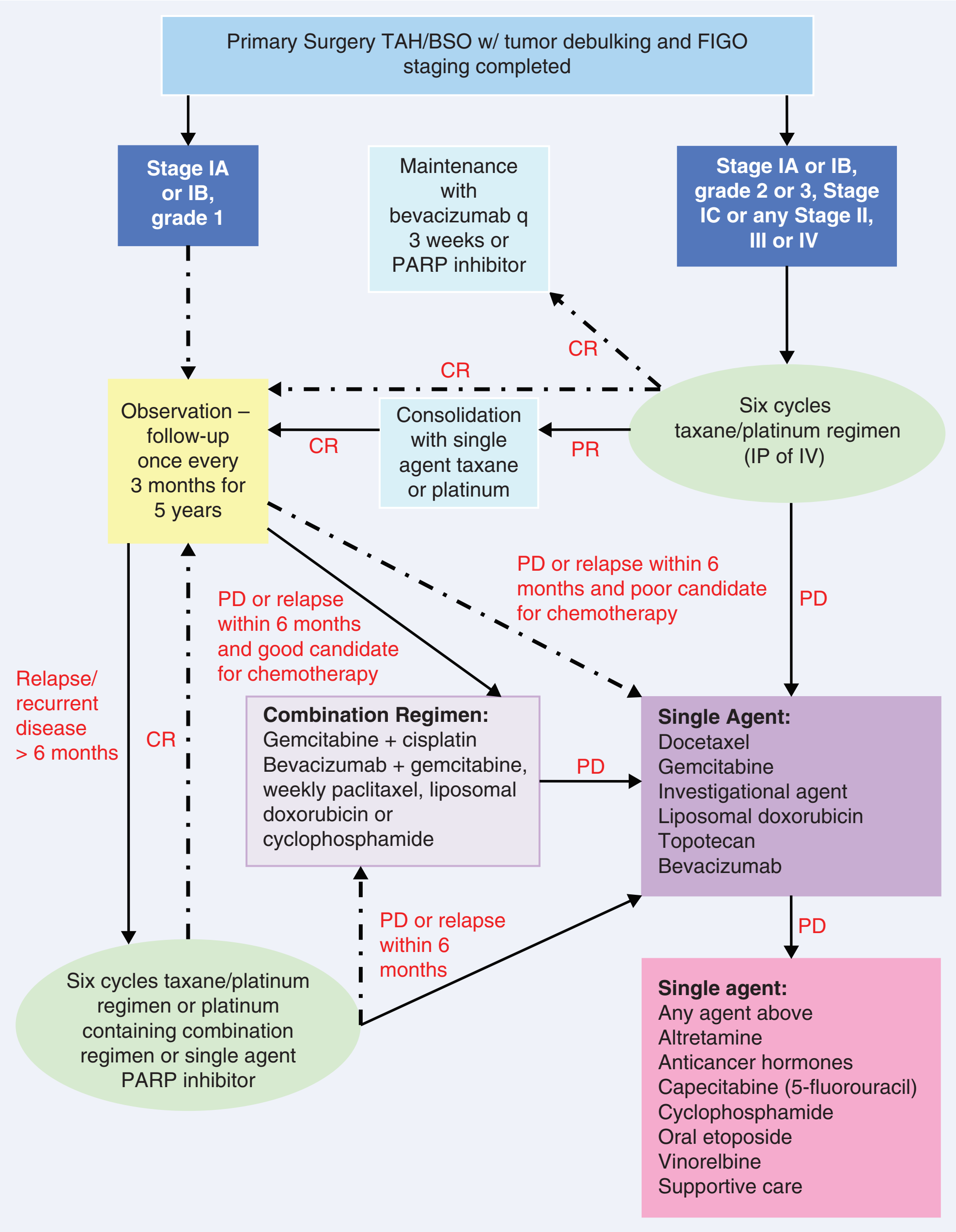
Primary Surgery TAH/BSO w/ tumor debulking and FIGO staging completed
Stage IA or IB, grade 1
Maintenance with bevacizumab q 3 weeks or PARP inhibitor
Stage IA or IB, grade 2 or 3, Stage IC or any Stage II, III or IV
CR
CR
Observation – follow-up once every 3 months for 5 years
CR
Consolidation with single agent taxane or platinum
PR
Six cycles taxane/platinum regimen (IP of IV)
PD or relapse within 6 months and poor candidate for chemotherapy
PD
PD or relapse within 6 months and good candidate for chemotherapy
Relapse/ recurrent disease > 6 months
CR
Combination Regimen:
Gemcitabine + cisplatin
Bevacizumab + gemcitabine, weekly paclitaxel, liposomal doxorubicin or cyclophosphamide
PD
Single Agent:
Docetaxel
Gemcitabine
Investigational agent
Liposomal doxorubicin
Topotecan
Bevacizumab
PD
PD or relapse within 6 months
Six cycles taxane/platinum regimen or platinum containing combination regimen or single agent PARP inhibitor
Single agent:
Any agent above
Altretamine
Anticancer hormones
Capecitabine (5-fluorouracil)
Cyclophosphamide
Oral etoposide
Vinorelbine
Supportive care

FIGURE 94–2. Summary of a chemotherapy treatment algorithm for epithelial ovarian cancer. (CR, complete response; FIGO, Federation of Gynecology and Obstetrics; PD, progressive disease; PR, partial response; TAH-BSO, total abdominal hysterectomy with bilateral salpingo-oophorectomy.)

route of administration should also be discussed. Although intravenous (IV) administration is often used, intraperitoneal (IP) administration has been shown to improve overall survival and should be considered an option for first-line treatment; however, patient selection for IP therapy is critical[28,29] (Table 94–1). Close monitoring of organ function, nausea/vomiting, myelosuppression, and neuropathies is necessary for all taxane/platinum regimens (Table 94–2).

▶ *Intraperitoneal Chemotherapy*

For more than four decades, numerous investigators have evaluated the IP route for administration of chemotherapy; however, it was not until the third report of an improvement in overall survival that brought its use to the forefront in the first-line setting.[30] However, the benefits of IP chemotherapy has again become controversial after a recent report that compared IP chemotherapy to addition of bevacizumab and showed equivalent outcomes.[31] Current, there is no consensus among experts on whether IP chemotherapy should remain standard of care for first-line treatment of advanced ovarian cancer.

The principal theory supporting IP administration is to increase drug concentration in the site of disease, specifically the abdominal cavity. Patient characteristics greatly influence response and tolerability of IP chemotherapy. To be selected to receive IP chemotherapy for first-line treatment of ovarian cancer, the patient should have tumor optimally debulked and no bowel resection with primary surgery, normal renal and liver function, younger age, and no significant comorbidities.

Table 94–1

Summary of First-Line Chemotherapy Regimens for Advanced Ovarian Cancer

Gold standard first-line chemotherapy after initial surgery for treatment of ovarian cancer:

Paclitaxel 175 mg/m^2 IV infused over 3 hours + carboplatin AUC = 5 IV infused over 1 hour. Regimen is given once every 21 days × 6 cycles (+/− bevacizumab 7.5 mg/kg once every 3 weeks × 6 cycles followed by additional 12 cycles after completion of primary chemotherapy)

Alternative first-line regimen: Paclitaxel IV with substitution of carboplatin IV with cisplatin IP and addition of paclitaxel IP therapy:

Patient selection is critical: must have optimally debulked disease (< 1 cm) and no significant comorbidities; younger patients tolerate better

Day 1: paclitaxel 135 mg/m^2 IV infused over 24 hours + day 2: cisplatin 100 mg/m^2 IP infused over 1 hour + day 8: paclitaxel 60 mg/m^2 IP infused over 1 hour. Regimen is given once every 21 days × 6 cycles

Alternative first-line regimen: Dose density. Consider for patients with optimal debulking, no comorbidities, good performance status:

Paclitaxel 80 mg/m^2 IV infused over 1–3 hours once a week with carboplatin AUC = 6 IV infused over 1 hour on day 1 only of 21-day cycle

Alternative first-line regimen: Substitution of cisplatin in place of carboplatin. Consider for patients experiencing difficulty with maintaining platelet counts:

Paclitaxel 135 mg/m^2 IV infused over 24 hours + day 2: cisplatin 75 mg/m^2 IV infused over 4 hours. Regimen is given once every 21 days × 6 cycles

Alternative first-line regimen: Substitution of docetaxel in place of paclitaxel. Consider for patients with preexisting or increased risk of neuropathies:

Docetaxel 75 mg/m^2 IV infused over 1 hour + carboplatin AUC = 5 IV infused over 1 hour. Regimen is given once every 21 days × 6 cycles

AUC, area under the curve; IV, intravenous.

When IP therapy is administered, the placement of an IP catheter should occur at the time of surgery unless otherwise contraindicated. During IP administration, chemotherapy is delivered to the peritoneal space in 1 L of normal saline (NS) that has been warmed followed by another liter of NS to enhance drug distribution as tolerated.[30,31] The current standard IP regimen includes the administration of paclitaxel IV on day 1 followed by cisplatin IP on day 2 and then paclitaxel IP on day 8 given on a 21-day cycle for a total of six cycles (see Table 94–2). IP chemotherapy is difficult to tolerate with significant patient toxicity. The most common toxicities associated with IP administration include abdominal pain, myelosuppression, neurotoxicity, and catheter-related infections. The substitution of carboplatin IP in place of cisplatin remains investigational and should not be recommended outside a clinical trial protocol.

▶ *Neoadjuvant Chemotherapy*

Neoadjuvant chemotherapy is first-line treatment for patients who are poor surgical candidates or patients with bulky or significant tumor burden.[32] For patients who are poor surgical candidates because of significant comorbidities, a combination of taxane with platinum agent is administered every 21 to 28 days as tolerated with the intent to relieve symptoms and slow progression of disease. In some cases, especially in elderly patients, single-agent carboplatin is used as palliative treatment instead. Chemotherapy alone has not been curative for patients with advanced ovarian cancer.[33]

In patients with bulky disease or significant tumor burden, neoadjuvant chemotherapy can be used to decrease tumor burden to increase the likelihood of optimal tumor debulking during surgery.[33] Typically, three cycles of the standard combination taxane/platinum regimen is administered once every 21 days. After surgery, patient will receive another three to six cycles depending on their response to chemotherapy.

▶ *Consolidation and Maintenance Chemotherapy*

Consolidation chemotherapy is the addition of cycles of the taxane/platinum regimen or the addition of single-agent platinum or single taxane after completion of first-line chemotherapy.[34] If the tumor has a partial response (PR) to first-line chemotherapy evident by a significant decline in CA-125 by greater than 50% presurgery level and/or tumor regression or decrease in size, then cancer is still considered taxane/platinum sensitive. Additional cycles of chemotherapy are given until CR is achieved (see Figure 94–2). In 2014, bevacizumab was approved as the first targeted therapy for maintenance treatment for ovarian cancer based on the improved overall survival observed in the ICON-7 study.[35] First-line maintenance chemotherapy is similar to consolidation chemotherapy except maintenance chemotherapy is given to patients who have achieved a clinically CR.[35] The rationale for first-line maintenance chemotherapy is used to extend progression-free and overall survival by eliminating any microscopic disease present after completion of primary chemotherapy. Two agents from the class of poly(ADP-ribose) polymerase (PARP) inhibitors, niraparib and olaparib, have also demonstrated benefit in improving progression-free survival as maintenance therapy following achieving clinical CR to primary treatment.[36-41] PARP inhibitors were the second class of targeted therapy agents approved for first-line maintenance treatment of ovarian cancer. While greater benefit has been observed in the presence of *BRCA1* mutations, clinical benefit has been observed even in the absence of *BRCA1* mutations as well.[38,39] In 2020, the combination of bevacizumab plus PARP inhibitor has emerged as another approved option for first-line maintenance for ovarian cancer after CR achieved. In these studies, patients had received bevacizumab as part of primary chemotherapy treatment, and the addition of a PARP inhibitor to bevacizumab for first-line maintenance was associated with significant improvement in progression-free survival.[40,41] The potential financial toxicity should be taken into consideration when selecting optimal regimen for first-line maintenance for advanced ovarian cancer.

For an extensive description of the common agents used in first-line, consolidation, and maintenance chemotherapy of ovarian cancer, please see Chapter 88. A brief overview of the regimens is provided in Table 94–1, and adverse effects are provided in Table 94–2.

Chemotherapy After Recurrence

In the recurrent setting, platinum sensitivity of the tumor is assessed first. If recurrence occurs in less than 6 months or disease progresses while the patient is receiving a platinum-based regimen, the cancer is considered platinum resistant (see Figure 94–2). These parameters are also used to determine if tumors are taxane sensitive or resistant. However, patients

Table 94–2

Summary of Chemotherapy Agents Used for First-Line and Maintenance Treatment of Advanced Ovarian Cancer

Mechanism of Action of First-Line Agents
Platinum analogues: Produce intra- and interstrand cross-links and DNA adducts to disrupt DNA replication
Taxanes agents: Stabilize microtubules and prevent depolymerization of tubulin
Mechanism of Action of Maintenance Agents
PARP Inhibitors: Result in double-stranded DNA breaks that cannot be repaired in cancer cells with BRCA mutations
Antiangiogenic Agents: Inhibit VEGF-R, decrease microvasculator growth

Agent	Common Adverse Effects	Monitoring/Comments
First-Line		
Paclitaxel	Peripheral neuropathy (DLT), nausea/vomiting, alopecia, hypersensitivity reactions	Use caution with any elevation in AST (SGOT) Give proper dosing for liver dysfunction. At least a 50% dose reduction generally recommended Do not give if total bilirubin is > 5 mg/dL (86 μmol/L) Premedicate for hypersensitivity reactions: dexamethasone, diphenhydramine, and cimetidine
Docetaxel	Neutropenia (DLT) hyperlacrimation, fluid retention, nail disorders, myelosuppression	Use with caution in liver dysfunction. Patients with bilirubin greater than the ULN and/or liver transaminases > 1.5 times, the ULN should not receive docetaxel Do not give if biliary tract is obstructed Premedicate for hypersensitivity reactions: dexamethasone
Carboplatin	Myelosuppression (DLT), nephrotoxicity, nausea/vomiting, electrolyte wasting, diarrhea, stomatitis, hypersensitivity reactions	Prehydration not required If using BSA dosing, give proper dosing for renal dysfunction CrCl ≥ 60 mL/min (1.00 mL/s): no dosage adjustment needed CrCl 41–59 mL/min (0.68–0.99 mL/s): give 250 mg/m^2 CrCl 16–40 mL/min (0.26–0.67 mL/s): give 200 mg/m^2 CrCl ≤ 15 mL/min (0.25 mL/s): do not give NOTE: Calvert formula (AUC dosing) is based on renal function, so no additional dose adjustment is needed Premedicate for hypersensitivity reactions: dexamethasone, diphenhydramine, and cimetidine Appropriate antiemetic regimen for prevention of acute and delayed nausea
Cisplatin	Neurotoxicity (DLT), nausea/vomiting, ototoxicity, nephrotoxicity, myelosuppression, electrolyte wasting, diarrhea	Prehydration and posthydration with electrolyte replacement (ie, potassium chloride 10 mEq [10 mmol] and magnesium sulfate 16 mEq [8 mmol]) required Do not use if SCr > 1.5 mg/dL (133 μmol/L) or BUN > 25 mg/dL (8.9 mmol/L) Give proper dosing for renal dysfunction CrCl 46–60 mL/min (0.77–1.00 mL/s): decrease dose by 50%. CrCl 31–50 mL/min (0.51–0.83 mL/s): decrease dose by 75%. CrCl ≤ 30 mL/min (0.50 mL/s): do not use Appropriate antiemetic regimen for prevention of acute and delayed nausea
First-line Maintenance		
Niraparib	Fatigue, nausea, thrombocytopenia, neutropenia, elevated liver function tests	Monitor CBC closely for first 4–6 weeks of treatment then monthly thereafter; Consider antiemetic PRN
Olaparib	Edema, fatigue, hypomagensemia, nausea, thrombocytopenia, neutropenia	Monitor CBC monthly Recommend antiemetics PRN
Rucaparib	Nausea, fatigue, elevations in liver function tests, rash, thrombocytopenia	1. Monitor CBC monthly 2. Recommend antiemetics PRN
Bevacizumab	Hypertension, proteinuria, infusion-related reactions, fluid retention, increase risk of thrombosis, myelosuppression	Monitor urine-to-creatinine baseline and every two cycles; hold therapy if ratio > 2 or measure urine protein every cycle and addition testing if positive for proteinuria Use caution in patients with a history of thrombosis

AST, aspartate aminotransferase; AUC, area under the curve; BSA, body surface area; BUN, blood urea nitrogen; CrCl, creatinine clearance; DLT, dose-limiting toxicity; SrCr, serum creatinine; ULN, upper limit of normal.

resistant to paclitaxel may still respond to docetaxel.[42] If the treatment goal is palliative care, then often single therapy will be used, but curative care typically is an aggressive combination regimen (see Figure 94–2 and Table 94–3). Immunotherapy, specifically pembrolizumab, has demonstrated modest benefit for patient with recurrent ovarian cancer that tumors have PDL-1 expression greater than 10%.[43] Sometimes an investigational agent may achieve responses equivalent or surpassing standard therapy and should be considered for most patients.

▶ *Platinum Sensitive*

In patients who experienced a CR to first-line chemotherapy and have had greater than a 6-month platinum-free interval, retreatment with a platinum-containing regimen is appropriate. The combination of carboplatin with gemcitabine, liposomal doxorubicin, or paclitaxel for the treatment of platinum-sensitive recurrent ovarian cancer with a curative intent is recommended[31,44,45] (see Table 94–3). However, in patients who are unable to tolerate additional combination chemotherapy regimens, carboplatin alone or any one of the second-line agents would be appropriate.[45]

Table 94–3

Summary of Regimens Used for Treatment of Recurrent Ovarian Cancer

Drug(s)	Regimen Dosing	Drug Monitoring Comments[b]
Combination Regimens		
Platinum Sensitive		
Paclitaxel and carboplatin	175 mg/m^2 IV (3-hour infusion) AUC 5–7.5 IV every 21 days	• Monitor closely for hypersensitivity reactions
Paclitaxel and cisplatin	135 mg/m^2 IV (24-hour infusion) 75 mg/m^2 IV	• Monitor closely for hypersensitivity reactions
Docetaxel and carboplatin	75 mg/m^2 IV AUC 5 IV every 21 days	• Monitor closely for hypersensitivity reactions
Gemcitabine and carboplatin	800 mg/m^2 IV days 1 and 8 AUC 5 IV day 1 every 21 days	• Monitor platelet counts closely • Monitor closely for hypersensitivity reactions
Liposomal doxorubicin and carboplatin	30 mg/m^2 IV over 1–3 hour AUC 5 IV every 28 days	• Monitor closely for hypersensitivity reactions • Liposomal doxorubicin infusion starts over 3 hour and decreases to 1 hour as tolerated • Counsel patient for PPE prevention
Niraparib	300-mg cap PO once daily	• Monitor CBC closely for first 4–6 weeks of treatment then monthly thereafter; dose reduction recommended in patients with platelet counts less than 150K • Consider antiemetics PRN
Olaparib	300-mg tab PO BID	• Monitor CBC monthly • Recommend antiemetics PRN
Rucaparib	600-mg tab BID	• Monitor CBC monthly • Recommend antiemetics PRN
Platinum-Resistant[a]		
Gemcitabine and cisplatin	1000 mg/m^2 IV days 1 and 15 40 mg/m^2 IV days 1 and 15 every 28 days	• Monitor renal function closely • Monitor ANC closely, consider primary use of growth factor • Monitor closely for hypersensitivity reactions
Liposomal doxorubicin and bevacizumab	40 mg/m^2 IV day 1 only and 10 mg/kg day 1 and day 15 every 28 days	• Liposomal doxorubicin infusion starts over 3 hour and decreases to 1 hour as tolerated • Counsel patient for PPE prevention • Monitor for hypertension; hold therapy blood pressure > 140/90 mm Hg • Monitor urine-to-creatinine baseline and every two cycles; hold therapy if the ratio is > 2 or measure urine protein every cycle and addition testing if positive for proteinuria • Use caution in patients with history of thrombosis
Gemcitabine and bevacizumab	800 mg/m^2 IV day 1 and day 15 and 10 mg/kg IV day 1 and day 15 every 28 days	• Use with caution in renal or liver dysfunction. No specific guidelines available • Counsel patient for PPE prevention • Monitor for hypertension; hold therapy blood pressure > 140/90 mm Hg • Monitor urine-to-creatinine baseline and every two cycles; hold therapy if the ratio is > 2 or measure urine protein every cycle and addition testing if positive for proteinuria • Use caution in patients with history of thrombosis
Paclitaxel and bevacizumab	80 mg/m^2 IV weekly days 1, 8, 15, and 21 and 10 mg/kg IV day 1 and 15 every 28 days	• Monitor closely for hypersensitivity reactions • Counsel patient for PPE prevention • Monitor for hypertension; hold therapy blood pressure > 140/90 mm Hg • Monitor urine-to-creatinine baseline and every two cycles; hold therapy if the ratio is > 2 or measure urine protein every cycle and addition testing if positive for proteinuria • Use caution in patients with history of thrombosis
Cyclophosphamide and bevacizumab	50 mg PO once daily 10 mg/kg IV once every 2 weeks every 28 days (continuous)	• Monitor for hypertension; hold therapy blood pressure > 140/90 mm Hg • Monitor urine-to-creatinine baseline and every two cycles; hold therapy if the ratio is > 2 or measure urine protein every cycle and addition testing if positive for proteinuria • Use caution in patients with history of thrombosis

[a] *Platinum resistance* = disease progression while on platinum agent or recurrence within 6 months of completion of platinum-based therapy.

[b] See Table 94–2 for specific monitoring parameters.

ANC, absolute neutrophil count; AUC, area under the curve; IV, intravenous; PO, oral; PPE, palmar-plantar erythrodysesthesia.

The PARP inhibitors (niraparib, olaparib, and rucaparib) are also approved for the treatment of platinum-sensitive recurrent ovarian cancer.[36,41] The terminology "switch maintenance" has emerged in management of recurrent, platinum-sensitive ovarian cancer. If patients have stable disease on a platinum-containing regimen and perhaps experiencing toxicity or just desire break from infusions, switching maintenance regimen over to oral PARP inhibitor has become common clinical practice to provide break from IV chemotherapy (see Table 94–2).

▶ *Platinum Resistant*

Recurrent or persistent ovarian cancer after platinum-based regimens has a discouraging prognosis. **KEY CONCEPT** Single-agent chemotherapy is standard practice for recurrent platinum-resistant ovarian cancer. Weekly paclitaxel achieves a response rate of 13%–50%, while liposomal doxorubicin achieves a response rate of 20% in this population and are the most commonly used regimens. In addition, two combination regimens have demonstrated promising activity in the recurrent setting: (a) gemcitabine plus cisplatin because gemcitabine may modulate platinum resistance, allowing it to regain its cytotoxic activity, and (b) bevacizumab with metronomic oral cyclophosphamide.[46-48] Other active agents include endocrine therapy, gemcitabine, liposomal doxorubicin, topotecan, bevacizumab, pembrolizumab, or investigational agents. In 2016, the FDA approved the addition of bevacizumab with paclitaxel, gemcitabine, or liposomal doxorubicin to improve outcomes in the recurrent ovarian cancer setting[49] (see Figure 94–2). **KEY CONCEPT** Because the efficacy of the agents is similar, the selection of agent for treatment of recurrent platinum-resistant ovarian cancer is dependent on residual toxicities, clinician preference, and patient convenience. Table 94–4 gives a short summary of the adverse effects and monitoring parameters for chemotherapy agents commonly used for the treatment of recurrent ovarian cancer.

OUTCOME EVALUATION

Overall survival is impacted by success of initial surgery to debulk tumor to less than 1 cm of disease and response to first-line chemotherapy. The CA-125 level should be monitored with each cycle, and at least a 50% reduction in CA-125 after four cycles of taxane/platinum chemotherapy is related to an improved prognosis. Patients who achieve CR should have follow-up examinations once every 3 months, including CA-125, physical examination, and pelvic examination, and appropriate diagnostic scans (ie, computed tomography [CT], magnetic resonance imaging [MRI], or positron emission tomography [PET] scan) should be evaluated for the detection of disease. While evaluating the patient, specifically assess resolution of any residual chemotherapy-related adverse effects including neuropathies, nephrotoxicity, ototoxicity, myelosuppression, or nausea/vomiting. Younger patients with an active menstrual cycle before surgery will encounter "surgical menopause" and often experience intense hot flushes. Because there are concerns about potential of hormones in the pathogenesis of ovarian cancer, the use of hormone replacement therapy is controversial. However, based on recent large retrospective analysis, it appears that hormone replacement with estrogen is safe and does not increase future risk of breast cancer or risk of recurrence of ovarian cancer.[50] The use of phytoestrogen supplements, such as black cohosh or soy, is also controversial. Alternative nutritional supplements with less controversy may include omega-3 (fish oil), fiber supplement, or maca root. An effective alternative has been the use of the class of serotonin reuptake inhibitors such as venlafaxine or sertraline.

Patient Encounter 3

A 67-year-old woman with history of stage IIIa high-grade, clear-cell carcinoma of the ovary had optimal tumor debulking and achieved clinical complete response to adjuvant chemotherapy with paclitaxel/carboplatin returns for her 6-month surveillance visit. Previous genetic testing revealed she and her tumor were negative for presence of any mutations and she is PDL-1 negative. CT scan reveals peritoneal implants and two enlarged lymph nodes and slight fluid accumulation in abdominal cavity. Her CA-125 is 67 U/mL (67 kU/L) today. She has history of poorly controlled diabetes and suffered significant peripheral neuropathy during her primary treatment leading to dose reduction of her paclitaxel to 135 mg/m^2 and initiation of gabapentin 300 mg three times a day. She continues to take the gabapentin but reports improvement of her peripheral neuropathy today.

Explain how to decide patient's tumor is platinum sensitive or resistant.

What tumor characteristics can you identify that would have suggested this patient was at higher risk for early recurrence?

Today is patient's first recurrence, compare and contrast treatment options to offer to this patient.

In the PD or recurrent setting, CA-125 levels should still be monitored with each cycle, but no change in therapy is recommended until after minimum of three cycles of chemotherapy. In addition, appropriate diagnostic scans (ie, CT scan, MRI, or PET scan) should be evaluated once every three cycles. Patients should also have routine physical examinations with each cycle of chemotherapy to evaluate for any physical toxicity associated with chemotherapy such as neuropathies, fluid retention, palmar-plantar erythrodysesthesia, myelosuppression, or nausea/vomiting.

Unfortunately, most patients will eventually progress through all chemotherapy options, and supportive care measures should be provided to maintain patient comfort and quality of life. Common complications while developing a plan for treatment of advanced or progressive ovarian cancer include ascites, uncontrollable pain, and SBO. Precaution should be used in removal of ascites because of the potential complications associated with rapid fluid shifts. Liberal use of opioids to control pain is appropriate as ovarian cancer patients cope with PD and approaching end of life. Appropriate bowel regimens with laxatives and stool softeners should be used to prevent constipation. However, when a patient with a well-controlled bowel regimen presents with new onset of constipation, additional workup is required before altering the bowel regimen. **KEY CONCEPT** In ovarian cancer patients, SBO is a common complication of progressive disease. In general, laxatives should not be used in patients with SBOs. Before treating constipation, patients should have a physical examination and abdominal X-ray to rule out SBO. Often, palliative surgery is required to correct SBO and alleviate patient pain. Patients should not eat any solid or liquids until resolution of SBO. If inoperable SBO exists, then parenteral nutrition can be considered but weighed against ultimate treatment objectives. Overall, providing any measures needed to maintain patient comfort is the priority for patients with progressive ovarian cancer.

Table 94–4

Summary of Chemotherapy Single-Agent Regimens Used for Treatment of Progressive and Recurrent Platinum-Resistant Ovarian Cancer

Agent	Dose	Response Rate (%)	Common Adverse Effects	Monitoring/Comments
Docetaxel	75 mg/m^2 IV over 1 hour repeat every 21–28 days vs 30–40 mg/m^2 IV over 1 hour once every week	22 NR	Neutropenia (DLT) hyperlacrimation, fluid retention, nail disorders, myelosuppression	1. Premedicate for hypersensitivity reactions with dexamethasone 2. Use with caution in liver dysfunction. Patients with bilirubin greater than the ULN and/or liver transaminases > 1.5 times the ULN should not receive docetaxel 3. Do not give if the biliary tract is obstructed
Gemcitabine	800 mg/m^2 IV infused over 30 minutes once a week on days 1, 8, and 15 followed by 1 week of rest	13.9–27	Myelosuppression (DLT), flulike symptoms, headache, somnolence, nausea/vomiting, stomatitis, diarrhea, constipation, rash	1. Use with caution in renal or liver dysfunction. No specific guidelines available
Liposomal doxorubicin	40 mg/m^2 IV infused over 3 hours cycle 1 and 2; then infused over 1 hour; thereafter repeat every 28 days	12.3–18	Myelosuppression, stomatitis, mucositis, alopecia, flushing, shortness of breath, hypotension, headaches, cardiotoxicity, hand–foot syndrome	1. Give proper dosing for liver dysfunction; total bilirubin 1.2–3 mg/dL (21–51 μmol/L): reduce dose by 50%; total bilirubin ≥ 3 mg/dL (51 μmol/L): reduce dose by 75% 2. Do not give if total bilirubin is > 5 mg/dL (86 μmol/L)
Topotecan	1.5 mg/m^2 IV infused over 30 minutes on days 1, 2, 3, 4, and 5; repeat every 21 days *OR* 4 mg/m^2 IV infused over 30 minutes once a week for 3 consecutive weeks followed by 1-week rest	6.5–17 31	Myelosuppression (DLT), nausea/vomiting, diarrhea, stomatitis, abdominal pain, alopecia, AST/ALT elevation	1. Give proper dosing for renal dysfunction; CrCl 40–60 mL/min (0.67–1.00 mL/s): no dosage adjustment needed; CrCl 20–39 mL/min (0.33–0.66 mL/s): reduce dose by 50% 2. Do not give if CrCl < 20 mL/min (0.33 mL/s)
Altretamine (Hexalen)	260 mg/m^2 PO daily for 14–21 days; repeat every 28 days	9.7	Nausea/vomiting, diarrhea, abdominal cramping, myelosuppression	1. Monitor for potential CYP450 drug interactions
Capecitabine	1800–2500 mg/m^2 PO as divided dose twice daily for 14 consecutive days followed by 1 week of rest	29	Myelosuppression, hand–foot syndrome, nausea/vomiting, edema, stomatitis, diarrhea, cardiotoxicity, rash	1. Monitor for PPE and recommend regular use of lotions on hands and feet 2. Use with caution in renal dysfunction; CrCl ≥ 51 mL/min (0.84 mL/s): no dose adjustment; CrCl 30–50 mL/min (0.50–0.83 mL/s): reduce dose by 25%; CrCl < 30 mL/min (0.50 mL/s): do not give 3. Use with caution in liver dysfunction; no specific guidelines available
Etoposide	50 mg/m^2/day PO in divided doses given daily for 3 weeks followed by 1 week of rest	18	Myelosuppression, nausea/vomiting, anorexia, alopecia, headache, fever, hypotension	1. Give proper dosing for liver dysfunction; total bilirubin 1.5–3 mg/dL (26–51 μmol/L): decrease dose by 50%; total bilirubin 3–5 mg/dL (51–86 μmol/L): decrease dose by 75% 2. Do not give if total bilirubin is > 5 mg/dL (86 μmol/L) 3. Give proper dosing for renal dysfunction; CrCl 60–45 mL/min (1.00–0.75 mL/s): reduce dose by 15%; CrCl 44–30 mL/min (0.74–0.50 mL/s): reduce dose by 20%; CrCl < 30 mL/min (0.50 mL/s): reduce dose by 25%
Letrozole	2.5 mg once daily	15	Headache, nausea, dyspepsia, skin rash	1. No protective effect on bone; recommend calcium supplementation
Tamoxifen	20 mg PO twice a day continuously until PD	10	Thrombocytopenia, anemia, thromboembolism, hot flashes, decreased libido, nausea/vomiting	1. Protective effect on bone and lipids 2. Increased risk for endometrial cancer

(Continued)

Table 94–4

Summary of Chemotherapy Single-Agent Regimens Used for Treatment of Progressive and Recurrent Platinum-Resistant Ovarian Cancer (*Continued*)

Agent	Dose	Response Rate (%)	Common Adverse Effects	Monitoring/Comments
Vinorelbine	30 mg/m^2 IV infused over 15 minutes on days 1 and 8; repeat every 21 days	29	Constipation, neutropenia, anemia, thrombocytopenia, neurotoxicity	1. Consider bowel regimen to prevent constipation
Bevacizumab	15 mg/kg IV infused over 30–90 minutes every 21 days	NR	Hypertension, proteinuria, infusion-related reactions, fluid retention, increase risk of thrombosis, myelosuppression	1. Monitor urine-to-creatinine baseline and every two cycles; hold therapy if ratio > 2 or measure urine protein every cycle and addition testing if positive for proteinuria 2. Use caution in patients with a history of thrombosis
Pembrolizumab	200 mg IV once every 21 days	10	Immune-related toxicities, rash, hypothyroidism, diarrhea, pneumonitis, fatigue	1. Close monitoring for dermatologic rash, change in thyroid function, gastrointestinal symptoms. 2. Use caution in patients with history of significant bowel obstructions.

CrCl, creatinine clearance; DLT, dose-limiting toxicity; IV, intravenous; NR, not reported; PD, progressive disease; PO, oral; PPE, palmar-plantar erythrodysesthesia; ULN, upper limit of normal.

Patient Care Process

Collect Information:

- Perform medication history for use of prescription and nonprescription medications and nutritional/herbal supplements. Confirm drug allergies/intolerances.
- Review the medical history, family cancer history, and current physical and laboratory assessment findings.
- Speak with patient and review records to identify socioeconomic factors that may affect medication access or compliance with care plan.

Assess the Information:

- Evaluate current symptoms and signs that are disease-related and would be associated with new diagnosis or drug-related side effects from prior treatment.
- Evaluate medication list to determine if there are any potential interactions, therapy duplication, or unnecessary medications. Determine if there is any need for acute or chronic pain medications.
- Review laboratory tests, diagnostic testing, and BRCA1/2 testing.
- Based on family cancer history, determine if additional genetic testing is recommended.
- Review chemotherapy history to determine potential for platinum sensitivity/resistance and consider genetic mutation status in selection of treatment options.

Develop a Care Plan:

If patient is a surgery candidate:

- Evaluate patient comorbidities to determine if additional workup is necessary before tumor debulking surgery.
- Decide if any medications or supplements need to be stopped or changed before surgery (ie, aspirin, warfarin, nonsteroidal anti-inflammatory agents, and omega-3s).

If patient is a chemotherapy candidate:

- Evaluate patient medications, residual toxicities, renal function, and liver function to determine if any potential dose adjustments ought to be recommended for the selected chemotherapy regimen (see Figure 94–2).
- Determine whether patient has insurance coverage for planned chemotherapy regimen and supportive care medications as indicated. Discuss if potential copays are financially feasible as well.

Implement the Care Plan:

Surgery:

- Review plan to use low molecular weight heparin for postoperation thrombosis prevention and submit request for insurance approval. Teach nonpharmacologic recommendations for thrombosis prevention post surgery.
- Discuss when any medications/supplements should be stopped and when to resume in relation to timing of surgery.
- Review the plan for acute pain management postoperation as well as bowel regimen to prevent constipation/reduce straining after abdominal surgery.

Chemotherapy:

- Provide appropriate patient education on chemotherapy agents. Explain treatment intent—curative verses palliative (relief of symptoms) and the plan for monitoring response to treatment.
- Explain prevention and management of expected side effects such as infection, nausea and vomiting, neuropathy, electrolyte wasting, and bowel habits.

(*Continued*)

Patient Care Process (*Continued*)

Follow-up: Monitor and Evaluate:

- After surgery, patient should have follow-up 2 to 3 weeks to evaluate wound healing, pain control/resolution, and determine if adjuvant chemotherapy is required.
- While on chemotherapy, patient should have a follow-up every cycle to assess symptom control and chemotherapy tolerability.
- A CBC with differential should be checked prior to each chemotherapy dose with complete laboratory values evaluated each cycle.
- Chemotherapy doses should be decreased or discontinued for unacceptable toxicity or organ dysfunction when indicated.
- Tumor markers are also monitored with each cycle but not acted upon unless greater than 50% increase or consistent trend upward each cycle.
- Assess tumor response to chemotherapy once every 3 months with CT scan/MRI/PET scan as indicated. Follow current RECIST criteria to determine stable disease, response, or progression of disease.

Abbreviations Introduced in This Chapter

AUC	Area under the curve
BRCA1	Breast cancer activator gene 1
BRCA2	Breast cancer activator gene 2
BSO	Bilateral salpingo-oophorectomy
CA-125	Cancer antigen-125
CA-19	Cancer antigen-19
CEA	Carcinoembryonic antigen
CR	Complete response
CrCl	Creatinine clearance
DLT	Dose-limiting toxicity
FIGO	International Federation of Gynecology and Obstetrics
HBOC	Hereditary breast and ovarian cancer
HNPCC	Hereditary nonpolyposis colorectal cancer
IP	Intraperitoneal
LFT	Liver function test
LOH	Loss of heterozygosity
NS	Normal saline
OC	Oral contraceptive
PARP	Poly(ADP-ribose) polymerase
PD	Progressive disease
PET	Positron emission tomography
PR	Partial response
SBO	Small bowel obstruction
TAH	Total abdominal hysterectomy
TVUS	Transvaginal ultrasound

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Lymphomas

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Discuss the underlying pathophysiologic mechanisms of the lymphomas and how they relate to presenting symptoms of the disease.
2. Differentiate the pathologic findings of Hodgkin lymphoma (HL), follicular indolent non-Hodgkin lymphoma (NHL), and diffuse aggressive NHL and how this information yields a specific diagnosis.
3. Describe the general staging criteria for the lymphomas and how it relates to prognosis; evaluate the role of the prognostic systems such as the International Prognostic Score for HL, the Follicular Lymphoma International Prognostic Index (IPI), and the IPI for diffuse, aggressive NHL.
4. Compare and contrast the treatment algorithms for early and advanced stage disease for HL.
5. Assess the role of autologous hematopoietic stem-cell transplantation for relapsed lymphomas.
6. Delineate the clinical course of follicular indolent and diffuse aggressive NHL and the implications for disease classification schemes and treatment goals.
7. Outline the general treatment approach to follicular indolent and diffuse aggressive NHL for localized and advanced disease.
8. Interpret the current role for monoclonal antibody therapy in NHL.

INTRODUCTION

The malignant lymphomas are a clonal disorder of hematopoiesis with the primary malignant cells consisting of lymphocytes of B-, T-, or natural killer (NK) cell origin. Lymphoma cells predominate in the lymph nodes; however, they can infiltrate lymphoid and nonlymphoid tissues, such as the bone marrow, central nervous system (CNS), gastrointestinal (GI) tract, liver, mediastinum, skin, and spleen. An overview of the lymph node regions typically involved in lymphomas is depicted in Figure 95–1. **KEY CONCEPT** There are two broad classifications of lymphoma, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), and both contain numerous histologic subtypes that are pathologically distinct disease entities.

The clinical course varies widely among histologies of lymphoma. More aggressive subtypes are highly proliferating cells that require aggressive therapeutic intervention with chemotherapy, radiation therapy, or both. By contrast, certain subtypes of NHL are characterized by a disease course that flares and remits intermittently over a period of years regardless of treatment.

HODGKIN LYMPHOMA

EPIDEMIOLOGY AND ETIOLOGY

Approximately 8830 new cases of HL were estimated to be diagnosed in the United States in 2021, with 960 deaths attributed to the disease.[1] Broadly, HL is divided into two types, classical HL and nodular lymphocyte-predominate HL. Classical Hodgkin lymphoma makes up approximately 95% of HL cases and will be the focus of this chapter. The incidence of HL is bimodal, with peaks occurring in the third decade of life and in patients over 50.[2] The precise cause of HL is unknown, but certain associations have been reported and provide insight about possible etiologic factors. Epstein-Barr virus (EBV) has been associated with HL, its viral genome is detected in Reed–Sternberg (RS) cells in up to 40% of cases in developed countries. Other viruses (cytomegalovirus, human herpes viruses, human immunodeficiency virus [HIV], and adenoviruses) have been associated with HL; however, data is conflicting.[3] Other possible risk factors identified include woodworking and a familial history of HL.

PATHOPHYSIOLOGY

Pluripotent stem cells in the bone marrow are able to differentiate to both lymphoid and myeloid progenitor cells. Lymphoid progenitor cells undergo normal gene rearrangement to yield either B-cell or T-cell lineage precursor cells. Normal maturation for naive B cells includes expression of cell surface antibody or the cells undergo apoptosis. These cells are differentiated from other B cells, such as memory cells, by virtue of cell surface antigen ($CD5^+$ or $CD5^-$ and $CD27^-$) and bound antibody (IgM+ and IgD+). When naive B cells recognize antigen with their cell surface antibody, they accumulate in the lymph nodes, spleen, or other lymphoid tissue.

The pathophysiology of HL is defined by the presence of the RS cell in a grouping of lymph nodes. The RS cell is a morphologically large cell with a multinucleated structure possessing pronounced eosinophilic nucleoli, thought to be B cell in origin.[4] In the affected lymph nodes, the RS cells are contained within an inflammatory background that is believed to be essential for their survival. RS cells have lost the expression of most B-cell markers.

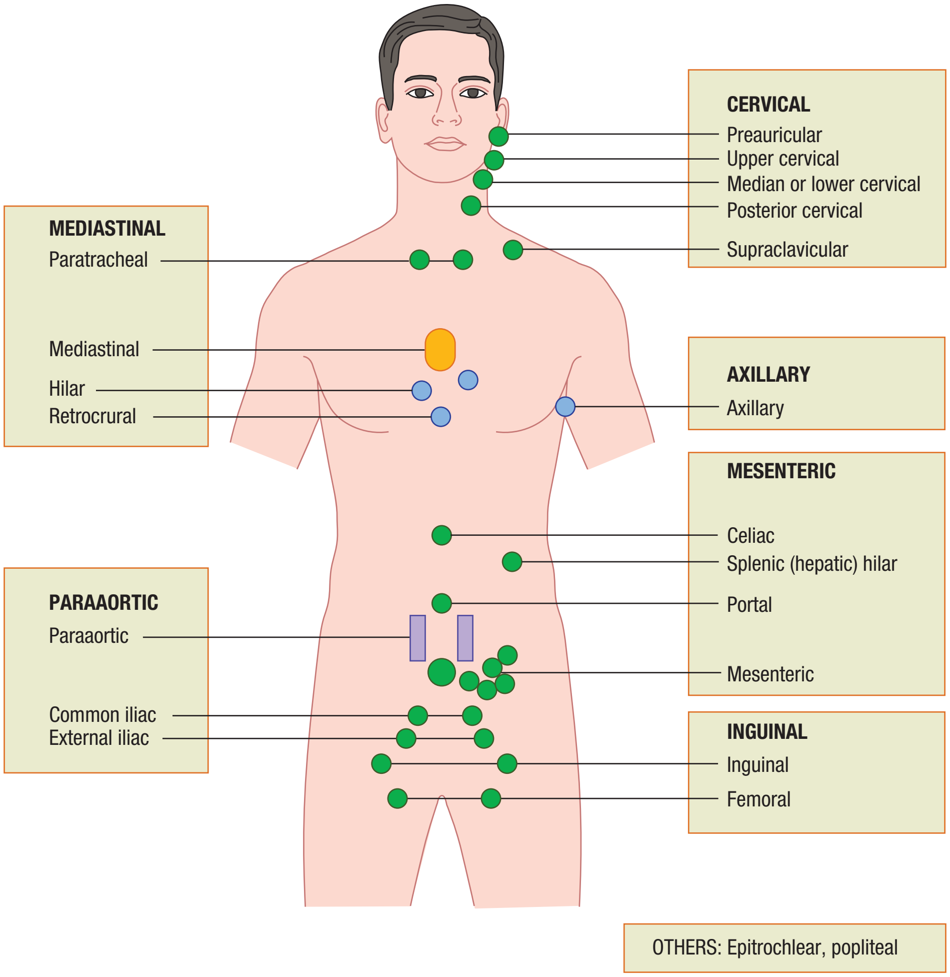
CERVICAL
Preauricular
Upper cervical
Median or lower cervical
Posterior cervical
Supraclavicular
MEDIASTINAL
Paratracheal
Mediastinal
Hilar
Retrocrural
AXILLARY
Axillary
MESENTERIC
Celiac
Splenic (hepatic) hilar
Portal
Mesenteric
PARAAORTIC
Paraaortic
Common iliac
External iliac
INGUINAL
Inguinal
Femoral
OTHERS: Epitrochlear, popliteal

FIGURE 95–1. Lymph node regions used in describing the extent of lymphoma involvement. (Reproduced with permission from DiPiro JT, Yee GC, Posey LM, et al. (eds). Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York: McGraw-Hill; 2020: Fig. 149–1.)

Common cell-surface antigens expressed by RS cells include CD30 and CD15, but other common B-cell antigens, such as CD20, are inconsistently expressed.[4] The Janus kinase-signal transduction and transcription (JAK-STAT) signaling pathway has also been found to be active in HL. Additionally, the overexpression of nuclear factor kappa-B (NF-κB), a proliferative and antiapoptotic transcription factor nuclear factor, is believed to contribute to the expansion and survival of RS cells.

HL is classified into disease subtypes based on the number and morphologic appearance of RS cells and the background cellular background. These are listed in the World Health Organization (WHO) classification of lymphoid neoplastic diseases in Table 95–1.[5] Nodular sclerosing (75%) is the most common form of classical HL. It is more common in young adults and marked by the presence of the RS variant cell, the lacunar cell. The second most common form of HL is mixed-cellularity variant (19%), with others accounting for the remainder of cases.[6] Factors identified as negative disease prognostic indicators are listed in Table 95–2.

TREATMENT OF HL

Desired Outcome

Staging of HL with a standard classification is necessary to guide treatment. The extent and location of involvement, localized or disseminated extranodal disease, and B symptoms are factors in assignment of stage. The Lugano modification of the original Ann Arbor classification is used in staging lymphomas and outlined in Table 95–3.[7] The role of PET imaging (including integrated PET and CT) is critical for accurate initial staging and assessing outcome of therapy. The Deauville criteria use a five-point scale that describes the ^{18}F-fluorodeoxyglucose uptake in the involved lymphoma sites. Interim or end of treatment PET scans with a Deauville score of 1, 2, or 3 are considered negative and scores of 4 and 5 are considered positive for disease.[8] PET positivity at the end of treatment is associated with poor outcomes. PET scans completed during therapy (interim PET imaging) can assess response to treatment and can help guide clinicians to escalate or deescalate therapy.

KEY CONCEPT The principal goal in treating HL is to cure the patient of the primary malignancy. HL is sensitive to both radiation and chemotherapy, resulting in an 80% rate of cure with modern therapy. Treatment strategy is generally divided into approaches for early stage I/II disease and stage III/IV advanced disease. Patients with stage I/II disease are further classified into favorable, unfavorable with bulky disease, and unfavorable with nonbulky disease. Regardless of stage, all patients are treated with curative intent. Other treatment goals include:

- Complete resolution of disease symptoms
- Incorporation of supportive care measures to optimize quality of life
- Minimization of acute and long-term treatment-related toxicity

Table 95–1

Abbreviated WHO Classification of Lymphoid Neoplasms

B-Cell Neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis
B-cell proliferative leukemia
Splenic marginal zone B-cell lymphoma
Hairy-cell leukemia
Lymphoplasmacytic lymphoma
Monoclonal gammopathy of undetermined significance
Plasma-cell myeloma
Plasmacytoma
Monoclonal immunoglobulin deposition disease
Extranodal marginal zone B-cell lymphoma of MALT type
Nodal marginal zone lymphoma
Follicular lymphoma
Primary cutaneous follicle center lymphoma
Mantle-cell lymphoma
Diffuse large B-cell lymphoma (DLBCL)
Primary DLBCL of central nervous system
Primary cutaneous DLBCL
Lymphomatoid granulmatosis
Primary mediastinal large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
Burkitt lymphoma

T-Cell and NK-Cell Neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Aggressive NK-cell leukemia
Hydroa vacciniforme-like lymphoproliferative disorder
Adult T-cell lymphoma/leukemia (HTLV1+)
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous T-cell lymphoproliferative disorders
Peripheral T-cell lymphoma
Angioimmunoblastic T-cell lymphoma
Follicular T-cell lymphoma
Anaplastic large-cell lymphoma

Hodgkin Lymphoma
- Nodular lymphocyte-predominant HL
- Classical HL
  - Nodular sclerosis HL
  - Lymphocyte-rich classical HL
  - Mixed cellularity HL
  - Lymphocyte depletion HL

Posttransplant Lymphoproliferative Disorders

Histiocytic and Dendritic Cell Neoplasms

AML, acute myeloid leukemia; HL, Hodgkin lymphoma; MALT, mucosa-associated lymphoid tissue; NK, natural killer.

Table 95–2

Negative Prognostic Factors for HL

Stages I–II HL as defined by NCCN
Age 50 years or older
ESR > 50 or any B symptoms
MMR > 0.33
> 3 nodal site
Bulky disease > 10 cm

International Prognostic Score—Advanced HL
Albumin < 4 g/dL (40 g/L)
Hemoglobin < 10.5 g/dL (105 g/L; 6.52 mmol/L)
Male sex
Age older than 45 years
Stage IV disease
WBC over15,000/mm^3 (15 $\times$ 10^9/L)
Lymphocytopenia (count < 600/mm^3 [0.6 $\times$ 10^9/L], < 8% [0.08] of WBC count, or both)

WBC, white blood cell.

ESR, erythrocyte sedimentation rate; MMR, mediastinal mass ration (maximum width of mass/maximum intrathoracic diameter); NCCN, National Comprehensive Cancer Network.

Nonpharmacologic Therapy

Radiation therapy is effective in the treatment of HL and has cured patients of their disease. Historically, patients with favorable early stage I/II disease were treated with radiation alone. However, long-term toxicities associated with this practice have precluded this approach. Current treatment strategies combine radiation with chemotherapy to reduce the irradiated volume and dose as well as the number of cycles of chemotherapy.

Today, the use of involved-site radiotherapy (ISRT) and involved-node radiotherapy (INRT) limits radiation to the involved area sparing other organs.[9] Acute effects of irradiation are typically transient and include nausea, anorexia, xerostomia, dysgeusia, pharyngitis, dry cough, fatigue, diarrhea, and rash. Delayed effects from radiotherapy are concerning as they may be permanent and present months to years after therapy. Pneumonitis, pericarditis, hypothyroidism, infertility (with pelvic field irradiation), coronary artery disease, deformities in bone and muscle

Table 95–3

Lugano Staging Classification for Lymphomas (2014 Modification of Ann Arbor Staging)

Stage	Involvement	Extranodal (E) Status
Limited		
Stage I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Stage II bulky	Same as II but with "bulky" disease	
Advanced		
Stage III	Nodes on both sides of diaphragm or nodes above the diaphragm with spleen involvement	Not applicable
Stage IV	Additional noncontiguous extralymphatic involvement	Not applicable

"A" (absence of B-symptoms) or "B" (presence of B-symptoms) is only used for Hodgkin lymphoma.

Clinical Presentation and Diagnosis of Malignant Lymphomas

General

Nonspecific; can range from an asymptomatic patient with a less aggressive lymphoma to a patient who is gravely ill with advanced disease.

KEY CONCEPT Symptoms

- Lymphadenopathy, generally in the cervical, axillary, supraclavicular, or inguinal lymph nodes
- Splenomegaly
- Shortness of breath, dry cough, chest pressure (patients with mediastinal mass)
- GI complications (nausea, vomiting, early satiety, constipation, and diarrhea)
- Back, chest, or abdominal pain

Signs

- Fever[a]
- Night sweats[a]
- Weight loss greater than 10% within last 6 months[a]
- Pruritus

Laboratory Tests

- LDH
- ESR
- Serum chemistries
- CBC with differential

KEY CONCEPT Other Diagnostic Tests

- Physical examination with careful attention to lymph node inspection.
- Imaging—chest X-ray, chest CT, abdominal or pelvic CT; integrated PET and CT are recommended as part of the initial workup.
- Bone marrow biopsy.
- Biopsy of suspected lymph node(s)—either open lymph node biopsy (preferred) or core biopsy; fine needle aspiration should only be performed if preferred biopsy methods are unobtainable.
- Hematopathology evaluation of biopsy specimen—morphologic inspection, immunohistochemistry for cell surface antigens to characterize lymphoma cells, cytogenetic analysis.

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[a] Known collectively as B symptoms.

CBC, complete blood count; CT, computed tomography; ESR, erythroid sedimentation rate; LDH, lactate dehydrogenase; PET, positron emission tomography.

growth in children, herpes zoster reactivation, and Lhermitte sign are not uncommon. Patients cured with radiotherapy are at increased risk for new cancers of the breast, lung, and stomach, as well as melanoma and new NHL, depending on the radiation field.

Patient Encounter Part 1: Initial Presentation

A 63-year-old man with a medical history of hypertension and COPD presents to the oncologist on referral from his primary care provider. He presented to his PCP with swollen lymph nodes and facial swelling. He was in his usual state of health until 2 months ago when he began experiencing "lumpy spots" in his bilateral axillary region and swelling in the neck. He states that he has experienced a 20-lb weight loss over the last several months. The PCP referred him for biopsy of palpable cervical lymph node. A fine needle aspiration was performed that showed a "lymphoproliferative process." Complete blood count revealed a WBC of 18,500/mm^3 (3.5 × 10^9/L), hemoglobin of 8.5 g/dL (8.5 g/L; 5.27 mmol/L), and platelets were 137,000/mm^3 (137 × 10^9/L). LDH was 353 U/L (5.9 μkat/L). The chemistry panel was unremarkable.

What tests should be performed to confirm a diagnosis of lymphoma and determine its overall stage?

Based on the information provided, what is his international prognostic score (IPS), and how does it impact treatment selection?

Pharmacologic Therapy

▶ *Early-Stage Disease*

KEY CONCEPT Initial treatment of HL includes combination chemotherapy; these regimens are effective and have acceptable long-term toxicities. Combined modality therapy for favorable disease consists of two cycles ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) followed by an interim PET (characteristics described in Table 95–2). For Deauville scores of 1 to 3, patients receive 20 Gy (Gray, the absorbed radiation dose) of ISRT.[10] Deauville score of 4 would receive 2 additional cycles of ABVD (total of 4) followed by 30-Gy ISRT. Patients with a positive Deaville score of 5 should have a biopsy to determine if persistent disease is present. Patients with a positive biopsy should be treated for refractory disease. Chemotherapy alone for favorable disease can be considered. After two cycles of ABVD, patients with a Deauville score of 1 to 3 may receive one to two additional cycles of ABVD.[11] Patients with Deauville scores of 4 receive two additional cycles of ABVD or two cycles of BEACOPP.[12]

ABVD followed by interim PET scans guide therapy for patients with stages I and II unfavorable bulky or nonbulky disease. Negative Deauville scores receive two additional cycles of ABVD (or AVD for bulky disease) and ISRT. However, Deauville scores of 4 are recommended to receive two cycles of BEACOPP (2–3 cycles for bulky disease) and ISRT.[11] Another option for patients with unfavorable nonbulky disease would be two cycles of BEACOPP and two cycles of ABVD followed by ISRT for patients with a Deauville score of 1 to 4.[13] All patients with Deauville score of 5 should undergo a biopsy to determine if lymphoma is present. Individuals with positive biopsies are treated for refractory HL. A list of chemotherapy regimens used in HL is presented in Table 95–4.

Table 95–4

Common Treatment Regimens in HL

ABVD—Every 28 Days
Doxorubicin 25 mg/m^2 IV × 1, days 1 and 15
Bleomycin 10 units IV × 1, days 1 and 15
Vinblastine 6 mg/m^2 × 1, days 1 and 15
Dacarbazine 375 mg/m^2 IV × 1, days 1 and 15

AVD—Every 28 Days
Doxorubicin 25 mg/m^2 IV × 1, days 1 and 15
Vinblastine 6 mg/m^2 × 1, days 1 and 15
Dacarbazine 375 mg/m^2 IV × 1, days 1 and 15

BEACOPP (Escalated)—Every 21 Days
Bleomycin 10 mg/m^2 IV, day 8
Etoposide 200 mg/m^2 IV, daily × days 1–3
Doxorubicin 35 mg/m^2, day 1
Cyclophosphamide 1200 mg/m^2 IV, day 1
Vincristine 1.4 mg/m^2 IV, day 8
Procarbazine 100 mg/m^2 po daily, days 1–7
Prednisone 40 mg po daily, days 1–14

BEAM (High-Dose with Autologous SCT)[a]
Carmustine 300 mg/m^2 IV × 1 day
Etoposide 100–200 mg/m^2 IV every 12 hours × 4 days
Cytarabine 100–200 mg/m^2 IV every 12 hours × 4 day
Melphalan 140 mg/m^2 IV × 1 day

[a] Used for both Hodgkin lymphoma and non-Hodgkin lymphoma.

IV, intravenous; po, oral; SCT, stem-cell transplantation.

▶ *Advanced Disease*

Patients with advanced disease can be further classified into two groups based on IPS (Table 95–2). Patients with three or fewer poor prognostic factors are considered to have favorable disease while patients with four or more factors have unfavorable disease. Patients with unfavorable disease may warrant more aggressive treatment.

The chemotherapy regimen MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) is of historical significance because it was the first chemotherapy regimen to cure HL in the 1960s. However, significant toxicity, including sterility and secondary leukemia, led to the development of new regimens. ABVD remains the preferred initial regimen for most patients with advanced HL. Two cycles ABVD are recommended followed by interim PET. The omission of bleomycin from the ABVD regimen has been evaluated. Exclusion of bleomycin (AVD regimen) decreases pulmonary toxicity without compromising outcomes (Table 95-5).[14] For a Deauville score of 1 to 3, four cycles of AVD are administered (total of 6). For patients with a Deauville score of 4, two cycles of ABVD or two cycles of escalated BEACOPP are recommended followed by a PET to assess response. Responses with a Deauville response of 1 to 3, two additional cycles of BEACOPP (total of 4) or ABVD (total of 6) are needed. Any patient with a Deauville score of 5 should undergo a biopsy. Patients with a positive biopsy should be treated as those patients with refractory disease.

Patients with advanced disease, IPS score > 4, and age less than 60 years may consider BEACOPP for two cycles as initial therapy.[15] For patients with an interim PET with a Deauville score of 1 to 3 may receive two additional cycles of BEACOPP (total of 4) or 4 cycles of ABVD (or AVD) followed by a PET to assess response. A Deauville score of 4 should receive two additional cycles of BEACOPP (total of 4) followed by a PET. Patients with a negative Deauville receive two additional cycles of BEACOPP (total of 6). Patients with a Deauville score of 4 or 5 should have a biopsy to determine response to therapy. While dose-escalated BEACOPP regimen is considered for patients with advanced HL with a high number of poor prognositic factors, it should be noted it is associated with more toxicity including infertility and secondary leukemia. Brentuximab with AVD may also be considered in this patient population. Patients should be free from symptoms of neuropathy, have an IPS score >4, and have a contraindication for bleomycin.[16]

Despite the high success rate in treating HL, approximately 5% to 10% of patients will be refractory to initial treatment and 10% to 30% will relapse after initial response.[17] Patients relapsing after treatment should be offered additional therapy as durable responses have been reported. The duration of remission after chemotherapy remains a vital prognostic factor for likelihood of response to future therapy.[18,19] This treatment offers a cure rate up to 50%.

Several studies have reported the importance of giving conventional chemotherapy before stem-cell transplant (SCT).

Table 95–5

Practical Information for ABVD and CHOP

Regimen	Drug Class	Pharmacokinetics	Unique Toxicities
ABVD			
Doxorubicin	Anthracycline	Hepatic metabolism[a]	Highly emetogenic Cardiomyopathy Maximum cumulative lifetime dose, 550 mg/m^2
Bleomycin	Antitumor antibiotic	Renal clearance[a]	Pulmonary fibrosis Maximum cumulative lifetime dose, 400 units
Vinblastine	Vinca alkaloid	CYP3A4/5 metabolism[a]	Neuropathy, constipation
Dacarbazine	Alkylating agent	Hepatic metabolism[a]	Myelosuppression
CHOP			
Cyclophosphamide	Alkylating agent	Prodrug; CYP3A4/5, 2D6	Highly emetogenic Hemorrhagic cystitis
Doxorubicin	Anthracycline	Hepatic metabolism	Cardiomyopathy
Vincristine	Vinca alkaloid	CYP3A4/5	Neuropathy, constipation
Prednisone	Corticosteroid	100% oral bioavailability	Hyperglycemia, osteopenia

[a] See dose adjustments (Chapter 88).

Patients who respond to second-line therapy (Deauville score of 1–3) should proceed to SCT. For those at high risk of relapse post SCT, 1 year of maintenance therapy with brentuximab vedotin may be considered.[20] The safety profile of autologous SCT continues to improve as refinements in supportive care advance. Current estimates of mortality from autologous SCT for HL are approximately 5%. Morbidity associated with preparative regimens in HL, aside from infectious and bleeding complications, includes pulmonary toxicity of bleomycin coupled with carmustine, inducing potentially fatal pulmonary pneumonitis. Patients who are not candidates for autologous SCT may receive brentuximab vedotin with or without standard salvage chemotherapy, such as etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP) or dexamethasone, cytarabine, and cisplatin (DHAP). Other regimens such as GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin), IGEV (ifosfamide, gemcitabine, and vinorelbine), and ICE (ifosfamide, carboplatin, etoposide) have also been effective. Other agents such as lenalidomide, bendamustine, and everolimus have also shown activity.[21] Programmed death 1 blocking monoclonal antibodies such as nivolumab and pembrolizumab are additional options for HL that have progressed after SCT with brentuximab maintenance or after three lines of systemic therapy including SCT.[22,23]

NONHODGKIN LYMPHOMA

EPIDEMIOLOGY AND ETIOLOGY

Approximately 81,560 cases of NHL were estimated to be diagnosed in the United States in 2021, with an estimated 20,720 deaths.[1] The median age for diagnosis is 50 years, although children and young adults may also be affected. The etiology of certain aggressive NHL subtypes is related to specific endemic geographic factors as well as exposure to various causative agents such as pathogens or environmental risks. Follicular or low-grade lymphoma is more common in the United States and Europe and relatively uncommon elsewhere. The incidence of Burkitt NHL is 7 cases per 100,000 people in Africa compared with 0.1 per 100,000 in the United States, likely related to malaria or EBV exposure. Human T-cell leukemia virus I, human herpesvirus 8, hepatitis C, *Helicobacter pylori*, and EBV have all been implicated in inducing NHL.[24] Due to the pathogen-related induction of NHL, immunocompromised patients are at increased risk of NHL. Environmental factors have been identified as contributing to the development of NHL. Certain occupations such as wood and forestry workers, butchers, exterminators, grain millers, machinists, mechanics, painters, printers, and industrial workers have a higher prevalence of disease. Industrial chemicals such as pesticides, herbicides, organic chemicals (eg, benzene), solvents, and wood preservatives are also associated with NHL.

PATHOPHYSIOLOGY

The pathophysiology of NHL is governed by numerous environmental and genetic events culminating with a monoclonal population of malignant lymphocytes. B cells represent the cells of origin in excess of 90% of cases. Cytogenetic abnormalities involving translocations of antigen receptor genes are prevalent in NHL. These include T-cell receptor genes in T-cell lymphomas and immunoglobulin genes in B-cell lymphomas. The principal defect appears to be an error in assembly of the regulatory gene segment of an antigen receptor gene, resulting in inappropriate binding to an oncogene. This results in dysregulation of cell growth and proliferation, leading to the malignant clone of lymphocytes. Oncogenes identified in different lymphomatous diseases include *MYC, BCL1, BCL2, BCL3, NFKB1* and *BCL6*.[25] Classic translocations for NHL include t(8;14) in Burkitt lymphoma, t(14;18) in follicular lymphomas, t(11;14) mantle-cell lymphoma, and t(11;18)/t(1;14) in mucosa-associated lymphoid tissue (MALT).

KEY CONCEPT Characterization of the morphology of lymphocytes, the reactivity of other cells in the lymph node, and architecture of the node are essential in obtaining a diagnosis and predicting disease course. The nodal presentation of NHL is divided into two main categories: follicular, corresponding to low-grade disease, and diffuse, corresponding to aggressive disease. A follicular disease pattern in the inspected lymph node is indicative of a more indolent or low-grade progression that has survival measured in years if left untreated. In contrast, a diffuse pattern of lymph node infiltration indicates highly aggressive disease, resulting in death within weeks to months if untreated. Follicular lymphoma (FL) is the most common indolent subtype, comprising 22% of NHL. Diffuse, large B-cell lymphoma (DLBCL) is the most common aggressive histology, comprising 31% of NHL. The cells of origin for FL tend to be more mature, nondividing lymphocytes, whereas aggressive NHL is derived from rapidly dividing lymphoid precursors. A unique feature of the biology of NHL is that follicular low-grade histologies can undergo further malignant transformation, transforming into a DLBCL population. This syndrome, also possible as a transition from chronic lymphocytic leukemia to an aggressive lymphoma, is called Richter transformation. Richter transformation involves multiple genetic events, including abnormalities of chromosomes 11 and 12 and tumor suppressor genes.[26]

The most commonly used classification system for lymphoid malignancies was proposed by the WHO. The WHO classification groups lymphomas based on cell of origin (B cell, T cell, NK cell) and considers each as its own unique disease entity (Table 95–1). Further description of tumors is based on cell characteristics such as aggressiveness, cell size, and proliferation.[5]

Prognostic factors present at diagnosis have been identified for NHL. Age, the presence of B symptoms, performance status, number of nodal and extranodal sites, LDH level, bulky disease (larger than 10 cm), advanced stage, and β_2-microglobulin concentration have been shown to be important prognostic features in NHL. The International Prognostic Index (IPI) is a predictive model for aggressive NHL to be treated with doxorubicin-containing chemotherapy regimens.[27] This index is used as a tool to identify patients who may benefit from a more intense treatment regimen. Tools to help identify patients with FL who appropriate for drug therapy include the Follicular Lymphoma International Prognostic Index (FLIPI)[28] and the GELF criteria (Table 95–6).[29]

TREATMENT OF NHL

Desired Outcome

NHL treatment depends primarily on histologic subtype (follicular low grade versus diffuse aggressive) and staging (local stage I/II versus advanced stage III/IV) to guide treatment with observation, chemotherapy, radiation, or chemotherapy and radiation. The Lugano modification of the Ann Arbor staging system for HL is also used in NHL.

Treatment goals depend on the specific subtype of NHL. For low-grade FL, the disease is considered to be incurable however

Table 95–6

Negative Prognostic Factors for NHL

International Prognostic Index—Diffuse, Aggressive NHL

Criteria	Risk Group	Number of Criteria
Age ≥ 60 years		
Stage III/IV disease	Low	0–1
Extranodal disease > 1 site	Low-intermediate	2
ECOG performance status 2 or greater	High-intermediate	3
Serum LDH > 1 × normal limit	High	4–5

Follicular Lymphoma International Prognostic Index

Criteria	Risk Group	Number of Criteria
Age ≥ 60 years		
Stage III/IV disease	Low	0–1
Hemoglobin < 12.0 g/dL (120 g/L; 7.45 mmol/L)	Intermediate	2
Serum LDH > 1 × normal limit	High	≥ 3
Number of nodal sites ≥ 5[a]		

GELF Criteria

Involvement of ≥ nodal sites, each with a diameter of ≥ 3 cm	Splenomegaly
Any nodal or extra nodal tumor mass with a diameter ≥ 7 cm	Pleural effusions or peritoneal ascites
Cytopenias (WBC < 1.0 × 10^9/L and/or platelets <100 × 10^9/L)	B-symptoms
Leukemia (>5 × 10^9/L malignant cells)	

[a]The nodal map used in the Follicular Lymphoma International Prognostic Index is different than the nodal map used in conventional staging.

long-term remission is possible. Many patients with FL are older than 60 years of age, making allogeneic SCT impractical due to high treatment-related mortality for older patients.

KEY CONCEPT The treatment goals for low-grade NHL include:

- Observation of the disease until the patient exhibits obvious progression that limits functional capacity or is life threatening
- Treatment that induces remission with manageable toxicity
- Judicious selection of treatment to avoid long-term toxicity
- Prevention of infectious complications

The intent of treatment for patients with aggressive histologies is cure. Some histologic subtypes exhibit a highly aggressive clinical course and are not considered to be curable. These patients are still treated with curative-intent chemotherapy or may be considered for a clinical trial.

Nonpharmacologic Therapy

For patients with low-grade FL, deferring initial therapy until progression of disease is a standard approach. The median survival time is 6 to 10 years. Some patients may be asymptomatic for several years after diagnosis, making observation a reasonable approach. Radiation therapy has a limited role in NHL relative to HL. NHL is more often a systemic disease, and radiation typically has been reserved for consolidation after chemotherapy in patients presenting with a large extranodal mass. However, ISRT without chemotherapy is the preferred treatment option for patients with nonbulky stage I/II FL.

For early-stage diffuse, aggressive NHL, combined-modality therapy, was tested versus a longer course of chemotherapy.[30] Five-year overall survival favored the CHOP–radiation arm (82% vs 72%). There was a trend toward increased toxicity, particularly hematologic and cardiac toxicity, in the prolonged CHOP alone arm. The results of this trial have established combined-modality therapy as first-line treatment for early-stage NHL.

Pharmacologic Therapy

▶ *Low-Grade FL*

Initial treatment of early stage (I/II) FL consists of ISRT. Patients with advanced disease (stage III/IV) and those with early stage bulky (larger than 7.5 cm tumor size) should be considered for systemic therapy. The decision to initiate drug therapy for FL should be based on patient-specific factors. The FLIPI and GELF models are used to help determine which patients should initiate therapy (Table 95–6**)**. Trials have shown that delaying the initiation of drug therapy until patients met at least one of the GELF criteria did not adversely affect survival and decreased overall chemotherapy exposure.[29]

Drug therapy for treatment of FL consists of chemoimmunotherapy. The chemotherapy component can include single-agent chemotherapy with bendamustine or combination regimens such as CHOP or CVP. In clinical trials, there has been no statistically significant difference in overall survival among the three regimens.[31] However, it is important to note that bendamustine-based regimens have been associated with opportunistic infections. Patients receiving bendamustine-based therapy should receive prophylactic therapy against *Pneumocytis jiroveci* pneumonia (PJP) and Varicella-Zoster virus (VZV). The immunotherapy component is a monoclonal antibody (MAB)-targeting CD20 on B-lymphocytes. Rituximab, a chimeric MAB, is the historical standard based on clinical trials. Recently, regimens containing obinutuzumab, another CD20-binding MAB, were compared to rituximab containing regimens. In the GALLIUM trial, obinutuzumab regimens resulted in improved progression-free survival compared to the same regimens combined with rituximab. However, response rates and overall survival were similar.[32] A recent regimen to be evaluated is rituximab with lenalidomide, a biological response modifier. This regimen demonstrated similar outcomes to the comparison chemotherapy/monoclonal antibody regimens.[33] These four acceptable regimens are outlined in Table 95–7. Following complete response, maintenance therapy with the MAB used should be considered. Rituximab was examined as maintenance therapy administered every 8 weeks for 2 years after rituximab chemoimmunotherapy. Compared with observation, rituximab increased 3-year progression-free survival (PFS).[34] Based on this evidence, the GALLIUM trial also included maintenance therapy in its treatment groups.

There are many treatment options available upon disease progression. At first progression, patients should change therapy to a different first-line regimen. Patients who are in relatively good health should be evaluated for stem-cell transplant upon achieving a second complete response.[35] Many new treatment options have demonstrated benefit for patients who have failed more than two therapies. The PI3K inhibitors idelalisib, copanlisib, and duvelisib have all demonstrated activity in these patients.[36] In patients who have failed at least two prior therapies, and whose disease has experienced transformation to diffuse large B-cell lymphoma,

Table 95–7

Chemotherapy Regimens for Low-Grade, Follicular NHL

CHEMOTHERAPY REGIMEN	ANTI-CD20 MAB
Bendamustine + CD20 MAB—Every 28 Days for 6 cycles Bendamustine 90 mg/m^2 IV days 1 and 2	Frequency and number of cycles match chemotherapy regimen MAB is used with
CVP+ CD20 MAB—Every 21 Days for 8 cycles Cyclophosphamide 750 mg/m^2 IV, day 1 Vincristine 1.4 mg/m^2 IV, day 1 Prednisone 40 mg/m^2 po daily, days 1–5 MAB only on cycles 7 and 8	**Rituximab** Rituximab 375 mg/m^2 IV day 1
CHOP+ CD20 MAB—Every 21 Days for 8 cycles Cyclophosphamide 750 mg/m^2 IV, day 1 Doxorubicin 50 mg/m^2 IV, day 1 Vincristine 1.4 mg/m^2 IV, day 1 Prednisone 100 mg/day po, days 1–5 MAB only on cycles 7 and 8	**Obinutuzumab** Obinutuzumab 1000 mg IV days 1, 8, 15 of cycle 1 day 1 only for subsequent cycles
Lenalidomide + Rituximab—Every 28 Days[a] Lenalidomide 20 mg po daily days 2–22 for at least 6 cycles Dose reduction to 10 mg daily upon achieving complete response Rituximab 375 mg/m^2 IV, days 1, 8, 15, and 22 of cycle 1 Day 1 only on cycles 2–6 Every 8 weeks for 12 additional cycles	

[a] Lenalidomide has not been studied in combination with obinutuzumab.

IV, intravenous; po, oral.

chimeric antigen receptor T-cell (CAR-T) therapy with axicabtagene ciloleucel or tisagenlecleucel have demonstrated efficacy.[37]

▶ *Diffuse, Aggressive NHL*

KEY CONCEPT The mainstay of therapy for diffuse, aggressive NHL, such as DLBCL, is anthracycline-based combination chemotherapy, generally consisting of four or more drugs. Therapy options for intermediate- and high-grade NHL generally are segregated between localized (stage I/II) and advanced (stage III/IV) disease. Combined-modality therapy with an abbreviated course of R-CHOP and local radiation is considered a standard of care for stage I/II disease. (Table 95-5)

The standard therapy for disseminated disease since the 1970s has been CHOP. This regimen conferred a response of 50% to 60%, with long-term survival of approximately 30%. The benefits of CHOP have been confirmed by multiple clinical trials including comparisons to regimens with more agents and varying schedules. None of these other options have improved on CHOP in patients with normal risk DLBCL.[38] There were no significant differences in response rate or overall survival between the groups and severe toxicity, and deaths were higher in the advanced-generation treatment regimens relative to CHOP, cementing CHOP as first-line chemotherapy in DLBCL.

Rituximab is also routinely used to treat DLBCL. A study randomized patients 60 to 80 years of age with newly diagnosed disease to either CHOP for eight cycles or CHOP plus rituximab (R-CHOP) for eight cycles.[39] Two-year follow-up showed rituximab improved CR (76% vs 63%) and median event-free survival (57% vs 38%) and long-term follow-up confirmed benefit with an improvement in 10-year survival (43% vs 27.6%). Similar findings have been reported in younger patients, making R-CHOP first-line therapy for advanced-stage DLBCL (Table 95–8).

KEY CONCEPT Rituximab is an effective treatment option for patients with various forms of NHL as long as patients are monitored appropriately. A limitation of rituximab is severe, potentially fatal infusion-related reactions. Deaths have been reported resulting from the profound hypotension and circulatory collapse, particularly with the first dose. The package labeling recommends premedication with acetaminophen and diphenhydramine before each infusion. The initial infusion should be given slowly, at 50 mg/hour and may be increased as tolerated to a maximum of 400 mg/hour. In the absence of infusion reactions, subsequent doses may be started at a higher rate and titrated more aggressively. Other associated toxicities of rituximab include fever, chills, headache, asthenia, nausea, vomiting, angioedema, bronchospasm, and skin reactions.

Despite advances in the treatment of NHL, relapse remains a concern. Salvage therapy plays a major role in the attempt to treat recurrence. Multiple drug regimens such as ESHAP and DHAP can induce a CR, but long-term cure with these regimens is less than 10%. When salvage regimens are used, rituximab is frequently added to the regimen. Further salvage therapy can induce remissions with subsequent relapses; however, the chance for a CR is further diminished.

High-dose chemotherapy with autologous SCT has been studied as an alternative to standard dose regimens in the setting of first relapse.[40] The best-studied indication for SCT is for patients with intermediate- or high-grade disease that fails to respond to first-line therapy. Modern results from autologous SCT have demonstrated a 5-year disease-free survival rate of 48% and overall survival at 5 years of 63%.[41] The procedure-related mortality rate has ranged from 5% to 10% in published reports. However, with improvements in SCT techniques and better supportive care, the mortality rate continues to decline. The role of allogeneic SCT in this setting is limited because of donor availability, older age of patients, and the high treatment-related morbidity and mortality. Outcomes between autologous and allogeneic transplant appear similar.

CAR-T therapy should be considered in patients with DLBCL who have failed at least two prior regimens. Both axicabtagene

Table 95–8

Treatment Regimens for Diffuse, Aggressive NHL

R-CHOP—Every 21 Days[a]
EPOCH-R—Every 21 Days[b]
Rituximab 375 mg/m^2 IV, day 1
Etoposide 50 mg/m^2/day CIVI, days 1–4
Prednisone 60 mg/m^2/day po, days 1–5
Vincristine 0.4 mg/m^2/day CIVI, days 1–4
Cyclophosphamide 750 mg/m^2 IV, day 5
Doxorubicin 10 mg/m^2/day CIVI, days 1–4

R-CNOP-Rituximab—Every 21 Days[c]
Rituximab 375 mg/m^2 IV, day 1
Cyclophosphamide 750 mg/m^2 IV, day 1
Mitoxantrone 10 mg/m^2 IV, day 1
Vincristine 1.4 mg/m^2 IV, day 1
Prednisone 100 mg/day po, days 1–5

R-Hyper-CVAD
Part A: The following drugs given on course 1, 3, 5, and 7
Rituximab 375 mg/m^2 IV, day 1
Cyclophosphamide 300 mg/m^2 IV every 12 hours, days 1–3 (with mesna)
Doxorubicin 50 mg/m^2 IV, day 1
Vincristine 1.4 mg/m^2 IV, days 1, 11
Dexamethasone 40 mg/day po, days 1–4 and 11–14
Methotrexate 15 mg intrathecal, day 2
Cytarabine 30 mg intrathecal, day 2
Hydrocortisone 15 mg intrathecal, day 2
Part B: The following drugs are given on courses 2, 4, 6, and 8
Rituximab 375 mg/m^2 IV, day 1
Methotrexate 1000 mg/m^2 IV over 24 hours, day 1
Cytarabine 3000 mg/m^2 IV every 12 hours, days 2 and 3
Leucovorin 25 mg IV × 1; then 25 mg po every 6 hours for seven doses
Methotrexate 15 mg intrathecal, day 2

Bendamustine/Rituximab—Every 28 Days[a]
ESHAP
Etoposide 40 mg/m^2 IV per day continuous infusion, days 1–4
Cisplatin 25 mg/m^2 IV per day continuous infusion, days 1–4
Cytarabine 2000 mg/m^2 IV × 1, day 5
Methylprednisone 250 mg IV every 12 hours, days 1–4

DHAP
Dexamethasone 40 mg po or IV daily, days 1–4
Cisplatin 100 mg/m^2 IV continuous infusion, day 1
Cytarabine 2000 mg/m^2 IV every 12 hours for two doses on day 2

ICE
Etoposide 100 mg/m^2 IV daily, days 1–3
Carboplatin AUC 5 (maximum dose, 800 mg) IV, day 2
Ifosfamide 5000 mg/m^2 IV continuous infusion × 1 on day 2 (with 100% replacement with Mesna)

[a] Refer to Table 95–8 for regimen.

[b] Doses listed are for cycle 1 only. Subsequent cycle dosing based on degree of myelosuppression experienced.

[c] Data are limited, use only for patients who are unable to receive an anthracycline.

AUC, area under the curve; CIVI, continuous intravenous infusion; IV, intravenous; po, oral.

ciloleucel and tisagenlecleucel have demonstrated significant benefit in patients who have progressed despite multiple prior therapies, achieving a complete response in 40% and 49% of patients.[37] CAR-T therapy carries significant risk with life-threatening cytokine-release syndrome and neurologic toxicity. Because of the potential toxicities, CAR-T therapy should only be given in specially designated treatment centers.

▶ *Special Populations*

There are histologic subtypes of diffuse, aggressive NHL which are less responsive to treatment with conventional regimens such as R-CHOP. Burkitt lymphoma, lymphoblastic lymphoma, mantle-cell lymphoma, primary mediastinal large B-cell lymphoma, and primary CNS lymphoma are examples of disease that benefit from more intensive therapy. Regimens such as R-hyper-CVAD, which alternate cycles of rituximab, hyperfractionated cyclophosphamide, doxorubicin, vincristine, and dexamethasone with rituximab, high-dose cytarabine and methotrexate,[42,43] or EPOCH-R, which contains etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab should be considered alternatives to R-CHOP.

The presence of *MYC* gene rearrangement in addition to either *BCL2* or *BCL6* gene rearrangements is known as double-hit lymphoma (DHL) and can occur in patients with DLBCL or other high-grade lymphomas. These lymphomas are highly aggressive and have inferior response to R-CHOP.[44] Aggressive chemotherapy regimens such as dose-adjusted EPOCH-R have been shown to superior outcomes and should be used in the treatment of DHL.[45]

Patients with CNS NHL have disease that is poorly responsive to therapy because of inadequate penetration of standard doses of chemotherapy across the blood–brain barrier. High-dose methotrexate, ranging from 2500 to 8000 mg/m^2, is a mainstay of therapy. Treatment may also include intrathecal chemotherapy. Antineoplastics that are commonly used intrathecally include methotrexate, cytarabine (conventional formulation and liposomal products), and corticosteroids.

The recognition of *H. pylori* colonization and MALT has spurred the more aggressive treatment of this organism with antibiotics. In patients with localized disease, aggressive, combination therapy for *H. pylori* has been shown to induce MALT remission. Patients with advanced disease may require chemotherapy with R-CHOP.

Patient Encounter Part 2: Treatment Selection

Complete evaluation revealed stage IV classic Hodgkin lymphoma that is positive for CD15, CD30, and negative for CD20. Therapy is scheduled to begin immediately.

What therapy (or therapies) is (are) most appropriate for this patient?

At this time, is this patient an appropriate candidate for stem-cell transplant?

What other information (eg, laboratory studies, diagnostic tests) is needed prior to initiating chemotherapy?

Patient Encounter Part 3: Creating a Care Plan

Based on the information presented, create a care plan for this patient, including the goals of therapy, antineoplastic therapy plan, and necessary supportive care.

Patients with HIV-related lymphoma represent a therapeutic dilemma considering many have high-grade NHL. A common presentation includes extranodal disease, frequently in the GI tract, CNS, or bone marrow. Because of the aggressive nature of HIV-related lymphoma, aggressive chemotherapy regimens such as Hyper-CVAD and EPOCH are recommended. Antiretroviral therapy is important to improving patients' ability to tolerate chemotherapy and should be initiated before chemotherapy. The use of CSFs to promote white blood cell counts is also recommended. Rituximab should be added to chemotherapy for CD20-positive lymphomas in patients with an adequate CD4 count.

▶ *Supportive Care*

Due to the high sensitivity to therapy of many lymphomas, most patients treated for lymphoma with chemotherapy or radiation notice a regression of palpable lymphadenopathy within days. This also necessitates implementation of tumor lysis syndrome precautions with aggressive intravenous hydration and allopurinol, particularly if the patient has a large tumor burden. Rasburicase should be considered for patients with moderate-to-high tumor burdens.

In addition to prophylaxis for PJP and VZV in patients receiving bendamustine, patients with lymphoma must be aware of potential infectious complications from their therapy. Combination regimens for both HL and NHL are associated with rates of severe leukopenia and/or neutropenia ranging from 20% to 100% of patients. Consideration must be given to supportive care with prophylactic colony stimulating factors or antibiotics. Additionally, the use of CD20-targeting monoclonal antibodies has been associated with reactivation of hepatitis B virus (HBV).[46] Prophylactic therapy should be initiated for all patients who test positive for HBV surface antigen (HBsAg) and patients who test positive for HBV core antibody (HBcAb) and who test negative for HBV surface antibody (HBsAb). Entecavir is preferred over lamivudine due to concerns of viral resistance.[47]

OUTCOME EVALUATION

Treatment response in lymphomas is measured using the response evaluation criteria in solid tumors (RECIST), a uniform criterion assessing tumor response developed by the National Cancer Institute. Lymphomas may have residual masses after completion of treatment, adding to the difficulty in establishing a definitive remission from treatment. Historically, imaging scans using positron emission tomography or computed tomography have been

Patient Care Process

Collect Information:

- Take a thorough medication history with particular attention to nonprescription or herbal medications.
- Review medical history with an emphasis on identifying causative factors of lymphoma and preexisting medical conditions that can affect chemotherapy.

Assess the Information:

- Evaluate home medications to identify any potential drug interactions with chemotherapy.
- Review findings of diagnostic tests including laboratory values, imaging results, pathology results, cancer diagnosis, and genetic profile of the malignancy.
- Determine the stage and prognostic index for the patient.
- Before initiation of treatment, assess patient for risk of tumor lysis syndrome.

Develop a Care Plan:

- Identify the optimal treatment regimen for the patient incorporating diagnosis, stage, and prognostic indicators (Tables 95–4, 95–7, 95–8)
- Verify chemotherapy regimen doses with a standardized reference and assess for dose adjustment based on height, weight, and body surface area and organ dysfunction (renal or hepatic).
- Assess appropriateness of supportive care for the chemotherapy regimens including need for prophylactic antiemetics and use of colony-stimulating factors.

Implement the Care Plan:

- Provide patient education regarding common toxicities associated with chemotherapy such as nausea/vomiting, mucositis, myelosuppression, and alopecia.
- For doxorubicin-containing regimens, maintain records of the cumulative doxorubicin dosage received by the patient to monitor for cardiac toxicity risk.
- For bleomycin-containing regimens, maintain records of the cumulative bleomycin dosage received by the patient to monitor for pulmonary fibrosis.
- Educate patients regarding the short- and long-term complications associated with radiation therapy.
- Provide contact numbers for patient in the event of a fever and a response plan if the patient is considered to be at risk for neutropenic fever.

Follow-up: Monitor and Evaluate:

- Schedule regulatory laboratory tests including complete blood count and blood chemistries to monitor for chemotherapy toxicities and tumor lysis syndrome.
- Use RECIST criteria to determine patient's response to therapy by reviewing PET-CT scan following completion of therapy.
- Develop a plan to monitor for long-term complications of chemotherapy such as cardiotoxicity and secondary malignancies.

used to evaluate patient with lymphomas. Now, PET combined with CT is recommended to evaluate patients with lymphoma for staging as well as for response assessment.[48]

Long-term follow-up monitors patients for continued disease remission with careful examination of the original areas of involvement and repeated follow-up imaging. Patients also require long-term monitoring for toxicities of their treatment.

Advances in the treatment of lymphoma have increased the number of long-term survivors. Identification of long-term complications of lymphoma therapy is vital to patient follow-up and may influence treatment decisions in newly diagnosed patients. Outcomes associated with the treatment of HL make up the majority of data. However, advances in NHL treatment have provided more information regarding long-term toxicities. Two leading causes of death associated with lymphoma treatment are secondary malignancies and cardiovascular disease. The use of combined modality of irradiation with doxorubicin-based therapy has been reported to increase the risk of cardiac dysfunction. Treatment-related pulmonary toxicity, hypothyroidism, and infertility have been associated with lymphoma therapy as well (Table 95-5). Lymphoma survivors have an increased risk for developing myelodysplasia, acute myelogenous leukemia, and various solid tumors.[49]

Abbreviations Introduced in This Chapter

BCL1	Important in the regulation of mitosis
BCL2	A regulator of apoptosis
BCK3	A regulator of nuclear transcription factor
BCL6	Regulates cell differentiation
MYC	Regulator of gene transcription
ABVD	Doxorubicin, bleomycin, vinblastine, and dacarbazine
AVD	Doxorubicin, vinblastine, and dacarbazine
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CVP	Cyclophosphamide, vincristine, prednisone
CT	Computed tomography
CSFs	Colony-stimulating factors
CVP	Cyclophosphamide, vincristine, and prednisone
DHL	Double-hit lymphoma
DLBCL	Diffuse large B-cell lymphoma
EBV	Epstein-Barr virus
FL	Follicular lymphoma
FLIPI	Follicular lymphoma international prognostic index
GELF	Groupe d'Etude des lymphomes folliculaires
HL	Hodgkin lymphoma
INRT	Involved-node radiation therapy
IPI	International Prognostic Index
IPS	International Prognostic Score
ISRT	Involved-site radiation therapy
LDH	Lactate dehydrogenase
MAB	Monoclonal antibody
MALT	Mucosa-associated lymphoid tissue
MOPP	Mechlorethamine, vincristine, procarbazine, and prednisone
NHL	Non-Hodgkin lymphoma
PET	Positron emission tomography
PFS	Progression-free survival
RECIST	Response evaluation criteria in solid tumors
RS	Reed–Sternberg
SCT	Stem-cell transplantation

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96

Acute Leukemias

Nancy H. Heideman and Dulcinea Quintana

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Identify the risk factors associated with a poor outcome for the acute leukemias.
2. Explain the importance of minimal residual disease (MRD) and its implication on early bone marrow relapse.
3. Explain the role of induction, consolidation, and maintenance phases for acute lymphocytic leukemia (ALL).
4. Define the role of central nervous system preventive therapy for the treatment of acute lymphocytic leukemia.
5. Identify new treatment options available based on specific biologic targets for the treatment of adult acute leukemias.
6. Describe the clinical presentation and diagnosis of acute myelogenous leukemia (AML).
7. Identify underlying considerations that would determine the most appropriate chemotherapeutic regimens for both acute lymphocytic leukemia and acute myelogenous leukemia.
8. Recognize the treatment complications associated with the therapy for acute leukemias.
9. Describe the late effects associated with the treatment of long-term survivors of acute leukemias.

INTRODUCTION

KEY CONCEPT The acute leukemias are hematologic malignancies of bone marrow precursors characterized by excessive production of immature hematopoietic cells. This proliferation of "blast" cells eventually replaces normal bone marrow and leads to the failure of normal hematopoiesis and the appearance in peripheral blood as well as infiltration of other organs. These blast cells proliferate in the marrow and inhibit normal cellular elements, resulting in anemia, neutropenia, and thrombocytopenia. Leukemia also may infiltrate other organs, including the liver, spleen, bone, skin, lymph nodes, testis, and central nervous system (CNS). Virtually anywhere there is blood flow, the potential for extramedullary (outside the bone marrow) leukemia exists.

KEY CONCEPT Acute leukemias are classified according to their cell of origin. Acute lymphocytic leukemia (ALL) arises from the lymphoid precursors. Acute myelogenous leukemia (AML) arises from the myeloid or megakaryocytic precursors. As a result of clinical trials defining various prognostic (risk) factors that helped guide treatment modifications, the outcomes of acute leukemias, especially pediatric ALL, have improved dramatically over the past several decades.[1] Risk-based treatment strategies that consider multiple phenotypic and biological risk factors and attempt to match the aggressiveness of therapy with the presumed risk of relapse and death are now the standard of care. Despite the overall success in treating patients with acute leukemias, further advances are needed in the treatment of relapsed ALL.[1]

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

Leukemia is a relatively uncommon disease. The current overall age-adjusted annual incidence of acute leukemia in the United States has remained relatively stable at 13.1 per 100,000 in children and 1–2 per 100,000 in adults. In 2021, it is estimated there will be 61,090 new cases of leukemia, or 3.2% of all new cancer cases.[2]

In the pediatric population, leukemia is a common cancer, accounting for almost one-third of all childhood malignancies. ALL accounts for 75% to 80% of all cases of childhood leukemia, whereas AML accounts for no more than 20%. Males generally are affected more often than females in all but the infant age-group, and its incidence is higher in White individuals than among other racial groups.

The incidence of AML in children is bimodal. Incidence peaks in infants less than 1 year, decreases steadily then increases again for ages 10–14 years.[3] The average age of diagnosis for AML is about 65 years and a result of an increasing incidence of AML with age.[4]

Etiology

The cause of acute leukemias is unknown; multiple influences related to genetics, socioeconomics, infection, environment, hematopoietic development, and chance may play a role. Table 96–1 lists the major conditions associated with acute

Table 96–1

Clinical Conditions Associated With an Increased Frequency of Acute Leukemias

Drugs
Alkylating agents
Anthracyclines
Epipodophyllotoxins

Genetic conditions
Amegakaryocytic thrombocytopenia
Ataxia telangiectasia
Down syndrome
Bloom syndrome
Diamond–Blackfan anemia
Familial monosomy 7
Fanconi anemia
Klinefelter syndrome
Kostmann syndrome
Langerhans cell histiocytosis
Li-Fraumeni syndrome
Neurofibromatosis type 1
Noonan syndrome
Shwachman syndrome
Severe combined immunodeficiency syndrome
Wiskott–Aldrich syndrome

Chemicals
Benzene
Pesticides

Radiation
Ionizing radiation

Viruses
Epstein–Barr virus
Human T-lymphocyte virus (HTLV-1 and HTLV-2)

Social habits
Cigarette smoking
Maternal marijuana use
Maternal ethanol use
Maternal caffeine consumption

Adapted from D DeRemer, T Higgins. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020.

leukemias. In most cases, however, there is no identifiable cause of the leukemia.

Although leukemia is rarely a hereditary disease, some genetic associations are evident. For example, among identical twins, the concordance for ALL in the initially unaffected twin is 20% to 25% within 1 year. Although the incidence in fraternal twins is much less, there is still a fourfold increase in the risk of leukemia in the initially unaffected twin compared with the healthy population. One explanation for this association may be a shared placental circulation, which allows for transmission of disease from one twin to the other. Additionally, leukemia has an increased incidence in several chromosomally abnormal populations. For example, patients with Down syndrome have 20 times increased risk of developing leukemia compared with the rest of the population.

Exposure to environmental agents, such as agricultural chemicals, pesticides, and radiation, is associated with leukemia, but none is conclusively related to the development of leukemia. An increased frequency of ALL is associated with higher socioeconomic status. It is postulated that less social contact in early infancy and, thus, a late exposure to some common infectious agents may have some impact.[1]

Risk factors for the development of AML include exposure to environmental toxins, Hispanic ethnicity, and genetics.[5] Also of concern is the increased prevalence of AML as a secondary malignancy, resulting from chemotherapy and radiation treatment for other cancers. Alkylating agents, such as ifosfamide and cyclophosphamide, and topoisomerase inhibitors, such as etoposide, are linked to an increased risk of AML and myelodysplastic syndrome (MDS).[4]

PATHOPHYSIOLOGY

Hematopoiesis is defined as the development and maturation of blood cells and their precursors. In utero, hematopoiesis may occur in the liver, spleen, and bone marrow; after birth, this process occurs exclusively in the bone marrow. All blood cells are generated from a common hematopoietic precursor or stem cell. These stem cells are self-renewing and pluripotent and, thus, are able to commit to any one of the different lines of maturation that give rise to platelet-producing megakaryocytes, lymphoid, erythroid, and myeloid cells. The myeloid cell line produces monocytes, basophils, neutrophils, and eosinophils, whereas the lymphoid stem cell differentiates to form circulating B and T lymphocytes, natural killer (NK) cells, and dendritic cells. In contrast to the ordered development of normal cells, the development of leukemia seems to represent an arrest in differentiation at an early phase in the continuum of stem cell to mature cell.

Both AML and ALL are thought to arise from clonal expansion of these "arrested" cells. As these cells expand, they acquire one and often more chromosomal aberrations, including translocations, inversions, deletions, point mutations, and amplifications. The translocation t(12;21) or *TEL–AML1* is found in approximately 25% of cases of pediatric ALL and is associated with a favorable prognosis.[1] This translocation is uncommon in adults. Another example is the t(9;22) translocation (Philadelphia chromosome, Ph^+), which results in the *BCR–ABL* fusion protein. This translocation produces a novel kinase that leads to uncontrolled proliferation, survival, and self-renewal of cells. It is uncommon in childhood ALL and commonly found in adult ALL, especially in older patients.

Patients with MDS or AML as a secondary neoplasm are often characterized by having had prior alkylator- or etoposide-based chemotherapy. Patients who have received treatment for Hodgkin disease or solid tumors are most at risk for this problem because they often treated with these agents. Patients with MDS have an abnormal bone marrow and a variety of cytopenias involving one or more of their marrow cell lines. They are at high risk of converting to overt leukemia over time. A variety of complex cytogenetic findings and monosomies of chromosome 5 or 7, and 11q deletions are often present in this population.[6]

Leukemia Classification

Classification methods for leukemia have evolved from simple schemes that were largely phenotypic and considered only age, gender, white blood cell (WBC) count, and blast morphology to now-complex methods that include biological features such as cell-surface receptors, DNA content (ploidy; more or less than normal chromosomal DNA content), and a variety of cytogenetic abnormalities.

For all newly diagnosed patients with leukemia, an aspirate of the liquid marrow and a bone marrow core biopsy are obtained. Analysis of the leukemic cell-surface markers (immunophenotyping) establishes three types of ALL, pre-B, mature B, and T-cell precursor ALL. There are eight subtypes of AML (M0 to M7) as classified by the French–American–British (FAB) scheme. The World Health Organization identifies specific entities within the diagnosis of AML based on a combination of karyotypic and molecular mutations (Tables 96–2 and 96–3).

Immunophenotyping by flow cytometry has taken on an increasingly important role in the diagnosis of leukemia. Owing to the ease of application, sensitivity, and quantifiable results, flow cytometry is the preferred method for leukemic lineage as well as prognostic assignment.[7] This approach takes advantage of

Table 96–2

Morphologic (FAB) Classification of AML

Subtype			Frequency of FAB Subtype	
		Adults (%)	Children Older Than 2 Years (%)	Children Younger Than 2 Years (%)
M0	Acute myeloblastic leukemia without maturation	5	Low	Low
M1	Acute myeloblastic leukemia with minimal maturation	15	17	7
M2	Acute myeloblastic leukemia with maturation	25		27
M3	Acute promyelocytic leukemia	10		5
M4	Acute myelomonocytic leukemia	20	30	26
M5a	Acute monoblastic leukemia, poorly differentiated	10	52	26
M5b	Acute monoblastic leukemia, well differentiated	5		
M6	Acute erythroleukemia	5		2
M7	Acute megakaryoblastic leukemia	5		7

FAB, French–American–British.

the development of diagnostic monoclonal antibodies (MABs) to many cell-surface antigens that are differentially expressed during hematopoietic differentiation. The antigens are referred to as antibody cluster determinants (CDs) that define cells at various stages of development and can easily separate ALL from AML and T cell from pre–B-cell ALL.[7,8] The combined approach of flow cytometric identification and cytogenetic DNA content, much of which is also revealed by flow cytometry and fluorescent in situ hybridization (FISH; microscopic, fluorescence identification of chromosomal features), has facilitated diagnosis and delineation of specific subtypes of the acute leukemias. Common immunophenotypic markers seen in AML and ALL are provided in Table 96–4.

Table 96–3

WHO Classification of AML and Related Neoplasms

AML with recurrent genetic abnormalities:
AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBEB-MYH11*
Acute promyelocytic leukemia (APL) with t(15;17)(q22;q12); *PML-RARA*
AML with t(9;11)(p22;q23); *MLLT3-MLL*
AML with t(6;9)(p23;q34); *DEK-NUP214*
AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
Provisional entity: AML with mutated NPM1
Provisional entity: AML with mutated CEBPA

AML with myelodysplasia–related change

Therapy-related myeloid neoplasms

AML, not otherwise specified:
Undifferentiated AML (M0)
AML with minimal differentiation (M1)
AML without maturation (M2)
AML with maturation (M2)
Acute myelomonocytic leukemia (M3)
Acute monoblastic/monocytic leukemia (M4)
Acute erythroid leukemia (M5)
Pure erythroid leukemia (M6)
Erythroleukemia, erythroid/myeloid (M6)
Acute megakaryoblastic leukemia (M7)

Acute basophilic leukemia

Acute panmyelosis with myelofibrosis

Myeloid sarcoma

Myeloid proliferations related to Down syndrome:
Transient abnormal myelopoiesis
Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

Adapted from Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016:2391–2405.

Prognostic Factors

KEY CONCEPT The goal of treatment is to match treatment to risk and minimize overtreatment or undertreatment. Patients with leukemia are categorized based on clinical and biological features that mirror their risk of relapse. Risk assessment is an important factor in the selection of treatment. Age, WBC, leukemic cell-surface markers, DNA content, and specific cytogenetic abnormalities predict response to therapy and are used to assign risk and associated treatment.[5] On the basis of these prognostic variables, patients are assigned to standard-, high-, or very high–risk groups that determine the aggressiveness of treatment. Much of the success has been driven by changes in risk stratification, including therapy for higher risk groups, deescalation for lower risk groups, and more recently novel targeted therapies.[1]

▶ *Prognostic Factors in ALL*

In both children and adults with ALL, clinical trials have identified several risk factors that correlate with outcome (Table 96–5).

Table 96–4

Common Immunophenotypes in Acute Leukemia

Leukemia	Common Immunophenotypes
AML	CD13, CD15, CD33, CD14, CD64, CD65, C-KIT
B-cell ALL	CD19, CD20, CD10, CD22, CD79a
T-cell ALL	CD2, CD3, CD4, CD5, CD7, CD1a, CD8

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CD, cluster determinant.

Adapted from Gajendra S. Flowcytometry in acute leukemia. Clin Oncol. 2016;1;1–5.

Table 96–5

Prognostic Factors in ALL

	Risk for Leukemic Relapse	
Factor	**Standard/Low**	**High**
Age at diagnosis	1 to < 10 years of age	>10 years of age; < 1 year of age
Immunologic phenotype	B ALL	T ALL
WBC count at diagnosis	$< 50 \times 10^3/mm^3$ ($50 \times 10^9/L$)	$> 50 \times 10^3/mm^3$ ($50 \times 10^9/L$)
Cytogenetics	ETV6-RUNX1, t(12;21), trisomy 4, 10, 17	t(9;22); t(4;11); t(17;19), iAmp21, Ph-like
Ploidy	Hyperdiploidy	Hypodiploidy, near haploid
CNS leukemia	Absent	Present
MRD at end of induction	< 0.01%	> 0.01%

WBC, white blood cell.

Adapted from Vrooman LM, Silverman LB. Treatment of childhood acute lymphoblastic leukemia: prognostic factors and clinical advances. Curr Hematol Malig Rep. 2016;11:385–394.

Prognostic features include age, WBC count, cytogenetic abnormalities, ploidy (DNA content), leukemic cell immunophenotype, and degree of initial response to therapy, and minimal residual disease (MRD; the degree of subclinical disease remaining at various times after starting treatment).[5] When these factors are combined, they predict groups of patients with varying degrees of risk for treatment failure.

The importance of age is evident in both children and adults. Children younger than 1 year or older than 10 years of age have a poorer outcome than others. Likewise, in adults, there is a steady decline in the rate of survival with increasing age. Patients greater than 60 years have particularly poor outcomes with only 10% to 15% long-term survival. Older patients tend to have disease with unfavorable biology, more medical comorbidities, and inability to tolerate standard chemotherapy.[9]

Similar to age, the WBC count at presentation is a reliable indicator of complete response (CR) rate and outcome. The WBC count is indicative of tumor burden, although the underlying biological mechanisms that account for the unfavorable outcomes associated with an elevated WBC count are unclear. Patients with WBC counts of less than $50 \times 10^3/mm^3$ ($50 \times 10^9/L$) are considered being at standard risk and have a better outcome than those with higher WBC counts at presentation, which is associated with higher risk of treatment failure (see Table 96–5).

Specific chromosomal abnormalities in leukemic cells also possess prognostic significance. Blast cells with a translocation of parts of chromosome 12 and 21 (the *TEL–AML1* fusion) or trisomies of 4, 10, and 17 are considered to have favorable genetic features. The presence of the Philadelphia chromosome (Ph^+), the result of a specific translocation between chromosome 9 and 22, t(9;22)(q34;q11.2), is a high-risk feature, which is present in about 3% of children but is much more common in adults with ALL.[9] This translocation results in a novel tyrosine kinase that drives cell proliferation. A variant with a similar expression profile to Ph+ ALL but without the BCR-ABL rearrangement has been identified.[10] This so-called Ph-like ALL occurs in approximately

Patient Encounter 1, Part 1

Your patient is a 22-year-old man who presents to the emergency department with a chief complaint of progressive shortness of breath for the past 10 days. Patient endorses night sweats, fatigue, and an unintentional weight loss of about 10 pounds. He has not had any recent contact with anyone who is sick.

Physical Exam:

General appearance—well-developed, well-nourished man in no acute distress

HEENT—normocephalic, atraumatic neck; neck supple, nontender, no lymphadenopathy.

Lungs—decreased breath sounds left >right; nonlabored respiration on oxygen 4L/min via nasal cannula

Heart—normal rate and regular rhythm

Abdomen—soft nontender, nondistended normal bowel sounds

Musculoskeletal—normal range of motion, no tenderness or swelling

Skin—warm, dry, and pink no rashes or lesions

Neurologic awake alert and oriented × 3

Genitourinary—no hematuria or CVA tenderness

Vital signs and uric acid within normal limits, weight 77 kg, and height 170 cm

CT scan chest, abdomen, and pelvis at an outside hospital demonstrate a mass in the anterior mediastinum associated with encasement of the adjacent vascular structures. There is a large left-sided pleural effusion. Chest tube placed at outside hospital. Disease involves the liver and bilateral kidneys.

MRI of brain revealed no acute intracranial abnormalities.

Mediastinal mass core biopsy: consistent with T-cell lymphoblastic leukemia

CBC: WBC $25 \times 10^9/L$ (reference 4–10); platelet count $146 \times 10^9/L$ (reference range 150–400); hemoglobin 10 g/dL (100 g/L, 6.21 mm/L; normal 11.7 to 15.7 g/dL, 117 to 150 g/L, 7.3 to 9.7 mmol/L), and hematocrit 30% (0.3; normal 35% to 47%, or 0.35 to 0.47) bone marrow biopsy and aspirate reveals 80 % blasts (normal 0)

Chemistries and uric acid are within normal limit, and CSF leukemic screen is negative

The patient is admitted to the inpatient hematology-oncology service at the hospital. He is started on a pediatric research protocol consisting of a four-drug induction with vincristine, daunorubicin, pegasparaginase, and prednisone. Patient also received 1 dose of intrathecal cytarabine for CSF prophylaxis.

What is the purpose of a 4 drug induction?

15% of pediatric patients and 20% to 25% of adult patients with B-cell ALL. This mutation also confers a poor prognosis.[11]

Among children younger than 1 year of age, as many as 70% possess a poor prognostic genotype represented by the presence of the *MLL* (11q23) gene rearrangement. This finding is rare among older patients. Leukemias with the *MLL* gene rearrangement are highly resistant to the key antileukemic agents such as glucocorticoids and L-asparaginase.[1,12]

The DNA content of blast cells, hyper-, hypo-, or diploid, corresponding to increased, decreased, or normal chromosome numbers, is also a prognostic factor. Lower risk patients with hyperdiploidy (more than 50 chromosomes per leukemic cell) generally include approximately 25% of children who have B-cell lineage ALL.[9] These children are between the ages of 1 and 9 years, but the higher risk patients with normal diploidy (50 chromosomes) generally are older. Hypodiploid ALL with less than 44 chromosomes occurs in 1% to 5% of pediatric patients with ALL and is an independent risk factor for poor prognosis with declining prognosis with decreased chromosome number.[9]

Patients with cell-surface markers indicating that the blasts are early in the B-cell lineage (CD markers) are considered favorable and standard risk, whereas those with mature B- and T-cell blasts are considered high risk. T-cell ALL is found in approximately 15% of childhood ALL. Compared with B-lineage ALL, T-cell ALL is relatively resistant to different classes of drugs, including methotrexate and cytarabine.[13]

Patients completing induction treatment and in apparent remission still harbor malignant cells in their bone marrow even though they appear disease free by peripheral blood and bone marrow morphology. Assuming that most patients present with about a 10^{11} leukemic cell burden at diagnosis, at least 10^9 cells remain after initial treatment. These residual leukemic cells are below the limits of detection using standard morphologic examination. Measurement of this population of cells has become an increasingly significant prognostic factor and a determinant of the aggressiveness of postinduction therapy. Through flow cytometric analysis and polymerase chain reaction, it is possible to detect one leukemic cell among 10^6 normal cells, representing 1000-fold greater sensitivity than morphologic examination.[9]

Patient Encounter 1, Part 2

Your patient was admitted for a line infection on day 18. Cefepime was started. Chest tube was removed after effusion was deemed clear. Chemistries and fibrinogen were obtained. All labs were within normal limits. The patient's fibrinogen was 95 mg/dL (normal 200 to 400 mg/dl or 11.1 to 22.2 mmol/L)

Which agent is responsible for the low fibrinogen?

What is the mechanism by which this agent causes low fibrinogen?

Patient received 7 days of broad-spectrum antibiotic. During this time, he also received his day 22 chemotherapy that included vincristine, daunorubicin, and continued prednisone. Upon discharge, the patient is complaining of significant tingling in his hands and feet.

Which of the following agents is responsible for causing peripheral neuropathy?

a. Prednisone
b. Vincristine
c. Daunorubicin
d. Intrathecal cytarabine

Patient Encounter 1, Part 3

On day 29, patient has a bone marrow aspirate to determine minimal residual disease (MRD) and an intrathecal methotrexate for CNS prophylaxis. The MRD was less than 0.01 %.

What is the significance of an MRD less than 0.01%?

KEY CONCEPT Minimal residual disease (MRD) is a quantitative assessment of subclinical remnant of leukemic burden remaining at the end of the initial phase of treatment (induction) when a patient may appear to be in a complete morphologic remission. This measure has become one of the strongest predictors of outcome for patients with acute leukemia. The elimination of MRD is a principal objective of postinduction leukemia therapy. Several studies in children, in whom ALL is common, have evaluated disease levels at the end of induction and correlated these values with event-free survival (EFS). For a patient with detectable MRD less than 0.01% at the end of induction, EFS is approximately 90% at 3 years. Conversely, a patient with high MRD (greater than 1%) has a 3-year EFS of only 30%.[9] Assessment of MRD is also emerging as an important indicator of disease recurrence in the adult population and in patients with AML.

▶ *Prognostic Factors in AML*

The major prognostic factors in newly diagnosed AML are age, subtype, molecular and cytogenetic changes, and performance status.[14]

Older adults with AML (older than 60 years), compared with younger patients with the same disease, have a dismal prognosis and represent a distinct population in terms of disease biology, treatment-related complications, and overall survival (OS). Older patients with secondary AML have an even poorer prognosis. Older patients also have a higher incidence of unfavorable chromosomal abnormalities, such as aberrations of chromosomes 5, 7, or 8, FLT_3–internal tandem duplication (ITD), and fewer abnormalities that are associated with a more favorable outcome, such as t(8;21) or inv(16) (Table 96–6).[15]

Recent studies suggest that ethnicity may be an important predictor of outcome in children with AML. Investigators found that African Americans treated with chemotherapy had a significantly worse outcome than White people, perhaps suggesting race-related pharmacogenetic differences. Body mass index may also affect the prognosis of children with AML. Underweight patients and overweight patients were less likely to survive than normal-weight patients because of a greater risk of treatment-related deaths. Current clinical trials in adults and pediatrics strongly suggest that patients with detectable MRD at the end of induction therapy or consolidation are strongly associated with the risk of relapse.[14]

TREATMENT

Desired Outcome

The primary objective in treating patients with acute leukemia is to achieve a continuous complete remission (CCR). Remission is defined as the absence of all clinical evidence of leukemia with the restoration of normal hematopoiesis. For both ALL and AML,

Clinical Presentation and Diagnosis of ALL[9,10]

General

- Typically, patients have symptoms for 1–3 months before presentation. These include fatigue, fever, and pallor, but patients generally are in no obvious distress.

Symptoms

- The patient may present with weakness, malaise, bleeding, and weight loss.
- Neutropenic patients are often febrile and highly susceptible to infection.
- Anemia usually presents as pallor, tiredness, and general fatigue.
- Patients with thrombocytopenia usually present with bruising, petechiae, and ecchymosis.
- Patients often present with bone pain secondary to expansion of the marrow cavity from leukemic infiltration.
- CNS involvement is common at diagnosis.

Signs

- Temperature may be elevated secondary to an infection associated with a low WBC count.
- Petechiae and bleeding are indicative of thrombocytopenia.
- Patients may present with organ involvement, such as peripheral adenopathy, hepatomegaly, and splenomegaly.
- T-lineage ALL may present with a mediastinal mass.

Laboratory Tests

- CBC with differential is performed.
- The anemia is usually normochromic and normocytic. Approximately 50% of children present with platelet counts of less than $50 \times 10^3/\text{mm}^3$ ($50 \times 10^9/\text{L}$). The WBC count may be normal, decreased, or high. About 20% of patients have WBC counts over $100 \times 10^3/\text{mm}^3$ ($100 \times 10^9/\text{L}$), which places them at risk for leukostasis.
- Uric acid is increased in approximately 50% of patients secondary to rapid cellular turnover.
- Electrolytes: Potassium and phosphorus often are elevated. Calcium usually is low.
- Coagulation disorders: Elevated prothrombin time, partial thromboplastin time, D-dimers; hypofibrinogenemia.

Other Laboratory Tests

Flow cytometric evaluation of bone marrow and peripheral blood is performed to characterize the type of leukemia as well as to detect specific chromosomal rearrangements. The bone marrow at diagnosis usually is hypercellular, with normal hematopoiesis being replaced by leukemic blasts. Diagnosis is established by the presence of 20% or more lymphoblasts in the bone marrow or peripheral blood. Lumbar puncture with CSF examination is standard of care at the time of diagnosis to assess for CNS involvement.

Clinical Presentation and Diagnosis of AML[14,15]

General

- Patients may have symptoms of AML for 1 to 3 months before presentation. These include fatigue, fever, and pallor, but patients generally are in no obvious distress.

Symptoms

- The patient may present with weakness, bone pain, malaise, bleeding, and weight loss.
- Neutropenic patients are often febrile and highly susceptible to infection.
- Anemia usually presents as pallor, tiredness, and general fatigue.
- Patients with thrombocytopenia usually present with bruising, petechiae, and ecchymosis.
- Chloromas (localized leukemic deposits named after their color) may be seen, especially in the periorbital regions and as skin infiltrates.
- Gum hypertrophy is indicative of AML M4 and AML M5 subtypes.
- Disseminated intravascular coagulation may be present in all AML subtypes but is common in AML M3 and is associated with generalized bleeding or hemorrhage.
- Lymphadenopathy, massive hepatosplenomegaly, and bone pain are not as common in AML as in ALL.

Signs

- Temperature may be elevated secondary to an infection associated with a low WBC count.
- Petechiae and bleeding are indicative of thrombocytopenia.

Laboratory Tests

- CBC with differential is performed.
- The anemia is usually normochromic and normocytic.
- Approximately 50% of children present with platelet counts of less than $50 \times 10^3/\text{mm}^3$ ($50 \times 10^9/\text{L}$).
- The WBC count may be normal, decreased, or high. About 20% of patients have WBC counts of over $100 \times 10^3/\text{mm}^3$ ($100 \times 10^9/\text{L}$), which places them at risk for leukostasis.
- Uric acid is increased in approximately 50% of patients secondary to rapid cellular turnover.
- Electrolytes: Potassium and phosphorus are often elevated. Calcium is usually low.
- Coagulation disorders: Elevated prothrombin time, partial thromboplastin time, D-dimers; hypofibrinogenemia.

Other Diagnostic Tests

Flow cytometric evaluation of bone marrow and peripheral blood to characterize the type of leukemia as well as to detect specific chromosomal rearrangements. The bone marrow at diagnosis usually is hypercellular, with normal hematopoiesis being replaced by leukemic blasts. The presence of greater than 20% blasts in the bone marrow is diagnostic for AML. At diagnosis, an LP is performed for monocytic differentiation, mixed **phenotype** acute leukemia, WBC count > 40,000/mcL at diagnosis, or extramedullary disease.

Table 96–6

Risk Assessment of AML

Risk Category	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Biallelic mutated *CEBPA* Mutated *NPM1* without *FLT3ITD* or *FLT3-ITD*$^{\text{low}}$
Intermediate	Mutated *NPM1 and FLT3-ITD*$^{\text{high}}$ Wild-type *NPM1* without *FLT3-ITD* or with *FLT3-ITD*$^{\text{low}}$ (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* Cytogenetic abnormalities not classified as favorable or adverse
Poor	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3)*; KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM(EVI1)* –5 or del (5q); –7; –17/abn(17p) Complex karyotype, monosomal karyotype Wild-type *NPM1* and *FLT3-ITD*$^{\text{high}}$ Mutated *RUNX1* Mutated *ASXL1* Mutated *TP53*

Adapted from National Comprehensive Cancer Network. Acute Myeloid Leukemia (Age >/= 18 years) (Verson 3.2020). Available from: http://www.nccn.org

remission induction is achieved with the use of myelosuppressive chemotherapy that initially induces a state of bone marrow aplasia as the leukemic cells die followed by a slow return and proliferation of normal cells. After this period, hematopoiesis is restored. Failure to achieve remission in the first 7 to 14 days of therapy is highly predictive of later disease recurrence. This again represents the growing importance of MRD in prognosis and treatment.

Nonpharmacologic Therapy

This year, roughly 1.8 million people will be diagnosed with cancer in the United States.[2] With improvements in detection and treatment, approximately two-thirds of those diagnosed with the disease can expect to be alive in 5 years. With improving longevity, the cumulative adverse effects of both the disease and treatment are becoming an increasingly important issue. "Late-effects" data show that both adult and pediatric cancer survivors are at greater risk for developing second malignancies, cardiovascular disease, diabetes, and osteoporosis than those in the general population. With respect to the growing population of pediatric cancer survivors, data confirm that they are eight times more likely than their siblings to have a severe or life-threatening chronic health condition. For example, the survivors of pediatric ALL have an increased risk of obesity, avascular necrosis, infertility, and associated comorbidities.[13] Thus, it is important to provide supportive care and counseling related to nutrition, smoking cessation, and exercise as a part of their active treatment. Healthcare professionals should think beyond the immediate treatment-related issues of their patients and provide appropriate, active assistance to promote healthy lifestyles and encourage patients to take active roles in pursuing general preventive health strategies.[13]

Pharmacologic Therapy: ALL

The treatment for ALL consists of five main elements: remission induction (the initial tumor reduction leading to morphologic remission), CNS-directed treatment, intensive postremission consolidation regimens, interim maintenance/delayed intensification followed by a prolonged maintenance phase. Different blocks of chemotherapy having differing intensity depend on the group of patients at risk with increasingly intensive regimens corresponding to more aggressive disease categories.[16] The total duration of treatment is 2–3 years.

▶ *Remission Induction*

KEY CONCEPT The initial treatment for acute leukemias is called remission **induction** lasting four to 6 weeks. The purpose of induction is to induce a remission, a state in which there are no identifiable leukemic cells in the bone marrow or peripheral blood with light microscopy.[16]

KEY CONCEPT Current induction therapy for ALL typically consists of vincristine, asparaginase, and a steroid (prednisone or dexamethasone). An anthracycline is added for higher risk patients. Although induction treatment produces 95% CR in children, it declines to no more than 60% in patients older than 60 years of age.

Patient Encounter 2, Part 1

A 34-year-old woman presents to urgent care with symptoms of rapid onset of fatigue and shortness of breath. On review of systems, she endorses new onset epistaxis. On physical exam, she is febrile with a temperature of 38.8°C, she appears pale, and she has petechiae on her palate.

The physician orders a CBC with differential which reveals a normochromic, normocytic anemia with a hemoglobin of 6 g/dL (60 g/L, 3.6 mmol/L; normal 11.7–15.7 g/dL, 117–150 g/L, 7.3–9.7 mmol/L), hematocrit of 18% (0.18; normal 35%–47%, or 0.35–0.47), and white blood cell (WBC) count of $2.6 \times 10^3/\mu L$ ($2.6 \times 10^9/\mu L$). The differential on the WBC count reveals 75% (0.75) lymphocytes (normal 20%–40%, or 0.2–0.4), 20% (0.2) neutrophils (normal 55%–62%, or 0.55–0.62), and 5% (0.05) myeloblasts (normal 0%). Based on this information, a bone marrow aspirate and biopsy are performed, which reveal 85% (0.85) myeloblasts. Cytogenetic studies are normal and molecular studies reveal an NPM1 mutation without FLT3-ITD.

What chemotherapy drugs should this patient receive as part of his AML induction?

a. Dexamethasone, vincristine, and pegaspargase

b. Daunorubicin, cytarabine, and gemtuzumab ozogamicin

c. Daunorubicin, vincristine, pegaspargase

d. Dexamethasone, vincristine, pegaspargase, daunorubicin

What is the role of postremission chemotherapy?

Patient Encounter 2, Part 2

This patient had a bone marrow aspiration performed on day 14 and again at the time of blood count recovery. Both showed that the patient was in a complete morphologic remission.

What is the role of allogeneic stem cell transplant?

Adults, unlike children, are universally considered to be at high risk for relapse; therefore, their induction regimens include an anthracycline (daunorubicin or doxorubicin) in addition to the standard steroid and vincristine treatment that have been the backbone of treatment for this disease for the last 50 years. Dexamethasone often replaces prednisone because of its longer half-life and better CNS penetration.[17] Although dexamethasone possesses more favorable pharmacologic characteristics than prednisone, its use may be associated with more aseptic osteonecrosis of the femoral and humeral heads as well as an increase in life-threatening infections.[16] Several different agents for asparagine depletion exist, including pegylated (PEG) asparaginase and Erwinia asparaginase. Pegylated asparaginase has been altered by covalently attaching a polyethylene glycol that has shown to result in an extended half-life and reduced immunogenicity. Erwinia is usually given to those patients who have had an allergic reaction to pegylated asparaginase and requires a more frequent administration schedule.[16]

▶ CNS Prophylaxis

KEY CONCEPT Leukemic invasion of the CNS is an almost universal event in patients even in those whose cerebrospinal fluid (CSF) cytology shows no apparent disease. Thus, all patients with ALL and AML leukemia receive intrathecal (IT) chemotherapy. Although this is often referred to as "prophylaxis," it more realistically represents treatment. CNS prophylaxis relies on IT chemotherapy (eg, methotrexate, cytarabine, and corticosteroids), systemic chemotherapy with dexamethasone and high-dose methotrexate, and craniospinal irradiation (XRT) in selected high-risk patients.[18] Cranial radiation use diminished substantially after the efficacy of IT treatment was evident, and the toxicities associated with radiation; learning disabilities, growth retardation, and secondary malignancies were recognized. IT therapy has replaced cranial XRT as CNS prophylaxis for all except the very high-risk patients and those with T-cell ALL who are at higher risk of CNS disease. Many protocols reserve radiation for those at higher risk of CNS relapse while some institutions defer its use altogether.[16]

Inexplicably, the treatment of CNS leukemia has not impacted the OS of adults as it has for childhood ALL. With IT chemotherapy alone, the incidence of CNS relapse in adults is 9% to 13% compared with less than 3% in children.[18]

▶ Postremission Consolidation Regimens

Consolidation After completion of induction and restoration of normal hematopoiesis, patients begin consolidation. The goal of consolidation is to administer dose-intensive chemotherapy to reduce the burden of residual leukemic cells. It is in this and subsequent treatment phases that the remaining leukemic burden is eliminated.[17] Several regimens use agents and schedules designed to minimize the development of drug cross-resistance. Consolidation is an effective strategy to prevent relapse in children with ALL, but its benefits in adults are less clear.

In children, the intensity of the consolidation treatment is determined by the child's risk classification and the degree of cytoreduction during induction (MRD). Patients who respond slowly to induction therapy (as determined by bone marrow examination early in induction) are at higher risk of relapse and treated with more aggressive regimens.[16]

Reinduction (Delayed Intensification and Interim Maintenance) The typical duration of interim maintenance is approximately 8 weeks. Treatment usually consists of low-intensity therapy added to continue remission and lower cumulative toxicity. The Berlin–Frankfurt–Munster (BFM) study group introduced a treatment element called delayed intensification (or reinduction) therapy. This therapy consisted of repetition of the initial remission induction therapy administered approximately 3 months after remission. This regimen, similar to consolidation, has been adopted as a component of treatment for children by virtually all institutions.[5]

Intensification regimens vary in their aggressiveness and drug regimens depending on the patient's risk group and immunophenotype. For example, the use of escalating doses of methotrexate intravenously (Capizzi methotrexate regimen) without leucovorin plus pegasparaginase was reportedly to be superior to high-dose methotrexate in 90% of patients receiving cranial radiation therapy.[19]

▶ Maintenance

The purpose of maintenance therapy is to further eliminate leukemic cells and produce an enduring CCR. The two most important agents in maintenance chemotherapy are a combination of oral methotrexate and 6-mercaptopurine. Improved outcome is associated with increasing 6-mercaptopurine doses to the limits of individual tolerance based on absolute neutrophil count (ANC). The benefit of adding intermittent "pulses" of vincristine and a steroid (usually dexamethasone) to the antimetabolite backbone remains unclear, but it is common practice in most modern treatment regimens.[5] The goal is to induce a moderate immunosuppression and leukemic cell kill.

6-Mercaptopurine is a key agent in maintenance therapy. It has a complex metabolism and is initially metabolized by thiopurine methyltransferase (TPMT).[1] TPMT activity is variable with about 90% of patients having normal activity, about 10% having intermediate activity, and fewer than 1% having very low or no activity. Genetic polymorphisms in *TPMT* are inherited in an autosomal recessive fashion and have a profound influence on 6-mercaptopurine tolerance.[16]

TPMT screening is recommended for children starting therapy with 6-mercaptopurine. Children who possess alleles that have diminished activity require 6-mercaptopurine dose reductions of 50% to 90% to prevent severe immunosuppression and infection. Many studies include guidelines to for dose modification in achieving the goal of balancing the risk of inadequate myelosuppression with the risk of severe neutropenia.[16] Despite these reductions, these children have equivalent OS when compared with those receiving full-dose 6-mercaptopurine. The optimal duration of maintenance therapy in both children and adults is unknown, but most regimens are given for 2 to 3 years; extension of the regimen beyond 3 years has not shown any additional benefit.

ALL in Infants and Young Children

Infants and children younger than 1 year of age account for approximately 5% of all children with ALL and have the worst outcome of any group with this disease. These patients have several poor prognostic features at diagnosis, including hyperleukocytosis, hepatomegaly, splenomegaly, and CNS leukemia.[11]

A characteristic finding in up to 80% in this group is a chromosomal translocation involving the *MLL* gene located at 11q23. There are multiple possible rearrangements of this gene with other chromosomes, and all confer a poor prognosis. In vitro, blasts of these patients showed greater drug resistance to prednisolone and L-asparaginase than those from other patients, although they are more sensitive to cytarabine.[12] Based on this information, several studies are testing the efficacy of intensified chemotherapy that includes high-dose cytarabine. Another achievement is the prevention of CNS relapse using IT cytarabine in conjunction with high-dose systemic cytarabine. This combination has eliminated the need for cranial XRT in this young population. Even with major advances in cure rates for the general pediatric ALL population, in whom survival is 80% or more, the long-term survival of infants is only about 50%.[1]

ALL in Adolescents and Young Adults

As noted previously, age is an important prognostic factor in ALL. Adolescents and adult patients have generally been shown to have poorer survival than children.[13] However, the group of patients between late adolescence and age 39 years (adolescents and young adults) have a substantially better outcome than older adult patients, but worse outcomes when compared to pediatric counterpart. When treated with pediatric protocols the disease-free survival (DFS) is 70%, compared historically to 30% to 45%.[13] The pediatric regimens used to treat this group of patients contain the BFM backbone: steroids, vincristine, asparaginase, and CNS prophylaxis.[20] The reasons for improved survival in this age-group are not entirely clear, and multiple factors are likely to play a role. Among the likely explanations is that pediatric protocols use more aggressive and prolonged postremission consolidation therapy before maintenance. Other proposed explanations are the potential differences in disease biology in this versus older age patients, more intense CNS prophylaxis, and the greater degree of social support and better compliance fostered in a pediatric environment. Current and planned trials are focusing on the potential of extending this treatment approach to patients age 40 years and possibly older.

Patient Encounter 3

Your patient is a 52-year-old woman who presented to the emergency department after a few days of petechiae on her left flank and inner thigh, diffuse myalgias, and intermittent fevers of 101°F. She was found to have hyperleukocytosis (white blood cell [WBC] count 150,000/L) with 75% blasts in peripheral blood and thrombocytopenia (platelet count 8,000/L). Cytogenetic analysis demonstrated a t(15;17) mutation.

Which of the following is the most appropriate remission induction therapy for EB based on this information?

a. Blinatumomab

b. Tretinoin (ATRA) plus arsenic trioxide

c. High-dose cytarabine

d. 7 + 3 with cytarabine and daunorubicin

On the third day of treatment, your patient begins to complain of fever, respiratory distress, and fluid retention. Chest imaging reveals pulmonary opacities and presence of a pleural effusion.

What is the most likely cause of this process?

a. Pneumonia

b. Acute respiratory distress syndrome

c. Differentiation syndrome associated with ATRA

d. Myocardial infarction

What is the primary treatment associated with the above condition?

a. Robitussin

b. Dexamethasone

c. Furosemide

d. Aspirin

ALL in Adults

The incidence of ALL in adults ages 30 to 60 years is only 2 per 100,000 persons per year compared with almost 10 per 100,000 in children. The conventional risk factors such as high WBC counts, older age, and CNS disease hold true in adults as in children. However, the significance of cytogenetic and molecular markers that are so important in children seems to be less predictive of outcome in adults. An exception is the adverse prognostic factor, the presence of the *BCR-ABL* translocation (Ph^+) just as in childhood ALL. This occurs in 25% of adults and in up to 50% of elderly patients.[21] The use of second-generation tyrosine kinase inhibitors, potent inhibitors of the Ph^+-associated BCR-ABL tyrosine kinase, has now become a standard of practice for all patient groups with Ph^+ disease.[22-24] Results show that the combination of these agents with conventional chemotherapy improves remission rates as well as OS compared with the use of conventional chemotherapy alone.[22-24]

Currently, induction and consolidation regimens in adults are similar to pediatric regimens. Aggressive postinduction regimens are not as well tolerated in this population, particularly in patients older than 60 years, and are associated with a much higher incidence of toxicity and treatment-related deaths.[7] Some investigators are studying "moderate-dose" consolidation regimens that are better tolerated, although long-term efficacy data are lacking. Even though remissions are achieved in 80% to 90% of adult patients, 5-year DFSs are only in the 30% to 40% range. Among elderly patients, the outcome is even poorer with no more than 20% having long-term survival.

Relapsed ALL

Relapse is the recurrence of leukemic cells at any site after remission has been achieved. Leukemic blasts recurring after remission are much more drug resistant than the blasts at initial diagnosis. **KEY CONCEPT** Bone marrow relapse is the major form of treatment failure in 15% to 20% of patients with ALL. Most relapses have the same immunophenotype and cytogenetic changes seen in the original disease. Extramedullary sites of relapse include the CNS and the testicles. Extramedullary relapse, although once common, has decreased to 5% or less because of effective prophylaxis. Site of relapse and the length of the first remission are important predictors of second remission and OS. Marrow relapses occurring less than 18 to 24 months into first remission are associated with a poor survival, but longer periods of remission (more than 36 months) have a much higher chance of survival.[25] Treatment strategies for relapsed ALL include chemotherapy or allogeneic hematopoietic stem-cell transplant (allo-HSCT). Even though patients undergoing allo-HSCT are less likely to relapse, treatment-related toxicity leads to a high incidence of morbidity and mortality. Clofarabine, a next-generation deoxyadenosine analogue, has shown considerable activity in children and adults with refractory acute leukemias.[26,27] Blinatumomab, a MAB that targets CD19, is approved for Ph-negative relapsed or refractory ALL in adults and pediatric patients.[28] Inotuzumab ozogamicin is an antibody–drug conjugate composed of a humanized anti-CD22 MAB that is conjugated to the cytotoxic agent calicheamicin. It binds with high affinity to CD22 that is expressed in the majority of B-cell blasts in patients with B-cell ALL and is approved in B-cell precursor relapsed or refractory ALL.[29] Nelarabine is an antineoplastic agent that appears to bind preferentially to T cells and does show a significant response rate in patients with relapsed or refractory T-lineage ALL.[30] Tisagenlecleucel is an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy that has been shown to induce durable remissions in patients with relapsed and refractory B-cell ALL.[31] A significant toxicity of this treatment is cytokine release syndrome, and it is only offered at select centers with training in managing this toxicity.[31]

Treatment of AML

As with ALL, the primary aim in treating patients with AML is to induce remission and thereafter prevent relapse. Treatment of AML is divided into two phases: induction and consolidation. The prognosis of patients with AML varies dramatically and is dependent on age and performance status as well as risk stratification established by cytogenetic and molecular changes established at the time of diagnosis.[14] Those in good risk categories may have 3-year overall survival rate as high as 66% while those with high-risk features have a significantly higher risk of treatment failure.[14]

KEY CONCEPT The current induction therapy for AML usually consists of a combination of cytarabine and daunorubicin. The second phase of treatment for AML is called consolidation. The purpose of this phase is to further enhance remission with more cytoreduction.[14]

▶ *Remission Induction*

The goal of induction chemotherapy in AML is essentially identical to that in ALL—"empty" the bone marrow of all hematopoietic precursors and allow repopulation with normal cells. The combination of an anthracycline (eg, daunorubicin, doxorubicin, or idarubicin) and the antimetabolite cytarabine forms the backbone of AML induction therapy. The most common induction regimen (7 + 3) combines daunorubicin for 3 days with cytarabine on days 1 to 7.[14] The remission rate for this combination is approximately 60% to 80% adults with AML.[14] Adding gemtuzumab ozogamicin, an anti-33 MAB, to induction therapy for patients with favorable cytogenetics improves overall survival.[32] Midostaurin, an oral multitarget kinase inhibitor, is approved by the FDA for treatment of FLT3-positive AML. It is added on days 8 to 21 of the convention 7 + 3 induction chemotherapy and also on days 8 to 21 of high-dose cytarabine consolidation.[33] Liposomal daunorubicin and cytarabine is a treatment option for those with therapy-related AML, antecedent myelodysplastic syndrome, or de novo AML with myeloysplastic-related cytogenetic abnormalities.[34]

▶ *Postremission Chemotherapy*

In AML, postremission chemotherapy is often referred to as consolidation therapy. Several cycles of intensive postremission chemotherapy combining non–cross-resistant agents given every 4 to 6 weeks substantially improve DFS. Without postremission treatment, all patients would relapse within several weeks. This is analogous to the consolidation and other phases of postremission chemotherapy in ALL. The use of high-dose cytarabine in postremission therapy is a standard option with doses ranging from 1.5 to 3 g/m^2 for two to four cycles.[14]

Allogeneic Hematopoietic Stem Cell Transplantation Hematopoietic stem-cell transplantation (HSCT) is the most effective treatment for AML. Its promising benefit must be weighed against the potential risk of transplantation-related sequelae. HSCT in first remission is generally reserved for those with higher risk disease and shows no benefit in patients with good risk disease profile.[14]

The availability of human leukocyte antigen (HLA)-matched sibling donors determines whether patients undergo HSCT as postremission treatment. To facilitate this process, it is important to obtain HLA typing on all younger patients and siblings shortly after diagnosis. Patients who do not have an HLA-matched sibling proceed to postremission therapy with chemotherapy alone.

Complications and benefits of allogeneic HSCT are described in Chapter 98. Transplant-related mortality following matched-sibling allo-HSCT is 20% to 30% in most series. Complications from transplantation increase with age; therefore, patients older than 60 years of age rarely receive a myeloablative allo-HSCT. Because the average age of AML patients is 65 years, most patients with this disease are not candidates for this form of therapy. For older patients up to 70 years of age, a reduced-intensity (mini- or nonmyeloablative allogeneic) transplant may be an option. These transplants use less intensive preparative regimens and rely on the allogeneic graft-versus-leukemia (GVL) effect to eliminate their disease.[35]

The role of HSCT, particularly whether it should be performed during the first CR or reserved for second remission, remains a controversial issue in AML. HSCT is often reserved for patients who are considered high risk.[14] Some AML patients may be curable with conventional-dose chemotherapy alone.

Autologous Hematopoietic Stem Cell Transplantation Because many AML patients lack an HLA-identical donor, investigators began to consider the use of the patient's own bone marrow, obtained while in CR, as a source of hematopoietic regeneration. However, relapse continues to be a problem secondary to the presence of residual disease in the graft. Despite the reduced morbidity and mortality associated with auto-HSCT, this type of transplant does not compare favorably to standard postremission chemotherapy.[35]

▶ *CNS Therapy*

The prevalence of CNS disease at diagnosis of AML is approximately 15%. Features associated with the risk of CNS leukemia include hyperleukocytosis, monocytic, or myelomonocytic leukemia (FAB M4 or M5), and young age.[15] Adequate CNS prophylaxis is an essential component of therapy. Patients with CNS disease at diagnosis can be cured with IT therapy alone without the use of cranial XRT. In most cases, IT cytarabine with or without methotrexate and systemic high-dose cytarabine provide effective treatment.

AML in Infants

AML in infants younger than 12 months of age shows clinical and biological characteristics different from those of older children. The disease phenotype is more commonly monoblastic or myelomonoblastic (M4, M5), and the patients usually present with hyperleukocytosis. Extramedullary involvement is common, often involving skin and other organs. As in infant ALL, there is a high incidence of translocations involving the *MLL* gene in infant

AML. The number of infant AML trials reported is limited, but the EFS of this population is similar to that of older children with AML. This is in marked contrast to the outcomes for infants with ALL for whom the EFS is much lower than in older children.[36]

AML in the Elderly

AML is the most common acute leukemia in the elderly. Compared with younger patients with the same disease, older adults have a poor prognosis and represent a distinct population with regard to the biology of their disease. Older adults have a lower incidence of favorable chromosomal aberrations and a higher incidence of unfavorable aberrations.[14] Fms-like tyrosine kinase 3 (*FLT3*) that is an AML oncogene plays an important role in AML pathogenesis and was associated with a poor outcome. *FLT3*-ITD is common in adults but is only found in 12% of the pediatric population.[37] Older patients also have more comorbidities, such as type 2 diabetes, obesity, and other physiologic limitations. Thus, the poor prognosis of AML in this population is only partly the result of unfavorable biology.

In older adults, in contrast to children, AML is more likely to arise from a proximal bone marrow–stem cell disorder, such as MDS, or present as a secondary, prior treatment-related leukemia. These forms of AML are notoriously poorly responsive to conventional chemotherapy and, thus, have a lower CR rate and poorer survival.[25]

As previously noted, age is an important prognostic factor. Older adults are not as tolerant of or as responsive to remission induction and consolidation chemotherapy as younger patients. Furthermore, even in good-risk disease, long-term survival for patients older than 60 years is only 33% compared with 66% for younger adults.[14] Liposomal daunorubicin and cytarabine is a treatment option for older patients who have secondary AML.[34] BCL-2 inhibitor, venetoclax, has also shown efficacy and tolerability in combination with either of two hypomethylating agents, decitabine, or azacitidine.[38]

Relapsed AML

Even though 75% to 85% of patients with AML achieve a remission, only about 50% survive. Patients who relapse usually respond poorly to additional treatment and have a shorter duration of remission. This is probably related to drug resistance induced during induction and certain chromosomal abnormalities.

Even though there is no standard therapy for relapse, most studies have shown that high-dose cytarabine-containing regimens have considerable activity in obtaining a second remission. Cytarabine has been used in combination with mitoxantrone, etoposide, fludarabine, 2-chlorodeoxyadenosine, and clofarabine.[39,40] For patients unable to tolerate intensive chemotherapy, low-dose cytarabine and the hypomethylating agent, azacitidine, are also options for relapsed disease.[41] Venetoclax in combination with either decitabine or azacitidine is also an alternative in the relapsed setting.[42] There are also targeted agents that can be used in the relapsed setting if patients harbor the appropriate mutations. Gilteritinib is an FLT3 inhibitor approved for AML patients with an *FLT3-ITD* mutation in relapsed setting.[43] Enasidenib is an oral inhibitor of mutant *IDH2* proteins and is approved for use in patients with relapsed AML who harbor *IDH2* mutations.[44] Similarly, ivosidenib is an *IDH1* inhibitor that is approved for use in relapsed AML patients with an *IDH1* mutation.[45]

After a patient has achieved a second remission with conventional chemotherapy, allo-HSCT is the therapy of choice. For patients without an HLA-matched sibling, a matched unrelated donor (MUD) or cord blood transplant may be a reasonable alternative. The combination of myeloablative high-dose chemotherapy and the GVL effect is thought to offer the best chance of survival in AML.

Complications of Treatment

▶ *Tumor Lysis Syndrome*

Tumor lysis syndrome (TLS) is an oncologic emergency that is characterized by metabolic abnormalities resulting from the death of blast cells and the release of large amounts of purines, pyrimidines, and intracellular potassium and phosphorus. Uric acid, the ultimate breakdown product of purines, is poorly soluble in plasma and urine. Deposition of uric acid and calcium phosphate crystals in the renal tubules can lead to acute renal failure. Many patients with acute leukemia, especially those with a high tumor burden, are at risk for TLS during the first several days of chemotherapy. Measures to prevent TLS include aggressive hydration to increase urine output, and allopurinol to reduce uric acid production. However, on some occasions, the use of rasburicase is indicated. Rasburicase is a urate oxidase that catalyzes the oxidation of uric acid to allantoin, which is much more soluble than uric acid and excreted more easily. Rasburicase reduces the hyperuricemia that subsequently reduces the risk of acute renal failure and other clinical manifestations.[46] Given its high cost, rasburicase generally is restricted to patients with high WBC counts ($> 50 \times 10^3/\text{mm}^3$, $50 \times 10^9/\text{L}$) and uric acid levels greater than 8 mg/dL (476 μmol/L).

▶ *Infection*

Infection is a primary cause of death in acute leukemia patients. Both the disease and aggressive chemotherapy cause severe myelosuppression, placing the patient at risk for sepsis.

The therapy for AML is extremely myelosuppressive. Adults with AML have a 10% to 20% induction mortality rate secondary to infection and bleeding complications. Therefore, patients receiving induction therapy usually are hospitalized for the first 4 to 6 weeks of therapy.

It is important to recognize that symptoms and signs of infection may be absent in a severely immunosuppressed or neutropenic patient. Fever (higher than 38.3°C [100.9°F]) in a neutropenic patient is a medical emergency. Because the progression of infection in neutropenic patients can be rapid, empirical antibiotic therapy is started whenever a fever is documented. A commonly used initial antibiotic agent is cefepime, a fourth-generation cephalosporin that has good antipseudomonal coverage as well as adequate coverage against *Streptococcus viridans* and pneumococci.

Disseminated fungal infections most commonly caused by *Candida* and *Aspergillus* species can be life-threatening in patients with AML. Antifungal prophylaxis is standard in neutropenic AML patients and posaconazole is generally recommended.[47] Fluconazole and itraconazole are not considered ideal, because they are not effective against *Aspergillus* species and other molds.

Antibiotic prophylaxis with a fluoroquinolone antibiotic is recommended in AML patients during times of neutropenia.[47]

Antiviral prophylaxis with acyclovir, famciclovir, or valacyclovir is recommended in AML patients during times of neutropenia.[47]

▶ *Secondary Malignancies*

Secondary malignancies are a risk of the successful treatment of a prior cancer or the use of cytotoxic agents in a variety of autoimmune diseases. The chemotherapy agents used, especially alkylating agents and topoisomerase II inhibitors, predispose patients to secondary hematopoietic neoplasms. As the aggressiveness of treatment and the number of survivors of AML increase, the risk of secondary neoplasms also may rise. There are two different types of second malignancies: acute leukemia, which is generally myeloid in origin, or MDS. There are also reports of secondary solid tumors, especially within regions of prior radiation exposure. The latency period between the end of treatment and the development of a secondary leukemia is generally in the range of 5 to 10 years. For those patients who develop secondary solid malignancies, the latency may be as long as 10 to 20 years.

The incidence of second cancers attributed to alkylators peaks 4 to 6 years after exposure and plateaus after 10 to 15 years. Higher cumulative doses and older age at the time of treatment are risk factors for this type of cancer.

Epipodophyllotoxins (etoposide and others) can induce a second malignancy characterized by balanced chromosomal translocations and short latency periods (2–4 years). The risk of this leukemia is related to schedule (dose intensity) and the concomitant use of other agents (L-asparaginase, alkylating agents, and possibly antimetabolites). The prognosis for topoisomerase II inhibitor–related secondary leukemia is extremely poor. Only about 10% of these patients survive after salvage chemotherapy, and only 20% survive after HSCT.

Ionizing radiation therapy is also a cause of secondary malignancies. These secondary tumors generally develop within or adjacent to the previous radiation field. These cancers often have a prolonged latency, typically 15 or more years, but shorter latencies (5–14 years) are known. Higher doses of radiation and younger age are associated with an increased risk of secondary malignancy.[1]

Unlike children, adults may have other factors that predispose them to secondary malignancies. Lifestyle choices such as tobacco use, alcohol use, and diet are implicated in influencing the development of secondary neoplasms in the adult population.

Now that 80% or more of children survive their primary cancers, the incidence of secondary neoplasms may increase. Recognizing this potential, many treatment regimens for children are being modified appropriately to reduce exposure to alkylators, topoisomerase inhibitors, and radiation.[1] Children in long-term follow-up are screened for secondary malignancies and other disease and treatment-related disabilities that accompany childhood cancer. Similar screening and educational opportunities are not as established in adult survivors.

▶ *Late Effects*

With increased success in pediatric clinical trials, the OS rate for pediatric cancers has increased markedly over the last 40 years. For acute lymphoblastic leukemia, the OS rate is now about 90% in pediatrics.[5] **KEY CONCEPT** Despite this significant increase in survival, many patients, particularly pediatric cancer survivors, have disease- or treatment-related disabilities. As many as 50% to 60% of these survivors are estimated to have at least one chronic or late-occurring complication of treatment.[1] In leukemia, the intensified use of methotrexate may be responsible for some sporadic neurotoxicity seen in children and adults. Likewise, the use of pharmacologic doses of glucocorticoids has been associated with avascular necrosis of bone in older children and adults. Adjustments to glucocorticoid administration schedules can reduce the risk.[5] High cumulative doses of anthracyclines can cause irreversible cardiomyopathy. Cranial XRT is now less frequently used for CNS leukemia prophylaxis but can cause neuropsychological and neuroendocrine abnormalities that may lead to obesity, short stature, or precocious puberty.[1] As newer and more intensive treatments enter clinical trials, continued long-term follow-up of childhood ALL survivors is imperative to define the risks and develop strategies to decrease toxicity.[5]

Supportive Care

Because of the need for repeated venous access, a central venous catheter or infusion port is placed before starting treatment. These devices are useful not only for delivery of chemotherapy but also to support patients during periods of myelosuppression. Infection and bleeding complications are the primary causes of mortality in patients with leukemia.

Platelet transfusions are a common tool to prevent hemorrhage. Patients with uncomplicated thrombocytopenia can be transfused when the platelet count falls below $10 \times 10^3/\text{mm}^3$ ($10 \times 10^9/\text{L}$). Patients who are either highly febrile or actively bleeding may require transfusions at higher levels. Red blood cell transfusions generally are not necessary for a hemoglobin concentration greater than 8 g/dL (80 g/L, 4.97 mmol/L).

There is much controversy regarding the routine use of colony-stimulating factors (CSFs) (eg, granulocyte colony-stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]) in neutropenic patients. Even though several clinical trials have shown the time to ANC recovery is decreased with a CSF, none have demonstrated that CSFs statistically influence infection-related mortality. At present, the use of CSFs (G-CSF most commonly) generally is limited to those chemotherapy regimens that place the patient at highest risk for prolonged neutropenia.

OUTCOME EVALUATION

Developing strategies for the treatment and monitoring of acute leukemias begin with risk stratification. Understanding the likely risk of relapse determines the aggressiveness and length of therapy. Remission status and MRD after the induction phase of treatment must be closely observed. Failure to obtain morphologic bone marrow remission by day 28 is a very adverse prognostic sign and dictates further induction treatment. For those who have a morphologic remission, quantification of MRD has become an increasingly important prognostic factor. Levels of residual less than 0.01% appear to be associated with better outcomes.

A clinician is generally charged with developing a plan to educate patients and families about their drugs and doses. This is a critical responsibility; it is imperative that the patients and their families understand why they are receiving their medications and how to take them. Frank, open discussion (with the family or patient in possession of their prescriptions) goes a long way toward preventing errors that occur as a result of "assuming" that they understand their medications. If modifications are necessary secondary to toxicity or inadequate response, establish a plan for treatment change. Remember that individual patients often do not fit the "average" patient profile, and dose modifications are frequently needed. The practitioner should be familiar with dosing ranges, WBC count, and other parameters that indicate appropriate treatment response. Based on response to prior phases of treatment, the clinician should recognize potential toxicities in subsequent phases of treatment with the same or different drugs at similar or different doses.

Patient Care Process

Collect Information:

- Using the medical record collect the pertinent information on the presenting symptoms that made the patient seek out a healthcare provider.
- Perform a medication history, including over-the-counter and herbal medications.
- Confirmation of diagnosis including molecular and cytogenetic information from a bone marrow.
- Laboratory information, including CBC with differential, chemistry panel, disseminated intravascular coagulation (DIC) panel (D-dimer, fibrinogen, PT, and PTT), hepatitis, cytomegalovirus (CMV), and human immunodeficiency virus (HIV) status.
- Speak with patient, or patient's family in the instance of a pediatric patient, and assess patient or family's socioeconomic situation to evaluate ability to obtain prescription medications and/or resources for transplantation if necessary.

Assess the Information:

- Review patient's medication history prior to admission evaluating for indications and drug interactions including interactions with antifungals and oral chemotherapy.
- Review the patient's medical history looking for any medical condition that might predispose the patient to adverse effects from chemotherapy and supportive care medications, for example, look for a history of prolonged QT interval or heart failure.
- Speak to the patient about any risk factors that may predispose him to adverse effects.
- Ascertain the patient's understanding of the process for the treatment of acute leukemias and the need for compliance in prophylactic medications.

Develop a Care Plan:

- If patient has baseline hepatic, renal, cardiac issues, anticipate the need for dose modifications or changes in therapy.
- If there is a barrier to acquiring medications, develop a plan early in the patient's treatment to ensure that the patient can get the medications needed when discharged.
- Review and discuss the importance of being compliant with prophylactic medications with the patient or patient's family.
- Educate patient and patient's families about adverse effects of treatment for leukemia, and when it is necessary to call the cancer clinic or go to the emergency room.

Implement the Care Plan:

- When the patient is discharged from the hospital and seen at a clinic appointment, perform a medication history and reeducate about the importance of the medications and compliance.
- Evaluate new laboratory data to make sure all medications are dosed appropriately.
- Review medication list for drug interactions.
- Review side effect management with patient and patient's family, reeducating on need for home medications to treat side effects.
- Suggest nonpharmacological ways to minimize adverse effects.
- If patient is not tolerating or unable to manage adverse effects at home, work with providers to implement a new plan.

Follow-up: Monitor and Evaluate:

- At each clinic visit review medication list with patient.
- Check for drug interactions with all new medications.
- Review labs for changes in hepatic and renal function. Adjust dose or eliminate medication based on these results.
- Review effectiveness of symptom management plan with patient and patient's family.
- Reeducate as needed.

Abbreviations Introduced in This Chapter

ALL	Acute lymphocytic/lymphoblastic leukemia
allo-HSCT	Allogeneic hematopoietic stem cell transplant
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
ANLL	Acute nonlymphocytic leukemia
BFM	Berlin–Frankfurt–Munster
CCR	Continuous complete remission
CD	Cluster determinant
CR	Complete remission
CSF	Cerebrospinal fluid
CSF	Colony-stimulating factor
CMV	Cytomegalovirus
DFS	Disease-free survival
DIC	Disseminated intravascular coagulation
EFS	Event-free survival
FISH	Fluorescent in situ hybridization
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GVL	Graft-versus-leukemia
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem cell transplantation
ITD	Internal tandem duplication
MAB	Monoclonal antibody
MDS	Myelodysplastic syndrome
MRD	Minimal residual disease
MUD	Matched unrelated donor
OS	Overall survival
Ph^+	Philadelphia chromosome
TLS	Tumor lysis syndrome
XRT	Irradiation

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Chronic Leukemias and Multiple Myeloma

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the role of the Philadelphia chromosome in the pathophysiology of chronic myelogenous leukemia (CML).
2. Identify the clinical signs and symptoms and laboratory findings associated with CML, chronic lymphocytic leukemia (CLL), and multiple myeloma (MM).
3. Discuss first- and second-line treatment options for CML, including options for those patients with drug-resistant disease.
4. Describe the clinical course of CLL and distinguish which patients may be observed and who require treatment.
5. Compare the treatment options available for CLL, noting treatment differences based on the drug's toxicity profile.
6. Describe the clinical presentation and symptoms of MM.
7. Recommend the appropriate treatment for patients with MM, recognizing the importance of combination therapy and the role of autologous hematopoietic stem-cell transplant.

INTRODUCTION

Several diseases comprise chronic leukemia. The two most common forms are chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL). The slower progression of the disease contrasts it from acute leukemia, with the survival of chronic leukemia often lasting several years without treatment. There have been numerous treatment advancements in the area of targeted therapy for each of these cancers, resulting in an increase in survival.

CHRONIC MYELOGENOUS LEUKEMIA

CML is a hematologic cancer that results from an abnormal proliferation of an early myeloid progenitor cell. The clinical course of CML has three phases: chronic phase (CP-CML), accelerated phase (AP-CML), and blast phase/crisis (BP-CML), with 90% of patients diagnosed in chronic phase.[1] Criteria for these phases is largely based on the percent blasts in the peripheral blood or bone marrow. Blast crisis resembles acute leukemia, and immediate aggressive treatment is required.

EPIDEMIOLOGY AND ETIOLOGY

There were an estimated 9110 new cases of CML diagnosed in 2021, accounting for 14% of all adult leukemias.[2] The incidence of CML increases with age, with the median age of diagnosis being 65 years.[3] Prior to the advent of imatinib, the annual mortality was 10% to 20%. Today, with the use of tyrosine kinase inhibitors (TKIs), the annual mortality has decreased to 1% to 2%.[1] In most newly diagnosed cases, the etiology cannot be determined. High doses of ionizing radiation and exposure to solvents such as benzene are recognized as risk factors.

PATHOPHYSIOLOGY

Cell of Origin

CML arises from a defect in an early progenitor cell. The pluripotent (noncommitted) stem cell is implicated as the origin of the disease; therefore, multiple cell lineages of hematopoiesis may be affected, including myeloid, erythroid, megakaryoid, and (rarely) lymphoid lineages. These cells remain functional in CP-CML, which is why patients in chronic phase are at low risk for developing infections.

Ph Chromosome

KEY CONCEPT The Philadelphia chromosome (Ph) results from a translocation between chromosomes 9 and 22, leaving a shortened chromosome 22. The Ph results in the formation of an abnormal fusion gene between the breakpoint cluster region and the Abelson proto-oncogene (*BCR-ABL1*), which encodes an overly active tyrosine kinase. The loss of tyrosine kinase activity control causes abnormal cellular proliferation and inhibition of apoptosis.[1] The molecular tools, quantitative reverse transcriptase-polymerase chain reaction and fluorescence in situ hybridization are used in the detection and monitoring of *BCR-ABL1* transcripts found in CML.[4]

Clinical Presentation and Diagnosis of CML[5]

Signs and Symptoms

- ~50% are asymptomatic at diagnosis
- Symptoms may include fatigue, fever, weight loss, and bleeding
- Organomegaly consisting of splenomegaly and hepatomegaly

Diagnostic Procedures

- Peripheral blood
- Bone marrow biopsy (percentage of blasts)
- Cytogenetic studies (presence of Ph and additional chromosomal abnormalities)
- Molecular testing (qPCR to detect *BCR-ABL1* transcripts as reported by International Scale (IS))

Laboratory Findings

- Peripheral blood
  - Leukocytosis (most present with WBC count > 100 × 10^9/L [100 × 10^3/mm^3])
  - Thrombocytosis (˜50% of patients in chronic phase)
  - Anemia
  - Basophilia
  - Presence of blasts
  - Elevated uric acid
- Bone marrow
  - Hypercellularity with the presence of blasts
  - Cytogenetics including the presence of Ph

Poor Prognostic Factors

- Older age
- Splenomegaly
- High percent blasts in the blood (ie, AP- or BP-CML at time of diagnosis)
- Abnormal platelet count (high or low)
- Additional chromosomal abnormalities (i.e., clonal evolution)

TREATMENT

Desired Outcome

The primary goal in the treatment of CML is to achieve long-term disease control with TKI therapy and possibly treatment-free remission (TFR). A deep, long-lasting molecular response is associated with long-term disease control and achievable for many patients with CP-CML through TKI therapy.[6] Most recently, TFR (i.e. TKI discontinuation) has emerged as a goal for select patients who sustain a deep molecular response while on a TKI. Treatment goals and disease progression are determined and assessed through the molecular monitoring of *BCR-ABL1* transcripts. A complete molecular response is defined as undetectable *BCR-ABL1* transcripts by the International Scale (IS).[5] International standardization of molecular response reflects a percentage of *BCR-ABL1* compared to standardized baseline.[4] Approximately 50% to 70% of patients with CML will achieve a major molecular response (<0.1% *BCR-ABL1* [IS]) and another 10% to 20% will achieve an even deeper molecular response.[6] Additional goals include achieving a complete hematologic and cytogenetic response. A complete hematologic response is defined as a normalization of peripheral blood counts and complete cytogenetic response being the elimination of Ph+ metaphases.[3] A cure from CML can only come from complete eradication of the Ph clone.

General Approach to Treatment

There have been significant advances in the treatment of CML since the discovery of the Ph in 1960. The success of therapy is largely dependent on patient adherence and the clinical phase of the disease. Treatment decisions are based on the patient age, phase of CML, and comorbidities. The National Comprehensive Cancer Network (NCCN) provides recommendations on the therapeutic treatment approach for CML.[5] Nearly all patients with CML are initially treated with a TKI. Depending on the clinical phase and *BCR-ABL* mutation profile, newer generation TKIs or omacetaxine may be options for patients who fail to respond or do not tolerate initial TKI therapy. Hydroxyurea may be used after diagnosis to rapidly reduce high white blood cell (WBC) counts and prevent potentially serious complications (respiratory and neurologic) associated with large numbers of circulating neutrophils. Hydroxyurea, though, does not alter the disease process. TKIs can also reduce peripheral WBC counts over several weeks; therefore, many patients are started on a TKI alone. Allogeneic hematopoietic stem-cell transplant (HSCT) is reserved for patients with TKI resistance. Figure 97–1 illustrates one approach for clinically managing newly diagnosed patients with CP-CML.

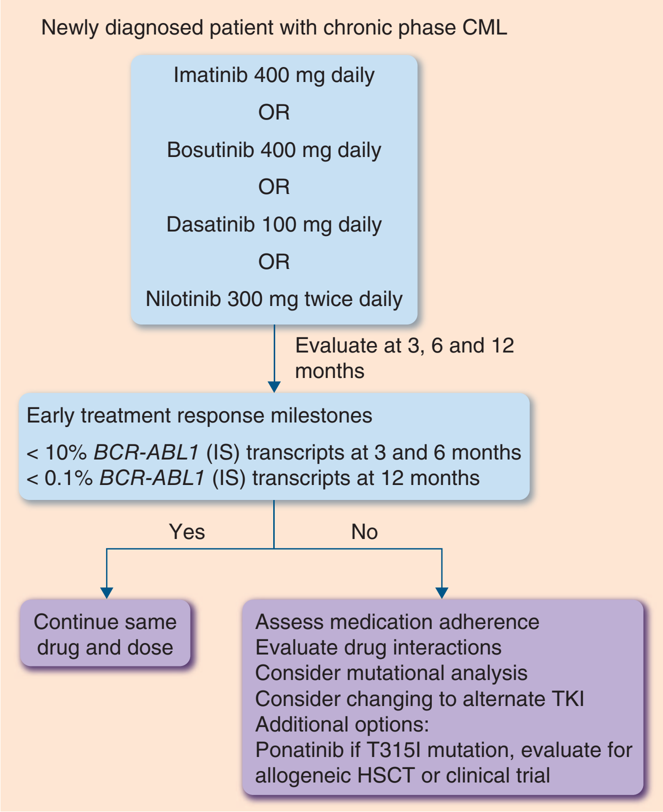
Newly diagnosed patient with chronic phase CML
Imatinib 400 mg daily
OR
Bosutinib 400 mg daily
OR
Dasatinib 100 mg daily
OR
Nilotinib 300 mg twice daily
Evaluate at 3, 6 and 12 months
Early treatment response milestones
< 10% BCR-ABL1 (IS) transcripts at 3 and 6 months
< 0.1% BCR-ABL1 (IS) transcripts at 12 months
Yes
No
Continue same drug and dose
Assess medication adherence
Evaluate drug interactions
Consider mutational analysis
Consider changing to alternate TKI
Additional options:
Ponatinib if T315I mutation, evaluate for allogeneic HSCT or clinical trial

FIGURE 97–1. Algorithm for TKI therapy in newly diagnosed patient with CP-CML. (Data from NCCN.)

Nonpharmacologic Therapy

▶ *Hematopoietic Stem-Cell Transplantation*

Allogeneic HSCT is the only curative treatment option for CML; however, the impressive outcomes with TKIs have limited the role of transplant. Allogeneic HSCT may be considered for the rare patient with *BCR-ABL* mutations that are resistant to or who fail TKI therapy. Transplant should also be considered for patients who present in BP-CML.[5] There are significant risks and long-term complications with allogeneic HSCT, including early mortality and graft-versus-host disease. For patients who do not achieve a complete molecular response or have disease relapse following allogeneic HSCT, the infusion of donor lymphocytes may place the patient back into a durable remission.[5]

Pharmacologic Therapy

The treatment of CML has dramatically changed since the introduction of *BCR-ABL1* TKIs. **KEY CONCEPT** Nearly all patients with CML are initially treated with a TKI. These oral agents do not cure CML but produce long-term disease control in the vast majority of patients. Four TKIs (imatinib, bosutinib, dasatinib, and nilotinib) may be used as first-line therapy for newly diagnosed CP-CML.[5] Many patients will require life-long use of TKIs. However, there is a growing body of evidence supporting the discontinuation of TKI therapy in select patients who have experienced stable molecular response for greater than 2 years (TFR).[7]

▶ *Imatinib mesylate (Gleevec)*

Imatinib mesylate (Gleevec) is a first-generation TKI and was the first TKI to show efficacy in the treatment of CML. Imatinib inhibits the phosphorylation of various proteins involved in cell proliferation by binding to the adenosine triphosphate–binding pocket of *BCR-ABL1*. The almost 11-year follow-up data shows that the use of imatinib in CP-CML results in an estimated overall survival (OS) of 83.3%, a complete cytogenetic response of 82.8%, and an estimated event-free survival of 79.6%.[8] Lower response rates are reported in accelerated phase and BP-CML.[1] However, only 48% of patients assigned to imatinib in the initial study remained on imatinib after 10 years. This was a lower percentage than expected, leading to concerns with imatinib failure/resistance (see TKI resistance) and intolerance.[8] Imatinib is generally well tolerated. Common side effects include myelosuppression, gastrointestinal disturbances, and myalgias. Dosing and additional adverse effects may be found in Table 97–1.

▶ *Advanced-Generation TKIs*

Imatinib resistance resulted in the need for advanced generation TKIs that could overcome specific mutations. Dasatinib (Sprycel), nilotinib (Tasigna), bosutinib (Bosulif), and ponatinib (Iclusig) are advanced generation TKIs that may overcome imatinib resistance or intolerance. These inhibitors are more potent than imatinib in inhibiting *BCR-ABL1*, with reports of dasatinib being 350 times and ponatinib being 520 times more potent.[1,9] The advanced generation TKIs can overcome most *BCR-ABL1* mutations. However, of the four, only ponatinib can overcome the *T315I* mutation.[5]

Bosutinib, dasatinib, and nilotinib are indicated for first-line therapy in CP-CML. Studies suggest bosutinib, dasatinib, and nilotinib are superior to imatinib in achieving faster and deeper cytogenetic and molecular responses.[10-12] Fewer patients progress to accelerated or blast phase on bosutinib, dasatinib, or nilotinib compared to imatinib, although there are no differences in OS reported between the agents. These TKIs are also generally well tolerated. Common side effects are similar to those of imatinib and may be found in Table 97–1. A significant and potentially severe side effect associated with the use of dasatinib is the development of pleural effusions. Concerning side effects of nilotinib include QT prolongation, requiring an electrocardiogram at baseline and 7 days after initiating therapy, and increases in indirect bilirubin.[5] These side effects are typically managed by treatment interruptions and/or selection of a different TKI.[8] Clinicians should be mindful of potential drug–drug interactions, since all TKIs are metabolized by cytochrome P450 3A4.[1]

Ponatinib is a third-generation multikinase inhibitor that overcomes the *BCR-ABL* domain mutation *T315I*. Ponatinib was initially approved for the treatment of patients in all phases of CML that were resistant or intolerant to prior TKI therapy. In postmarketing analysis, an increase in serious arterial thrombotic events was shown in 24% of patients.[5,9] The revised label restricts the use of ponatinib to patients harboring the *T315I* mutation or that have failed multiple prior TKIs. Arterial occlusive events are a boxed warning. Other, serious adverse effects include heart failure and liver failure.

▶ *Omacetaxine Mepesuccinate*

Omacetaxine mepesuccinate (Synribo) is a semisynthetic formulation of homoharringtonine. Omacetaxine reversibly inhibits protein synthesis, thereby causing cell death.[13] Unlike TKIs, the mechanism of action affects both normal and malignant hematopoietic cells. Omacetaxine is a subcutaneous injection indicated for patients in CP- or AP-CML who are resistant or intolerant to two or more TKIs.[5] It may also be used in patients with the *T315I* mutation. Nonhematologic adverse reactions may be found in Table 97–1. Clinicians should note omacetaxine may cause hyperglycemia that requires monitoring, which is particularly important in patients with diabetes.

▶ *TKI Resistance*

CML disease progression is typically attributed to primary or secondary TKI resistance. A common mechanism of resistance involves point mutations in the *BCR-ABL1* kinase domain. Some of these mutations are associated with poorer prognosis.[5] The *ABL* kinase mutation *T315I* is one mechanism of secondary resistance that results in reactivation of *BCR-ABL1* activity. The *T315I* mutation renders imatinib and the second-generation TKIs ineffective; therefore, alternative therapy with agents that overcome this mutation (ie, ponatinib) must be selected.[4] *BCR-ABL1* mutational analysis is recommended for any patient who does not achieve the desired response outcomes and milestones. The NCCN Guidelines can assist clinicians with selecting the most appropriate TKI based on mutational analysis.[5]

OUTCOME EVALUATION

Successful treatment for CML depends on an optimal response to TKI therapy (eg, hematologic, cytogenetic, and molecular). Nearly all newly diagnosed CP-CML patients will be placed on a TKI and will remain on TKI therapy for an indefinite amount of time. First-line treatment options include imatinib, bosutinib, dasatinib, and nilotinib. Which agent to use depends on several factors, including disease risk score, age, comorbid conditions, medication safety profile, and financial accessibility. Patients should be

Table 97–1

Drugs Used in CML

Drug	Adverse Effects	Comments	Renal Dosing	Hepatic Dosing
Bosutinib (Bosulif)	Diarrhea, nausea vomiting, thrombocytopenia, neutropenia, increased liver function tests, fluid retention	Dose: 400–500 mg po once daily depending on phase Dose may be increased to 600 mg po once daily if complete hematologic response not seen at 8 weeks or complete cytogenetic response by 12 week Take with food Drug interactions: metabolized by CYP 3A4; inhibitor and substrate of P-glycoprotein	CrCl 30–50 mL/min (0.50–0.83 mL/s): 500 mg daily and may decrease to 400 mg if cannot tolerate CrCl < 30 mL/min (0.50 mL/s): 300 mg daily	Any baseline liver impairment: 200 mg daily
Dasatinib (Sprycel)	Thrombocytopenia, neutropenia, headache, rash, edema, pleural effusions	Dose: 100 mg po once daily for chronic phase CML or 140 mg po daily for accelerated phase or blast crisis Avoid concomitant medications that prolong the QT-interval; low levels of potassium and magnesium should be corrected before initiating therapy Drug interactions: metabolized by CYP 3A4 Dasatinib exhibits pH-dependent absorption; avoid medications that alter gastric pH (eg, H_2 antagonists and PPIs)	No reductions	No reductions
Imatinib mesylate (Gleevec)	Neutropenia, thrombocytopenia, diarrhea, rash, nausea, edema, fatigue, arthralgias, myalgias, headache, increased liver function tests, congestive heart failure (rare)	Dose range: 400–800 mg po per day depending on phase Take with meals and a full glass of water Drug interactions: metabolized by CYP 3A4; weak inhibitor of CYP 2D6 and 2C9 Avoid taking with acetaminophen to reduce hepatic toxicity Diarrhea usually responds to loperamide	CrCl 20–39 mL/min (0.33–0.66 mL/s): 50% reduction in dose CrCl < 20 mL/min (0.33 mL/s): use with caution	Mild to moderate impairment: no adjustment Severe impairment: reduce dose by 25% Discontinue imatinib if liver transaminases are > 5 × upper limit of normal or if serum bilirubin > 3 × upper limit of normal
Nilotinib (Tasigna)	Thrombocytopenia, neutropenia, elevated bilirubin, elevated serum lipase	Dose: 400 mg po twice daily Take on an empty stomach Black-box warning for QT prolongation; avoid concomitant medications that prolong the QT interval; low levels of potassium and magnesium should be corrected before initiating therapy Drug interactions: metabolized by CYP 3A4; competitive inhibitor of CYP 2C8, 2C9, 2D6, and UGT1A1 Pharmacogenomic testing of UGT1A1 polymorphisms can be used to identify patients who may have hyperbilirubinemia	No reductions	Child-Pugh class A, B, or C: 200 mg po twice daily for chronic phase CML; may increase to 300 mg if tolerating nilotinib therapy; discontinue nilotinib if experiencing grade 3 or 4 elevations in bilirubin or liver transaminases
Omacetaxine mepesuccinate (Synribo)	Myelosuppression, hyperglycemia	Dose: 1.25 mg/m^2 subcutaneous injection twice daily × 14 days, repeat every 28 days until hematologic response achieved Maintenance therapy: 1.25 mg/m^2 subcutaneous injection twice daily × 7 days every 28-day cycle Drug interactions: P-glycoprotein substrate	No reductions	No reductions
Ponatinib (Iclusig)	Arterial and venous thromboembolisms, hepatotoxicity, congestive heart failure, pancreatitis, gastrointestinal bleeding, fluid retention, myelosuppression, fatigue, headaches	Dose: 45 mg daily Boxed warnings for arterial occlusive events. Monitor CBC, lipase and liver function tests Drug interactions: metabolized by CYP 3A4,2C8, 2D6 competitive inhibitor of P-glycoprotein	No reductions	Child-Pugh class A, B, or C: 30 mg daily Hold ponatinib if liver transaminases are > 3 × upper limit of normal May resume but reduce dose when < 3 × upper limit of normal

CML, chronic myeloid leukemia; CrCl, creatinine clearance; po, oral; PPI, proton pump inhibitor.

Patient Encounter 1

A 38-year-old Hispanic woman presents to her primary care physician with complaints of "feeling tired over the past couple months" and "occasional abdominal pain". Her medical history consists of poorly controlled type 2 diabetes. Her A1C is 10.8% despite treatment on metformin 1 g twice daily and 30 units of glargine (weight: 100 kg). She also takes OTC omeprazole for GERD. A CBC is drawn and shows the following:

Total WBC: 104 × 10^9/L (104 × 10^3/mm^3) (5% [0.05] blasts, 75% [0.75] segs, 20% [0.20] lymphs)

Hgb/Hct: 7.7 g/dL (97 g/L; 6.014 mmol/L)/29% (0.29)

Platelets: 510 × 10^9/L (190 × 10^3/mm^3)

The patient is referred to an oncologist for further workup. A bone marrow biopsy is performed and reveals hypercellular marrow with 5% (0.05) blasts. Cytogenetics are positive for t(9:22).

What information is suggestive of CP-CML?

Which specific treatment do you recommend for initial treatment and why?

Identify your treatment goals for this patient.

What drug information and patient counseling will you provide to the patient?

Identify factors that may contribute to this patient having a suboptimal response.

Assuming this patient has a suboptimal response to your initial therapy, what would you recommend for second-line therapy?

counseled on the importance of medication adherence. Patients should understand that poorer outcomes may result if they are not adherent to daily TKI therapy. The NCCN guidelines provide response criteria.[5] Molecular responses at 3, 6, and 12 months are assessed, as the milestones are associated with improved progression-free survival (PFS) and OS. Patients failing to achieve these milestones should undergo *BCR-ABL1* domain mutation testing to determine TKI resistance and be evaluated for medication adherence and possible drug interactions. Second-line CP-CML therapy should be selected based on mutational analysis with second-generation TKIs utilized. These drugs may also be used in patients who have AP-CML. Ponatinib may be considered if the *T315I* mutational status is present with an understanding that it is associated with serious vascular effects. Omacetaxine, allogeneic stem-cell transplantation, and clinical trials are options for those patients that do not respond to or tolerate a TKI. Some patients will not respond to treatment and will progress to BP-CML where they will receive treatment for acute leukemia. Although its use is limited, allogeneic transplant offers the only cure for CML and may be useful in patients with advanced disease who have failed other options.

CHRONIC LYMPHOCYTIC LEUKEMIA

EPIDEMIOLOGY AND ETIOLOGY

CLL is the most common type of leukemia diagnosed in adults, accounting for 30% of all adult leukemias. It was estimated that in 2021, 21,250 new cases will be diagnosed in the United States.[2] The median age at diagnosis is 70 years with the incidence increasing with age.[14] The etiology of CLL is unknown, but hereditary factors may have a role. First-degree family members of CLL patients have up to an 8.5-fold increased risk of CLL.[15]

PATHOPHYSIOLOGY

Cell of Origin

CLL is characterized by small, relatively mature, yet incompetent B lymphocytes that accumulate in the blood and bone marrow over time. While the exact cell of origin remains controversial, early genetic abnormalities that impair apoptosis appear to be involved in the transformation to malignancy.[16] The lack of apoptotic mechanisms, including B-cell lymphoma 2 (BCL-2) overexpression, leads to the persistence and accumulation of B lymphocytes. Chromosomal abnormalities, such as deletions of the long arm of chromosome 13 or 11 (del(13q) or del(11q)), are

Clinical Presentation and Diagnosis of CLL

Signs and Symptoms (~50% Are Asymptomatic at Diagnosis)

- Lymphadenopathy
- Organomegaly consisting of splenomegaly and hepatomegaly
- Fatigue, weight loss, night sweats, fevers
- Chronic infections caused by immature lymphocytes

Diagnostic Procedures

- Peripheral blood smear
- Bone marrow biopsy
- Cytogenetic studies
- Molecular testing

Laboratory Findings[18]

- Peripheral blood
  - Lymphocytosis (absolute lymph count > 5 × 10^9/L [5 × 10^3/mm^3]) sustained for 3 months—required for diagnosis
  - Leukocytosis (WBC count > 100 × 10^9/L [100 × 10^3/mm^3])
  - Anemia
  - Thrombocytopenia
  - **Hypogammaglobulinemia**
- Bone marrow
  - Hypercellular with increased mature lymphocytes
- Molecular markers
  - Cytogenetic abnormalities in >80% of patients

Poor Prognostic Factors

- Lymphocytosis with accompanying:
  - Anemia (hemoglobin ≤ 11.0 g/dL [110 g/L; 6.83 mmol/L])
  - Thrombocytopenia (platelets < 100 × 10^9/L [100 × 10^3/mm^3])
  - Higher percentage of **ZAP-70**, CD49d, and CD38 antigen expression
  - Cytogenetics such as deletions of chromosomes 17p and 11q, *TP53* mutations, and unmutated *IgVH*

frequently observed in most cases of CLL and additional mutations often correlate with progressive disease.[16] Numerous kinases appear to be involved in CLL, including the activation of Bruton tyrosine kinase (BTK) and phosphoinositide 3-kinase (PI3K) delta.[17] Detection of these markers may predict clinical course and prognosis and may influence treatment decisions.

Clinical Course

CLL can have a variable clinical course with survival ranging from months to decades. Patients are classified as low, intermediate, or high risk. Approximately 90% of patients are diagnosed with asymptomatic, low-risk CLL, where the median survival times exceed 10 years.[19] The typical low-risk patient is an asymptomatic elderly patient who is diagnosed on routine blood draw. Intermediate risk is associated with lymphadenopathy and has median survival times of about 7 years. High-risk patients with anemia have median survival times of only 2 years.[20] The typical high-risk patient is a symptomatic middle-aged patient. Some patients with slightly elevated B lymphocytes may not meet the diagnostic criteria for CLL and may be diagnosed with monoclonal B-lymphocytosis (MBL). Observation is recommended for MBL instead of treatment. The progression from MBL to CLL/small lymphocytic lymphoma is between 1% and 2% per year.[21] The International Workshop on Chronic Lymphocytic Leukemia (iwCLL) has published consensus guidelines that can assist clinicians with diagnosis, indications for treatment, and response assessment.[18]

STAGING AND PROGNOSTIC FACTORS

Two staging systems, Rai and Binet, have been developed to help practitioners determine the overall prognosis of patients with CLL. They are comparable systems and useful to broadly determine good, intermediate, and poor prognostic disease.[20] Risk stratification includes both physical criteria such as lymphadenopathy, splenomegaly, and hepatomegaly, and cytopenias. Increasingly, biological markers of the disease such as deletion of chromosome 17p (del(17p)), del(11q), and mutational status of immunoglobulin heavy chain variable region gene (*IgVH*) are used to predict the likely clinical course.[20,26] These biological markers are not included in the Rai or Binet staging systems. Additionally, elevated levels of serum beta-2 microglobulin and lactate dehydrogenase are important prognostic indicators for survival.[19] Patients with del(17p) or *TP53* mutations tend to have a poor response to therapy.

TREATMENT

Desired Outcomes

The primary goals in the treatment of CLL are to provide palliation of symptoms and achieve a long-term remission. Oral kinase inhibitors have become the backbone of therapy. These drugs are continued until disease progression or unacceptable toxicity. Because the current treatments for CLL are not curative for most patients, reduction in tumor burden and improvement in disease symptoms are reasonable end points, particularly in older patients. A complete response (CR) to therapy can be defined as a resolution of lymphadenopathy and organomegaly, normalization of peripheral blood counts, and elimination of lymphoblasts in the bone marrow.

Nonpharmacologic Therapy

KEY CONCEPT Asymptomatic early-stage CLL can be observed without treatment until evidence of disease progression.[18] Past studies with chlorambucil suggest that chemotherapy does not improve OS in early-stage CLL, although there is question whether this remains true with the development of newer therapies. In addition, deferring therapy until a patient becomes symptomatic does not alter OS.[18] For this reason, the notion of "watch and wait" is considered reasonable for older patients with low risk disease. Several factors will influence this approach, including life expectancy, disease characteristics, and ability to tolerate therapy.[20]

▶ *Hematopoietic Stem-Cell Transplantation*

The use of HSCT in CLL is limited. Allogeneic HSCT offers longer disease-free remissions in patients with poor prognosis than autologous HSCT but is associated with higher treatment morbidity and mortality. Several factors must be considered before pursuing allogeneic HSCT. The lack of a donor, older age, and poor performance status make transplantation an uncommon procedure in these patient populations. Allogeneic HSCT remains an option for younger patients with aggressive disease who have failed prior therapies, including small molecule inhibitor therapy.[20]

Pharmacologic Therapy

The treatment options for CLL have significantly expanded in the past decade, improving patient outcomes. Oral small molecule inhibitor therapy (eg, ibrutinib, venetoclax) has established a pivotal role in the front-line treatment of symptomatic CLL. This has minimized the use of traditional chemotherapy-based regimens (eg, purine analogs and alkylating agents). Monoclonal antibodies targeting CD20 antigen may also be incorporated into front-line therapy. The NCCN guidelines provide recommendations on first-line and subsequent CLL therapies based on mutational status, age, and whether comorbidities are present.[20]

Figure 97–2 illustrates one approach for initial therapy in newly diagnosed patients with CLL.

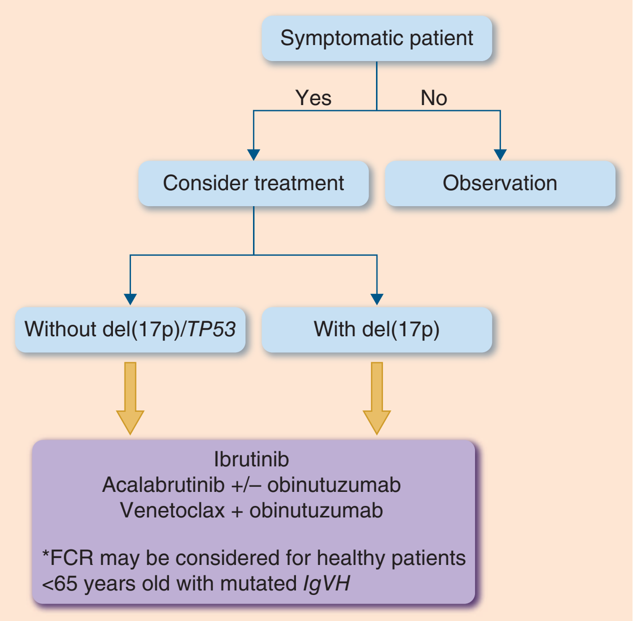
Symptomatic patient
Yes
No
Consider treatment
Observation
Without del(17p)/*TP53*
With del(17p)
Ibrutinib
Acalabrutinib +/– obinutuzumab
Venetoclax + obinutuzumab
*FCR may be considered for healthy patients <65 years old with mutated *IgVH*

FIGURE 97–2. Possible treatment approach for first-line therapy in newly diagnosed CLL patients. (B, bendamustine; C, cyclophosphamide; F, fludarabine; R, rituximab.) (Data from NCCN.)

▶ *Cytotoxic Chemotherapy*

Prior to the development of targeted therapy, cytotoxic chemotherapy was the mainstay for the treatment of CLL. Patients would receive either a higher or lower intensity regimen based on age, comorbidities, and their ability to tolerate the selected chemotherapy regimen. Regimens incorporating the purine analog fludarabine (Fludara) and the alkylating agents, chlorambucil (Leukeran) or cyclophosphamide (Cytoxan), were routinely used. Today, the treatment for CLL has changed with the development of newer agents. Numerous trials have shown a survival benefit with the newer agents, resulting in declined use of traditional chemotherapy.[22] However, NCCN still recommends fludarabine, cyclophosphamide, and rituximab (FCR) as the preferred regimen for younger (< 65 years old) patients with *IgVH*-mutated CLL.[20] *IgVH*-mutated CLL has a better prognosis than *IgVH*-unmutated CLL.[19] The aggressive use of FCR may offer a potential cure for these select patients. Fludarabine is associated with myelosuppression and prolonged immunosuppression. Clinicians should consider antibacterial and antiviral prophylaxis for *Pneumocystis* and herpes virus when using fludarabine-based therapy.[20]

▶ *Monoclonal Antibodies*

Anti-CD20 monoclonal antibodies are widely used in the treatment of CLL. Like most other B-cell malignancies, CLL expresses CD20 antigens. The exact function of CD20 isn't clear but CD20 appears to be involved in B-cell receptor signaling and expansion of the CLL clone.[17] Several anti-CD20 monoclonal antibodies are used in the treatment of CLL. Rituximab (Rituxan), a naked chimeric anti-CD20 monoclonal antibody, was the first approved for the treatment of CLL. Rituximab has been largely replaced by the next-generation monoclonal antibodies, obinutuzumab (Gazyva), and ofatumumab (Arzerra). The mechanism of action is complex and includes activation of complement-dependent cytotoxicity, triggering of antibody-dependent cell-mediated cytotoxicity, and direct toxicity, depending on the drug.[23] Obinutuzumab is different than the other anti-CD20 monoclonal antibodies, having a higher binding affinity to the CD20 epitope and causing direct cell death.[23] The anti-CD20 monoclonal antibodies are often used in combination with targeted therapy or chemotherapy. They are less frequently used as a monotherapy. The selection and combination of the monoclonal antibody depends on clinical studies.

The most common side effects for monoclonal antibodies include infusion reactions consisting of fever, chills, hypotension, nausea, vomiting, and headache. Premedication with diphenhydramine and acetaminophen is recommended to minimize infusion reactions. Reactivation of hepatitis B virus (HBV) is also a concern for patients on anti-CD20 therapy. Patients should be tested for hepatitis B surface antigen and hepatitis B core antibody prior to starting therapy. Prophylactic hepatitis B antiviral therapy or treatment with entecavir may be warranted. Clinicians should continue to monitor hepatitis B viral load throughout treatment, recognizing that HBV prophylaxis should be continued up to 1 year after treatment ends.[20] Table 97–2 lists additional adverse effects seen with the anti-CD20 monoclonal antibodies.

▶ *Small Molecule Inhibitors*

KEY CONCEPT An understanding of the B-cell receptor signaling pathways of CLL has led to the approval of numerous novel oral targeted therapies. Many of these therapies have had impressive results and improved the median OS of CLL.

Ibrutinib (Imbruvica) has transformed the treatment of CLL. Ibrutinib is an inhibitor of BTK, an essential enzyme in the B-cell receptor pathway. Inhibition of BTK prevents the activation of additional downstream pathways involving other kinases, including phosphatidylinositol-3-kinase (PI3-K) and nuclear factor-kappa B. These pathways are involved in cellular survival and proliferation. Ibrutinib was originally studied as a single agent in patients with relapsed CLL reporting an overall response rate of 71%, an impressive percentage for this subset of patients. Ibrutinib's indications have expanded to first-line therapy and is the preferred treatment for most patients with CLL, including patients with or without del(17p), regardless of age.[20] Ibrutinib is used as monotherapy as the addition of rituximab to ibrutinib did not improve PFS compared to ibrutinib alone.[22] Clinicians should be aware that most patients on ibrutinib experience a transient increase in absolute lymphocyte count. The lymphocytosis will persist for several weeks and then subside. Continuation of therapy is warranted and does not suggest disease progression.[17,20] An increased risk of atrial fibrillation has been also associated with ibrutinib. Additional adverse effects may be found in Table 97–2.

Acalabrutinib (Calquence) is a second-generation BTK inhibitor approved for the treatment of patients with CLL. Acalabrutinib has a higher BTK selectivity than ibrutinib which has led to promising results.[16] The indications are similar to ibrutinib with acalabrutinib being used with or without obinutuzumab for first-line therapy of CLL and in relapsed and refractory CLL. There is an ongoing head-to-head clinical trial of ibrutinib to acalabrutinib which will provide insight into the efficacy and toxicity differences.

The recognition of PI3-K's involvement in the pathogenesis of CLL has led to the development of PI3-K inhibitors. Idelalisib (Zydelig) and duvelisib (Copiktra) are oral inhibitors of PI3-K. Idelalisib has been studied as monotherapy as well as combination therapy with rituximab. Both idelalisib and duvelisib may be used for patients with relapsed/refractory CLL.[20] Boxs warnings for idelalisib and duvelisib include hepatotoxicity, for idelalisib and colitis, infestion, cutaneous reactions and pneumonitis for duvelisib.[16] Patients should receive *Pneumocystis* pneumonia prophylaxis and CMV antiviral prophylaxis should also be considered to prevent CML infection and reactivation.[20] Like the BTK inhibitors, patients may experience a transient increase in absolute lymphocyte count and continuation of therapy is warranted. Nonhematologic side effects for both drugs may be found in Table 97–2.

BCL-2 is an antiapoptotic protein overexpressed in patients with CLL.[17] Venetoclax (Venclexta) is an oral small molecular inhibitor that targets BCL-2 and may be used as first-line therapy or in relapsed/refractory CLL.[23,24] Venetoclax is used in combination with anti-CD20 monoclonal antibodies. Research continues to explore venetoclax-combination therapy and the most efficacious sequencing with BTK inhibitors. Adverse effects for venetoclax include tumor lysis syndrome, in which prophylaxis with allopurinol or rasburicase and oral hydration is recommended, and prolonged neutropenia, which may require growth factor support.[20]

OUTCOME EVALUATION

Successful outcomes depend on the appropriate treatment selection for a specific patient. Risk-versus-benefit should be determined in the treatment of older CLL patients. Because CLL is incurable, "watch and wait" is a reasonable approach for those with indolent, asymptomatic disease. Treatment can begin when the patient becomes symptomatic. Ibrutinib is the first-line

Table 97–2

Drugs Used in CLL

Drug	Adverse Effects	Comments	Renal Dosing	Hepatic Dosing
Acalabrutinib (Calquence)	Opportunistic infections, hemorrhage, cytopenias, secondary malignancy, atrial fibrillation (grade 3 in 1.1%)	Dose: 100 mg po twice daily Avoid concomitant use with CYP 3A4 inhibitors/inducers Avoid administering with PPI	No reductions	Avoid in severe hepatic dysfunction
Duvelisib (Copiktra)	Boxed warnings: Serious and fatal infections, diarrhea, colitis, cutaneous reactions, pneumonitis	Dose: 25 mg po twice daily Avoid concomitant use with CYP 3A4 inducers. Reduce dose when administered with strong CYP 3A4 inhibitors	No reductions	No reductions
Fludarabine (Fludara)	Myelosuppression; prolonged immunosuppression, resulting in secondary infectious complications; edema; neurotoxicity	Dose: 20 mg/m^2 IV daily for 5 days Often given in combination	CrCl 30–70 mL/min (0.50–1.17 mL/s): 20% reduction of dose (IV and po) CrCl < 30 mL/min (0.50 mL/s): do not use IV; reduce dose of oral by 50%	No reductions
Ibrutinib (Imbruvica)	Opportunistic infections, hemorrhage, cytopenias, secondary malignancy, atrial fibrillation (grade 3 in 4%), hypertension, TLS	Dose: 420 mg po once daily Avoid the use of concomitant CYP 3A4 inhibitors/inducers Drug metabolism: CYP 3A4 and 2D6	No reductions in CrCl > 25 mL/min (0.42 mL/s) Insufficient data in < 25 mL/min (0.42 mL/s)	Insufficient data exists; interruption if hepatotoxicity occurs
Idelalisib (Zydelig)	Boxed warnings: severe hepatotoxicity, diarrhea, colitis, pneumonitis, intestinal perforation Serious allergic reactions	Given in combination with rituximab Dose: 150 mg po twice daily Drug metabolism: CYP 3A4; strong inhibitor of 3A4, 2C8, 2C9, 2C19	No reductions in CrCl > 15 mL/min (0.25 mL/s) Insufficient data in < 15 mL/min (0.25 mL/s)	Insufficient data exists
Obinutuzumab (Gazyva)	Infusion reactions, reactivation of hepatitis B, progressive multifocal encephalopathy, TLS, neutropenia	Premedicate with acetaminophen, IV antihistamine, and an IV steroid to alleviate infusion-related reactions Consider antimicrobial, antiviral, and antifungal prophylaxis Hold antihypertensives 12 hours prior, during, and after due to the risk of hypotension	No reductions in CrCl > 30 mL/min (0.50 mL/s) Insufficient data in < 30 mL/min (0.50 mL/s)	No reductions
Ofatumumab (Arzerra)	Severe infusion reactions: bronchospasm, edema, fever, chills, rigors, hypotension; prolonged myelosuppression	Premedicate with acetaminophen, IV antihistamine, and an IV steroid to alleviate infusion-related reactions Rate of infusion should be increased gradually to minimize reactions Monitor for reactivation of hepatitis B	No reductions	No reductions
Rituximab (Rituxan)	Infusion reactions: fever, chills, rigors, hypotension	Premedicate with acetaminophen, diphenhydramine with or without a steroid to alleviate infusion related reactions Rate of infusion should be increased gradually to minimize reactions Monitor for reactivation of hepatitis B	No reductions	No reductions
Venetoclax (Venclexta)	TLS requiring hydration and anti-hyperuricemics, neutropenia, thrombocytopenia, infections	Initial dose: 20 mg po once daily × 7 days; then increased weekly over 5 weeks to a max dose of 400 mg po once daily Drug metabolism: do not coadminister with a strong CYP3A inhibitor and caution with strong/moderate CYP3A inducers	No reductions in CrCl > 30 mL/min (0.50 mL/s) Insufficient data in < 30 mL/min (0.50 mL/s)	No reductions for mild to moderate; insufficient data exists for severe

CrCl, creatinine clearance; IV, intravenous; po, oral; PCP, pneumocystits pneumonia; PPI, proton pump inhibitor; TLS, tumor lysis syndrome.

Patient Encounter 2

Your patient is a 54-year-old man presents to his healthcare provider with complains of a "lump in his neck". Medical history includes well-controlled hypertension and benign prostatic hypertrophy. Physical examination reveals cervical lymph node enlargement and splenomegaly. Blood work reports the following:

WBC: 30×10^9/L (30×10^3/mm^3)

Hgb: 8.2 g/dL (112 g/L; 6.944 mmol/L)

Platelets: 182×10^9/L (18.2×10^3/mm^3)

Peripheral Smear: Lymphocytosis with small, mature-appearing cells suggestive of chronic lymphocytic leukemia

FISH analysis: del(13q)

***IgVH* analysis:** mutated (>2%)

Identify your treatment goals for this patient.

How does the IgHV mutation influence your treatment approach?

What treatment do you recommend and what would you monitor?

How would your treatment change if the patient had a del(17p) mutation?

Would your treatment options change if this patient were asymptomatic? If so, what would be your new treatment?

therapy for most patients, regardless of age. A desirable response to therapy includes a reduction in lymphocytes, decrease in stage of the disease, and resolution of symptoms. Supportive care, including herpes virus and *Pneumocystis* prophylaxis, may be required depending on the treatment chosen.

MULTIPLE MYELOMA

Multiple myeloma (MM) is a malignancy of the plasma cell and characterized by an abnormal production of a monoclonal protein in the bone marrow. Features of the disease include bone lesions, anemia, and renal insufficiency. MM is an incurable disease; however, advancements in the treatment of myeloma have significantly extended survival.

EPIDEMIOLOGY AND ETIOLOGY

MM is the second most common hematologic malignancy. It is estimated that approximately 34,920 new cases would be reported in 2021, accounting for approximately 2% of all cancers.[2,24] The median age at diagnosis is 69 years, and fewer than 2% are diagnosed before the age of 40 years.[24] The incidence of MM is two times higher in African Americans compared to Caucasians and occurs slightly more frequently in men than women.[25] The etiology of MM remains largely unknown although exposure to environmental factors such as ionizing radiation and agricultural pesticides has been proposed.[26]

PATHOPHYSIOLOGY

The pathogenesis of MM is quite complex with multiple-step models created to postulate the process. Myeloma must be distinguished from a condition called monoclonal gammopathy of unknown significance (MGUS), which is characterized by a

Clinical Presentation and Diagnosis of Multiple Myeloma

Signs and Symptoms

- **KEY CONCEPT** Multiple myeloma defining events ("CRAB")
  - "C"—hyperCalcemia
  - "R"—Renal failure (serum creatinine > 2 mg/dL [177 μmol/L])
  - "A"—Anemia (fatigue)
  - "B"—Bone disease (pain, lesions, fractures)
- Weight loss
- Recurrent infections

Diagnostic Procedures

Diagnosis requires at least one myeloma defining event and ≥ 10% clonal bone marrow plasma cells.

- Laboratory
  - CBC, chemistry panel, β_2-microglobulin
  - Peripheral blood smear
  - Serum protein electrophoresis and immunofixation
  - Urine protein electrophoresis and immunofixation
  - Serum free light chains
- Radiologic evaluation (low-dose CT scan or MRI)
- Bone marrow biopsy
- Cytogenetic studies
- Molecular testing

Laboratory Findings

- Peripheral blood
  - Monoclonal protein (M protein) in serum (usually IgG or IgA)
  - High **β_2-microglobulin**
  - Low platelets and hemoglobin
  - High creatinine, urea, lactate dehydrogenase, C-reactive protein, and calcium
  - Rouleaux formation
- Urinalysis
  - Urinary free light chains (**Bence-Jones Protein**)
- Bone marrow
  - Plasma cells (10% or more)
  - Abnormal cytogenetics
- Radiologic findings
  - Bone lesions, fractures, osteoporosis

Poor Prognostic Factors

- High serum β_2-microglobulin and low serum albumin
- Elevated C-reactive protein
- Elevated lactate dehydrogenase
- IgA isotype
- Low platelet count
- High-risk cytogenetics such as t(4;14), t(14;16), and del(17p)

monoclonal immunoglobulin without malignant plasma cells, and smoldering myeloma (SMM), which lacks clinical manifestations from the high monoclonal immunoglobulin. Yearly, about 1% of patients with MGUS will progress to MM. The risk of progression from SMM to MM is higher, with approximately 10% progressing per year for the first 5 years.[27] Chromosomal abnormalities and changes in gene expression appear to be involved early in the disease process and are associated with disease progression. These genetic changes lead to cell cycle dysregulation, with certain cytogenetic characteristics associated with a higher risk of transformation (ie, translocation of 4 and 14).[27] The pathophysiology of MM involves a complex bone marrow microenvironment and cytokine interactions. Interleukin-6, tumor necrosis factor, vascular endothelial growth factor, and stromal-derived factor-1 support the establishment and proliferation of myeloma cells.[28] The understanding of these interactions has led to novel agents used in the treatment of MM.

PROGNOSTIC FACTORS

Prognostic factors for myeloma include tumor, and patient related factors. The Revised International Staging System for Multiple Myeloma is used for clinical staging.[29] Staging is stratified based on the levels of serum β_2-microglobulinemia, serum albumin, and incorporates high-risk cytogenetics. High β_2-microglobulinemia and low albumin are poor prognostic factors and indicative of high tumor load.[29] The Mayo Stratification for Myeloma and Risk-Adapted Therapy (mSMART) classification may also be used to determine a treatment approach.[30,31] mSMART incorporates tumor biology to stratify patients according to their disease risk. Chromosomal changes are used to predict high-risk patients with perhaps the most important being translocations of chromosome 14 with chromosome 4, 16, or 20.[31,32] Double or triple hit myeloma (eg, multiple high-risk genetic abnormalities.), older patients, renal impairment, and other comorbidities also predict poorer outcomes.

TREATMENT

Desired Outcomes

The primary goal in the treatment of MM is to prolong PFS and OS while minimizing complications associated with the disease. A "watch and wait" approach is an option for patients with SMM since it may be years before disease progression (eg, symptomatic disease).[32] When symptoms occur, treatment is required. The treatment of MM includes primary therapy, transplantation, and maintenance therapy. All patients should be evaluated early on to see if they are transplant candidates. Autologous stem-cell transplantation prolongs OS in patients who can tolerate high-dose chemotherapy. Regardless of transplant eligibility, all patients will be placed on primary therapy to reduce tumor burden. Since most patients will progress despite primary therapy and transplantation, maintenance therapy, often with lenalidomide, is used to prolong the duration of response. Almost all patients eventually become refractory to primary treatment, requiring the use of numerous salvage therapies. Figure 97–3 illustrates possible treatment approaches for transplant-eligible and transplant-ineligible patients.

Patient Encounter 3, Part 1

A 68-year-old woman presents to the emergency room after a fall in her home. Her medical history includes controlled hypertension and osteoporosis. She notes severe bilateral hip pain. Workup reveals:

Radiology: X-ray of right and left hips: Pathologic fracture of right hip; Osteolytic lesions in both right and left hip

Labs: Hemoglobin: 8.4 g/dL (84 g/L; 5.208 mmol/L); platelets: 220×10^9/L (220×10^3/mm^3); corrected calcium: 11.8 mg/dL (2.95 mmol/L); serum creatinine: 2.3 mg/dL (203 μmol/L); serum IgG: 6200 mg/dL (42 g/L) (normal: 620–1500 mg/dL) (6.2–15 g/L); serum IgM: 80 mg/dL (8 g/L) (normal: 50–200 mg/dL [0.5–2 g/L]); bone marrow: 72% plasma cell infiltrates

What signs and symptoms are suggestive of multiple myeloma?

Nonpharmacologic Therapy

▶ *Autologous Hematopoietic Stem-Cell Transplantation (HSCT)*

KEY CONCEPT Autologous HSCT results in higher response rates, extends PFS, and improves median OS by 12 months compared with those who receive conventional chemotherapy alone.[25] The exact timing of transplant continues to be examined. Recent data suggests early autologous HSCT may have improved PFS but timing has not translated to a difference in OS.[25] Autologous HSCT remains the standard of care and should be considered in all patients who can tolerate high-dose chemotherapy. High-dose melphalan is the most common preparative regimen. Multiple randomized trials examining two sequential transplants (tandem transplants) have reported inconclusive results.[25] Thus, tandem transplantation may be considered for relapsed disease or in the setting of a clinical trial. Maintenance therapy, consisting of lenalidomide, bortezomib, or ixazomib, can be used after autologous transplantation to extend PFS.[32,33]

Pharmacologic Therapy

Symptomatic MM requires pharmacologic treatment. There have been numerous drugs approved in the last 15 years, changing the pharmacological management of MM. There are four main classes of drugs used in the treatment of MM: immunomodulatory agents, proteasome inhibitors, corticosteroids, and monoclonal antibodies. A three-drug regimen is often utilized in the treatment of MM. See Table 97–3.

▶ *Conventional-Dose Chemotherapy*

The use of conventional-dose chemotherapy with alkylating agents or anthracyclines has declined with the advent of immunomodulators and proteasome inhibitors, especially in the first-line setting. Cyclophosphamide or doxorubicin may be incorporated into selected treatment regimens. The regimen of cyclophosphamide, bortezomib, and dexamethasone (CyBorD) is commonly used as primary therapy in patients presenting with acute renal dysfunction.[32]

▶ *Corticosteroids*

Dexamethasone is incorporated into almost all MM treatment regimens to improve outcomes. Clinicians should recognize the daily dose of dexamethasone is often higher than the dose used in the treatment of other diseases (eg, 40 mg/day on specified days).[34] The higher doses of dexamethasone may increase the risk of infections and central nervous system toxicities. Short-term antibiotic prophylaxis at diagnosis may be warranted for those patients at high risk for infection.

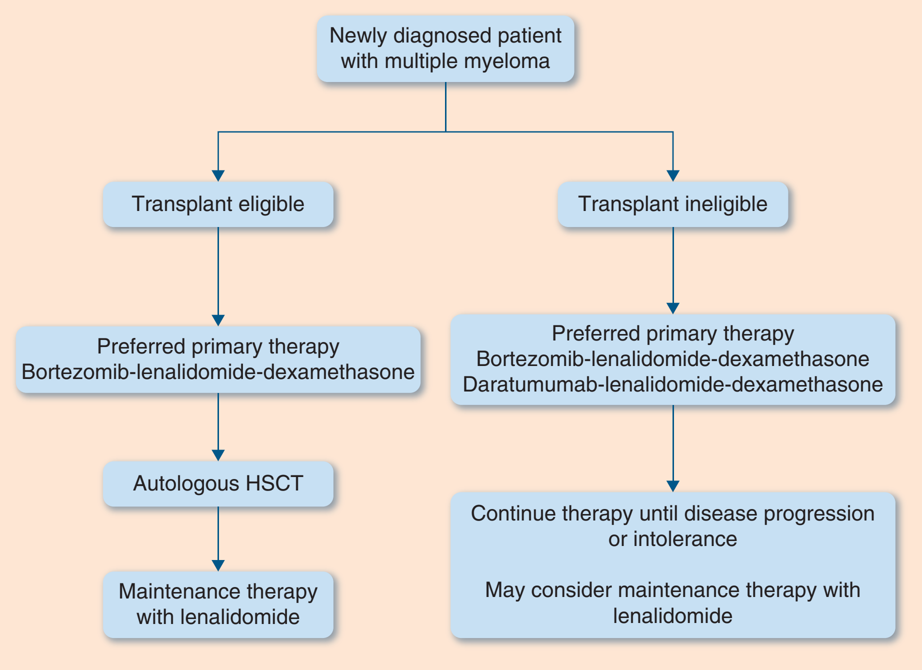
Newly diagnosed patient with multiple myeloma
Transplant eligible
Transplant ineligible
Preferred primary therapy Bortezomib-lenalidomide-dexamethasone
Preferred primary therapy Bortezomib-lenalidomide-dexamethasone Daratumumab-lenalidomide-dexamethasone
Autologous HSCT
Continue therapy until disease progression or intolerance
May consider maintenance therapy with lenalidomide
Maintenance therapy with lenalidomide

FIGURE 97–3. Possible treatment approach for a newly diagnosed patient with multiple myeloma. (HSCT, hematopoietic stem-cell transplantation.) (Data from NCCN.)

▶ *Immunomodulatory Drugs*

KEY CONCEPT Immunomodulary agents are the backbone of most myeloma regimens. The immunomodulatory drug lenalidomide (Revlimid) is often used in combination therapy for the treatment of MM. The precise mechanism of action is unknown, but lenalidomide's antimyeloma activity may be attributable to its antiangiogenic and anticytokine properties.[35] Response rates are improved when an immunomodulatory agent is added to a treatment regimen.

Thalidomide was the first immunomodulatory agent to be studied with impressive responses (87%) in combination with a steroid and bortezomib.[36] Today lenalidomide has largely replaced thalidomide due to high potency and a more favorable safety profile over thalidomide.[32] The combination of bortezomib, lenalidomide, and dexamethasone (VRd) has emerged as one of the most commonly used primary regimens in the treatment of newly diagnosed, transplant-eligible, and transplant-ineligible patients with MM.[25,32] Low-dose dexamethasone (40 mg once per week) with lenalidomide offers improved OS compared with high-dose dexamethasone (40 mg on days 1–4, 9–12, and 17–20 of each 28-day cycle).[32] Lenalidomide and dexamethasone may also be used in combination with other proteasome inhibitors or daratumumab. Lenalidomide lacks many of the common side effects seen with thalidomide, although all immunomodulatory drugs are considered teratogenic based on the known teratogenicity of thalidomide. Significant adverse effects of lenalidomide include myelosuppression and VTEs. VTE prophylaxis is recommended in patients at high risk for thrombosis.[32] For transplant-eligible patients, stem cells should be collected shortly after starting lenalidomide because CD34-positive stem-cell counts tend to decrease with prolonged lenalidomide exposure. Maintenance lenalidomide after autologous HSCT is also widely utilized. Although maintenance lenalidomide therapy has been associated with an increase in PFS, there has also been an increase in the incidence of secondary malignancies.[37]

Pomalidomide is a newer, more potent immunomodulatory drug that is approved for use in patients who have progressed on two or more prior therapies.[32]

▶ *Proteasome Inhibitors*

Bortezomib (Velcade), carfilzomib (Kyprolis), and ixazomib (Ninlaro) are proteosome inhibitors approved for the treatment of MM. Proteosome inhibitors induce myeloma cell death by modulating nuclear factor kappa-B products, including inflammatory cytokines and adhesion molecules that support myeloma cell growth.[36] These drugs also disrupt the myeloma microenvironment by inhibiting the binding of myeloma cells to the bone marrow stromal cells.[36] Bortezomib-based regimens are frequently used as primary therapy for MM. The response rates with bortezomib have been reported as high as 97% in newly diagnosed myeloma.[36] Bortezomib has also shown impressive outcomes in patients with high risk disease, making it a preferred agent for these patients.[31] Adverse effects of bortezomib include fatigue, nausea, peripheral neuropathy, and hematologic effects.[36] Subcutaneous bortezomib is the preferred route of administration, offering convenience over IV access and lower risk of peripheral neuropathy with no difference in OS.[32] The incidence of VTE is lower than the immunomodulators; thus, bortezomib does not routinely require prophylactic anticoagulation. However, prophylactic antiviral therapy should be considered to reduce the risk of herpes zoster reactivation.[32]

Carfilzomib and ixazomib are second-generation proteasome inhibitors used in the treatment of MM. While carfilzomib is administered intravenously, ixazomib is the first oral proteasome inhibitor that may be given in an all orally administered regimen with lenalidomide and dexamethasone. The adverse effect profiles of carfilzomib and ixazomib are similar to bortezomib with potentially less neurotoxicity. Clinicians should note that carfilzomib requires monitoring for cardiac and pulmonary toxicities.

Table 97–3

Drugs Used in Multiple Myeloma

Drug	Adverse Effects	Comments	Renal Dosing	Hepatic Dosing
Bortezomib (Velcade)	Constipation; decreased appetite; asthenia; fatigue; fever; thrombocytopenia; dose related, reversible peripheral neuropathy	Dose: 1.3 mg/m^2 IV bolus or subQ twice weekly for 2 weeks; week 3 off; repeat Concentration for IV is 1 mg/mL and 2.5 mg/mL for SC Consider herpes zoster prophylaxis with daily acyclovir	No reductions	Bilirubin > 1.5 × the upper limit of normal: reduce dose to 0.7 mg/m^2
Carfilzomib (Kyprolis)	Neutropenia, thrombocytopenia, cardiac toxicity including cardiac arrest, congestive heart failure, infusion reactions, TLS	Dose: 20 mg/m^2 IV bolus on days 1, 2, 8, 9, 16, and 16; days 17–28 off; repeat every 28 days Patients with a BSA greater than 2.2 m^2 should have dose calculated based on 2.2 m^2 Premedicate with dexamethasone 4 mg to reduce infusion-related reactions Hydration with normal saline prior to carfilzomib is recommended	No reductions	May need to dose reduce or hold dose depending on degree of hepatic dysfunction
Daratumumab (Darzalex)	Infusion reactions, diarrhea, nausea, vomiting, respiratory concerns including cough and dyspnea, infection	Dose: 16 mg/kg IV or 1800 mg subQ weekly on weeks 1–8, every other week starting week 9–24 and every 4 weeks starting week 25 Premedicate with acetaminophen, steroid, and antihistamine to reduce infusion-related reactions Bronchodilators may be needed Antiviral prophylaxis should be initiated and continued for 3 months post-last dose Corticosteroid should be started for 2 days following each infusion	No reductions	Mild/moderate: No reductions Severe: Insufficient data exists
Dexamethasone	Hyperglycemia, edema, adrenal cortical insufficiency	Dose given po once daily	No reductions	No reductions
Elotuzumab (Empliciti)	Infusion reactions, infections including opportunistic, diarrhea, secondary malignancies	Given in combination with lenalidomide and dexamethasone Premedicate with acetaminophen, ranitidine, diphenhydramine and dexamethasone to reduce infusion-related reactions	No reductions	Mild: No reductions Moderate/severe: Insufficient data exists
Ixazomib (Ninlaro)	Neutropenia, thrombocytopenia, rash, peripheral neuropathy, drug-induced hepatotoxicity	Dose: 4 mg po on days 1, 8, and 15 in combination with lenalidomide 25 mg po on days 1–21 and dexamethasone 40 mg po on days 1, 8, 15, and 28. Repeat every 28-day cycle Thromboprophylaxis is recommended with this regimen	CrCl > 30 mL/min (0.50 mL/s): no adjustments CrCl < 30 mL/min (0.50 mL/s): reduce dose to 3 mg	Mild: no reductions Moderate/severe: reduce dose to 3 mg
Lenalidomide (Revlimid)	Possible birth defects neutropenia, thrombocytopenia, DVT, PE, pruritus, fatigue	Dose: 25 mg taken with water once daily Women of childbearing age must use two forms of contraception Pregnancy test must be taken before and during use Enrollment into monitoring program required	CrCl 30–60 mL/min (0.50–1.00 mL/s): 10 mg/day CrCl < 30 mL/min (0.50 mL/s): 15 mg every 48 hours Dialysis and CrCl < 30 mL/min (0.50 mL/s): 5 mg every 24 hours given after dialysis	No reductions
Pomalidomide (Pomalyst)	Severe birth defects, DVT, neutropenia	Dose: 4 mg po daily on days 1–21; off 21–28 and repeat Drug metabolism: CYP 1A2 and 3A4	Do not use if SCr > 3 mg/dL (265 μmol/L)	Do not use if bilirubin > 2 mg/dL (34 μmol/L) and AST/ALT > 3 × the upper limit of normal
Thalidomide (Thalomid)	Severe birth defects, peripheral neuropathy, DVT, somnolence, constipation	Titrate initial doses; doses are taken nightly Women of childbearing age must use two forms of contraception Pregnancy test must be taken before and during use Enrollment into monitoring program required	No reductions	No reductions

DVT, deep venous thrombosis; IV, intravenous; PE, pulmonary embolism; po, oral; subQ, subcutaneous, TLS, tumor lysis syndrome.

▶ *Monoclonal antibodies*

Monoclonal antibodies are also incorporated into the treatment of MM. Daratumumab (Darzalex) and, most recently, isatuximab-irfc (Sarclisa) target CD38, which is a glycoprotein highly expressed on MM cells.[38] A novel formulation of daratumumab was recently approved allowing for subcutaneous administration, significantly shortening infusion times. Elotuzumab (Empliciti) has a different mechanism of action and is directed against signaling lymphocytic activation molecular F7 (SLAMF7), which is also expressed on MM cells.[25] Daratumumab is a preferred regimen used in combination with lenalidomide and dexamethasone for nontransplant eligible candidates. Additional combinations include use with bortezomib and in the quad-drug regimen, daratumumab, bortezomib, thalidomide, dexamethasone, used as primary therapy in transplant-eligible candidates. Elotuzumab and isatuximab-irfc are less frequently used, reserved for use in the treatment of relapsed disease. Patients receiving monoclonal antibodies should receive premedications to lessen the risk of infusion reactions. Herpes-zoster prophylaxis is recommended for elotuzumab and daratumumab.[32]

▶ *Additional Agents*

Several drugs continue to be explored for the treatment of relapsed/refractory myeloma. Panobinostat (Farydak) is an inhibitor of histone deacetylase and used in various combinations. Panobinostat has boxed warnings consisting of ischemic events, arrhythmias, and severe diarrhea.[32] Another agent recently receiving accelerated FDA approval is selinexor (Xpovio). Selinexor is an oral drug, blocking the cellular protein XPO1, and is reserved for patients who have failed at least four prior MM therapies.[39]

▶ *Bone-Modifying Agents*

Bone disease is a common manifestation of MM. Bisphosphonates or denosumab should be initiated in symptomatic patients with bone lesions to slow osteopenia and reduce the fracture risk associated with the disease. Pamidronate 90 mg and zoledronic acid 4 mg have equivalent efficacy in the management of osteolytic lesions.[32] The use of zoledronic acid decreases pain and bone-related complications and improves quality of life. Denosumab 120 mg Q4 weeks is also frequently used, as it is noninferior to zoledronic acid 4 mg Q4 weeks in delaying time to first skeletal event.[40] Denosumab is preferred in patients with renal insufficiency, which is often observed in patients with MM.[40] Osteonecrosis of the jaw is a major concern with bone-modifying therapy. Risk factors are unclear, but osteonecrosis of the jaw is more common in patients receiving IV administration of bisphosphonates and having dental procedures performed. It is recommended that patients have dental restoration work before starting therapy. Updated consensus guidelines have been published on the use of bone-modifying agents and myeloma, which recommend that bone-modifying agents be continued for up to 2 years.[41]

Patient Encounter 3, Part 2

The patient was diagnosed with multiple myeloma.

What treatment options are available for this patient?

What is a primary consideration when determining first line treatment?

What would be an appropriate regimen for primary therapy?

What may be used for maintenance therapy after an autologous stem-cell transplantation?

OUTCOME EVALUATION

Newly diagnosed, asymptomatic patients with MM may be observed without treatment. This asymptomatic period may last for months to several years. All patients with MM become symptomatic, and when this occurs, treatment is required. All patients should be evaluated for an autologous stem-cell transplant. Primary therapy, regardless of transplantation, often consists of bortezomib lenalidomide, and dexamethasone. Maintenance therapy with lenalidomide or bortezomib may be used, depending on risk. Nearly all patients will experience disease progression, requiring additional therapy. There are numerous treatment options for relapsed and refractory MM. Bisphosphonates or denosumab should be given to patients who have bone lesions with the hope of reducing pain and fractures.

Patient Care Process

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements.
- Review medical history, including patient's age, comorbid conditions, and current medications to avoid drug–drug interactions.
- Review laboratory values and physical assessment findings.

Assess the Information:

- Determine whether the patient requires immediate treatment based on laboratory values, physical assessment, and medical history.
- Identify whether the patient is taking any medications that could interact with the possible treatment selections for the given cancer.
- Discuss with the patient the financial costs of the possible treatment and determine if one agent is more cost-effective than another.
- If goals are not achieved, assess whether a change in medication is warranted or if nonadherence is suspected.
- If the patient experiences intolerance to therapy including any severe adverse effects, a change in medication may be warranted.

(*Continued*)

Patient Care Process (*Continued*)

Develop a Care Plan:

- Select the most appropriate treatment based on the assessment findings for the patient.
- Consider whether additional supportive care medications are needed such as prophylactic antimicrobials, growth factors, or anticoagulants.
- Discuss the importance of medication adherence and long-term outcomes.
- Address any concerns about the selected medication including cost and management of adverse effects.
- Identify the required monitoring and determine treatment outcomes and goals.

Implement the Care Plan:

- Educate the patient on the selected drug therapy, medication administration, importance of adherence, potential adverse effects, and how to manage and report adverse effects that occur.
- Address any patient concerns about the selected drug therapy and its management.

Follow-up: Monitor and Evaluate:

- Drug therapy should be frequently monitored to assess treatment efficacy and safety.
  - For CML, follow-up should be scheduled every 3 months to determine whether molecular, cytogenetic, and hematologic goals of therapy are being met.
  - For CLL, follow-up should include a review of symptoms and laboratory findings including lymphocytes and hemoglobin.
  - For MM, monitor myeloma monoclonal protein in urine and serum, renal function, hemoglobin, and platelets.
- Review medication adherence.
- If patients continue to have disease progression or have relapsed disease, another regimen should be utilized.
- Out of office follow-up (ie, phone calls) may be helpful to reinforce the importance of adherence and identify and manage any adverse effects.

List of Abbreviations

AP	Accelerated phase
BCL-2	B-cell lymphoma 2
BP	Blast phase/crisis
BTK	Bruton tyrosine kinase
CLL	Chronic lymphocytic leukemia
CML	Chronic myelogenous leukemia
CP	Chronic phase
CR	Complete response
FISH	Fluorescence in situ hybridization
HBV	Hepatitis B virus
HSCT	Hematopoietic stem-cell transplantation
MBL	Monoclonal B-lymphocytosis
MGUS	Monoclonal gammopathy of unknown significance
MM	Multiple myeloma
OS	Overall survival
Ph	Philadelphia chromosome
PFS	Progression-free survival
PI3-K	Phosphatidylinositol-3-kinase
qPCR	Quantitative polymerase chain reaction
SMM	Smoldering myeloma
TFR	Treatment-free remission
TKI	Tyrosine kinase inhibitor
WBC	White blood cell

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98 Hematopoietic Stem-Cell Transplantation

Gianni Scappaticci and David G. Frame

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the rationale for using hematopoietic stem-cell transplant (HCT) to treat cancer, immune disorders, or hemoglobinopathies.
2. Compare the different types of HCTs, specifically (a) the types of donors (ie, autologous and allogeneic), (b) the source of hematopoietic cells (ie, peripheral blood progenitor cells, bone marrow, and umbilical cord blood), and (c) the type of preparative regimen (ie, myeloablative and nonmyeloablative).
3. Develop a plan for monitoring and managing engraftment of hematopoiesis and potential complications of engraftment.
4. List the nonhematologic toxicity to high-dose chemotherapy used in myeloablative preparative regimens, specifically busulfan-induced seizures, hemorrhagic cystitis, gastrointestinal toxicities, and sinusoidal obstruction syndrome.
5. Explain graft-versus-host disease (GVHD) including pathophysiology, differences between acute and chronic, and grading of acute GVHD.
6. Recommend a prophylactic and treatment regimen for GVHD.
7. Choose a regimen to minimize the risk of infectious complications in HCT patients.
8. Evaluate the long-term health care of HCT survivors.

INTRODUCTION

KEY CONCEPT Hematopoietic stem-cell transplant (HCT), which is often referred to as bone marrow transplant (BMT), involves the administration of CD34+ hematopoietic stem cells (HSCs) into a recipient with damaged, dysfunctional, or depleted HSCs and immune cells after administration of a preparative (or conditioning) regimen of chemotherapy, radiotherapy, or both.[1] While this process is a life-saving procedure most often used in malignant conditions, it may be used to replace dysfunctional immune deficiency syndromes like severe combined immunodeficiency syndrome (SCID), hemoglobinopathies such as sickle cell anemia, and other disorders such as scleroderma, an autoimmune disorder.[2] **KEY CONCEPT** There are two main types of HCTs, autologous HCT where the recipient receives their own HSCs and an allogeneic HCT where the recipient receives HSCs from either a related or unrelated donor (URD). Hematopoietic stem cells may be obtained from bone marrow (BM), peripheral blood progenitor cells (PBPCs), or umbilical cord blood (UCB). BM and PBPCs contain pluripotent stem cells and postthymic lymphocytes, which are responsible for long-term hematopoietic reconstitution (engraftment) and immune recovery.[1]

The rationale of an autologous HCT for a malignant condition is to administer high doses of chemotherapy to maximize therapeutic activity against the cancer and then “rescue” the BM with the patient’s own HSCs. This high-dose therapy, called the conditioning (or preparative) regimen, results in ablation of the cells in the BM. HSCs are collected from the patient prior to administering the high-dose chemotherapy and then are reinfused after the chemotherapy as a rescue to restore hematopoiesis. Allogeneic HCTs use HSCs from another donor to both rescue the recipient after chemotherapy and to generate a new immune system which can develop an immunologic response toward the recipient’s residual tumor, called the graft-versus-tumor (GVT) or graft-versus-leukemia (GVL) effect, or may replace the recipients dysfunctional immune system or hemoglobinopathy.[3] Unfortunately, this new immune system may also generate an immunologic response toward the recipient’s normal tissue causing an immune condition known as graft-versus-host disease (GVHD). It is important to distinguish that the main purpose of an autologous transplant is to deliver high-dose chemotherapy and the cells are just a rescue, while the main purpose of the allogeneic transplant is to develop an immune response against the malignancy or to replace a defective immune process or hemoglobinopathy.

The type of HCT performed depends on a number of factors, including the type and status of disorder, availability of a compatible donor, patient age, performance status, and organ function. Examples of disorders treated with HCT are listed in Table 98–1.

While outcomes of HCTs have improved significantly over the years, the field still faces the highest mortality from relapsed primary disease as well as severe GVHD.[4] New strategies including maintenance therapies after transplant to decrease relapse rates and new therapies based on better understanding of the pathophysiology of GVHD have emerged continuing to advance clinical outcomes through better pharmacotherapy.

Table 98–1

Diseases Commonly Treated with HCT

	Autologous Graft	Allogeneic Graft
Cancers	Multiple myeloma Non-Hodgkin lymphoma Hodgkin disease Neuroblastoma Germ-cell tumors	Acute myeloid leukemia Acute lymphoblastic leukemia Chronic myeloid leukemia Myelodysplastic syndrome Myeloproliferative disorders Non-Hodgkin lymphoma Hodgkin disease Chronic lymphocytic leukemia Multiple myeloma
Other Diseases	Autoimmune diseases Amyloidosis	Aplastic anemia Paroxysmal nocturnal hemoglobinuria Fanconi anemia Thalassemia major Sickle cell anemia Severe combined immunodeficiency Inborn errors of metabolism

With more patients living longer, it is important that long-term complications be addressed in a multidisciplinary approach after HCT. Many patients have multiple long-term complications which can include issues relating to several organs including cardiology, renal, hepatic, endocrine, and pulmonary as well as poor bone health, infections, and secondary malignancies.[5]

EPIDEMIOLOGY AND ETIOLOGY

In 2018, approximately 14,000 autologous HCTs and 9000 allogeneic HCTs were performed in the United States and over 50,000 HCTs are performed worldwide.[4] The most common indications for autologous HCT were multiple myeloma (MM) and lymphoma while the most common indications for allogeneic HCTs were acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). The annual number of transplants continues to steadily increase due to the use of alternative donors, the use of transplant expanding to older patients, and the use of transplants for nonmalignant conditions.[4]

The ability to collect stem cells from peripheral blood by the use of apheresis has made this a much easier and safer procedure for both autologous patients and allogeneic donors and has greatly increased the numbers of individuals willing to participate in donor marrow programs such as the National Marrow Donor Program. In the United States, URD recipients account for approximately 50% of allogeneic HCTs while human leukocyte antigen (HLA) identical siblings and transplants using “other relatives” account for approximately 22% each and UCB approximately 5%.[4] The rise in “other relatives” as donors has increased exponentially since 2014 with the onset of haploidentical transplants, which allows for more immunologically diversity and may be a donor that is a parent or child or only partially matched sibling.[4]

PATHOPHYSIOLOGY

Autologous HCT, or infusion of a patient’s own HSCs, allows for the administration of high doses of chemotherapy, radiation, or both to treat the malignancy or autoimmune disorder. In this setting, the sole purpose of the hematopoietic cells is to “rescue” the recipient’s BM from otherwise dose-limiting hematopoietic toxicity. Autologous HCT is commonly used to treat intermediate- and high-grade non-Hodgkin lymphoma (NHL), MM, relapsed or refractory Hodgkin lymphoma, and rarely autoimmune disorders such as scleroderma.[4] Patients do not benefit from an immunologic GVT effect while undergoing an autologous transplant; instead, the administration of high-dose chemotherapy followed by an autologous stem-cell transplant in chemotherapy-sensitive malignancies relies on the high-dose preparative regimen alone to eradicate the malignant disease. Autologous HCT circumvents the need for histocompatible donors, does not risk GVHD, and is associated with a lower transplant-related mortality rate.[4] However, since many malignancies are derived from stem cells or early progenitor cells, this approach is limited to certain malignancies as there is the potential of removing malignant cells during apheresis and transplanting those back into the patient.

Allogeneic HCT involves the transplantation of HSCs obtained from a different person’s (donor) BM, peripheral blood stem cells (PBSCs), or UCB to the recipient (also called the host). The type of donor, as described in Table 98–2, is distinguished by whether or not they are a relative to the recipient and by the shared number of common immunologic cell surface HLAs.[6,7]

HLAs are encoded by a group of genes on the short arm of chromosome 6, called the major histocompatibility complex (MHC). These are proteins expressed on cell surfaces that have a critical role in alloimmunity.[6] A set of HLA gene alleles, or haplotype, is inherited from each parent. HLA compatibility with the donor is usually defined by high-resolution typing for 10 alleles: HLA-A, HLA-B, HLA-C, HLA-DR, and HLA-DQ.[6] A 10 out of 10 match would be all of the alleles match, while a 9/9 would means there was 1 allele mismatch, an 8/8 would be 2 allele mismatch, etc. Recently there has been evidence that DPB1 matching may be of value as well and may be included in typing.[8]

KEY CONCEPT The transplanted donor HSCs are immunologically active, and thus, there is potential for bidirectional graft rejection. When host-versus-graft reactions occur, cytotoxic T cells and natural killer (NK) cells belonging to the host (recipient) recognize HLA antigens of the graft (donor HSCs) as foreign, and this can lead to a rejection of the transplanted cells in which case there would be a failed engraftment.[9] To prevent this complication, part of the preparative regimen is always targeted toward the recipient’s immune system and recipients are given immune suppression. The immune suppression is also to prevent GVHD, in which the immunologically active cells in the graft recognize host HLA antigens as foreign and elicit an immune response against them.[10]

Graft-versus-Host Disease Pathophysiology

One of the most important principles in the pathophysiology of allogeneic HCT is the understanding of GVHD and HLA

Table 98–2

Classification of Allogeneic Transplants

Type of Donor	HLA 8/8 Match or greater	Less than HLA 8/8 Match
Sibling	Matched related donor (MRD)	Haploidentical (Haplo)
Parent or child		Haploidentical
Unrelated	Matched unrelated donor (MUD)	Mismatched unrelated donor (MMUD)
Umbilical cord blood	Matched UCB	Mismatched UCB (MMUCB)
Identical twin	Syngeneic	

histocompatibility. Histocompatibility differences in HLA-A, HLA-B, HLA-C, HLA-DR, and HLA-DQ between the donor and the recipient are the primary risk for GVHD. The degree of HLA mismatching is associated with the risk of acute GVHD, graft rejection, and mortality.[11] An HLA identical sibling donor is generally considered the best donor for allogeneic HCT; however, less than 30% of patients have a matched sibling.[9] For URDs, 10/10 matches are the best; however, matching at the HLA-A, HLA-B, HLA-C, and HLA-DRB1 loci (an 8/8 HLA match) is comparable.

GVHD involves a complex network of inflammation and cellular interactions of both innate and adaptive immunity. Three sequential phases have been described including activation of antigen presenting cells (APCs), donor T-cell activation, proliferation, differentiation, migration, and finally target tissue destruction.[11-14] Understanding these phases and the molecular processes is essential for understanding potential drug targets and therapies for GVHD. The GVHD pathophysiology is summarized in Figure 98–1.

▶ *Phase 1: Activation of Antigen Presenting Cells (APCs)*

In the first phase, host APCs (eg, dendritic cells, macrophages) are activated. The end result is increased cytokine activation including TNFα, interleukin (IL)-6, IL-2, and IL-1, and chemokines such as CCL2-5 and CXCL9-11.

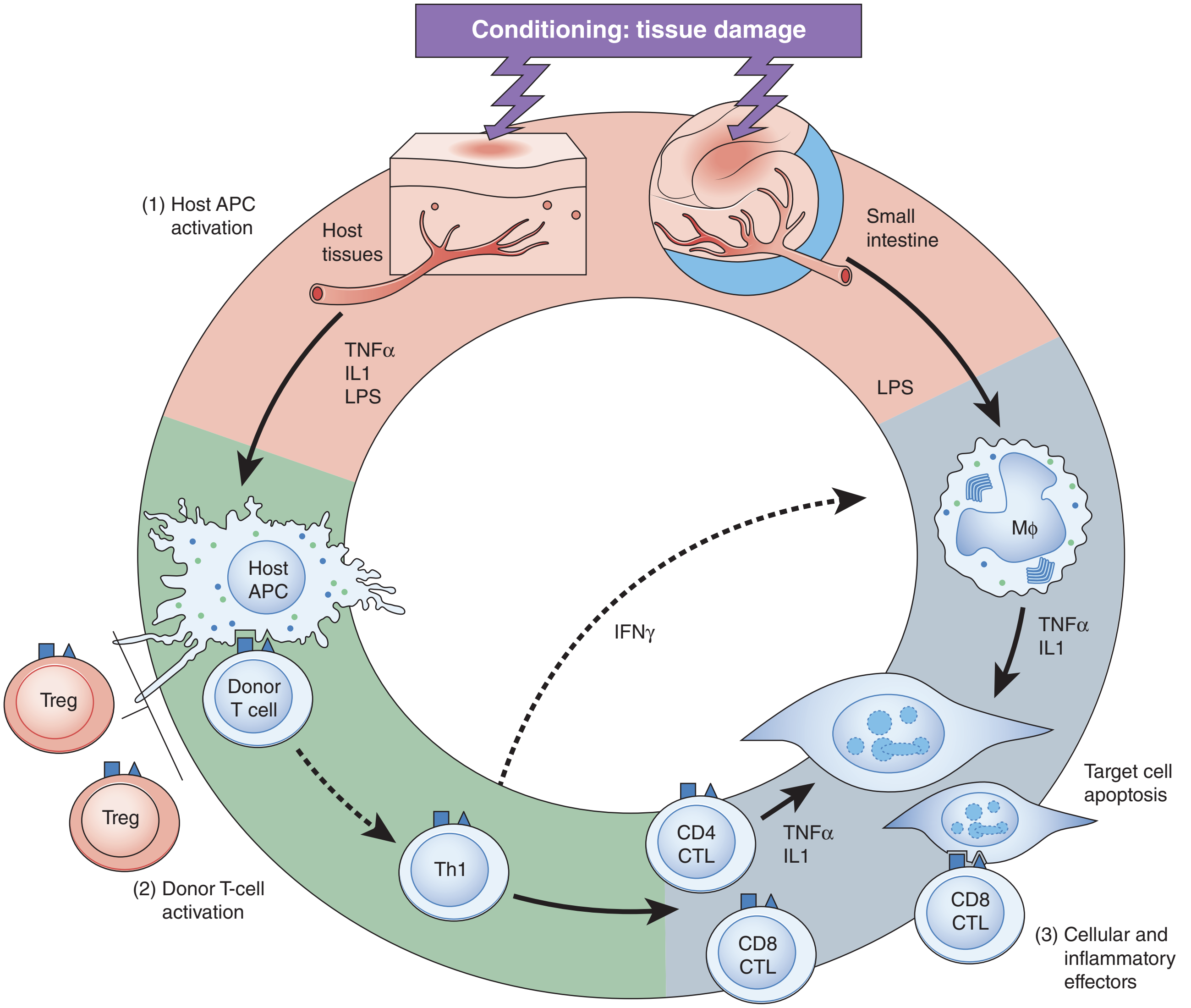

FIGURE 98–1. Pathophysiology of acute graft-versus-host disease. During the first phase (1), recipient conditioning regimen damages patient tissues and causes release of inflammatory cytokines such as TNF-α, IL-1, and IL-7, which leads to activation of host APCs. In the second phase (2), host APCs activate mature donor cells through IL-12 and IL-23 to produce T helper cell type 1 (Th1) cytokines, such as IL-2, IL-6, and IFN-γ. The synthesis of inflammatory cytokines is partly inhibited by IL-10. Activated Th1 cells induce increased indoleamine 2,3-dioxygenase (IDO) secretion from host APCs through IFN-γ secretion, thus stimulating immunotolerizing Tregs. IFN-γ also stimulates mononuclear cells to secrete inflammatory cytokines, such as IL-1 and TNF-α. (3) Th1 cells promote proliferation and differentiation of activated cytotoxic T lymphocytes (CTLs) and stimulate natural killer (NK) cells, which, in turn, induce apoptosis. Lipopolysaccharide (LPS) and bacterial cell wall components that have leaked through the damaged intestinal mucosa stimulate mononuclear cells through interactions with NOD2 and other innate immunity proteins, thus triggering additional inflammatory cytokine production causing apoptosis. (Reprinted with permission from Harris, A.C., J.L.M. Ferrara, and J.E. Levine, *Advances in predicting acute GVHD*. Br J Haematol. 2013;160(3):288–302.)

Patient Encounter Part 1

A 65-year-old African American male is diagnosed with FLT3+ acute myeloid leukemia who smoked until 20 years ago and has diabetes controlled with oral medications. The patient achieved partial remission with induction chemotherapy and complete remission on reinduction. He is now being evaluated for stem-cell transplant. He has one sibling who is 79 years old and a 6/10 (4/6) match. He has two children that underwent HLA typing: a 35-year-old son is a 7/10 (4/6) HLA match and a 42-year-old daughter, with three children, who is an 8/10 (4/6) match. A search from the national registry, the closest match is a female with 8/10 (4/6).

What type of transplant would be best for this patient (autologous or allogeneic)?

Does the choice of transplant depend on the HLA results?

Which of these donors would be the best selection for this patient?

Can allogeneic transplants use a patient's child as a donor?

▸ Phase 2: Donor T-Cell Activation, Expansion, and Trafficking

The donor T cells interact with the APCs from phase 1 causing T-cell activation, proliferation, and differentiation. While much emphasis has been placed on the CD8+ T cells, there may be several types of T cells involved including CD4+ T cells, Th1, Th2, Th17, T follicular helper (Tfh), and the GVHD suppressing regulatory T cells (Tregs). This is all controlled by cytokines secreted by the activated T cells. These cytokines are classified as Th1 (IFN-γ, IL-2, and TNFα) or Th2 (IL-4, IL-5, IL-10, and IL-13) and Th17 (IL-17). The cascade of Th1 cytokines clearly can induce GVHD; however, the balance of Th1 and Th2 cytokines is important as well. During this phase, T cells also start to move from the lymphoid system to target tissues through chemokine signaling such as CCL2, CCL3, CCL4, CCL5 and CXCL9, CXCL10, and CXCL11 and then bind by adhesion molecules like integrins. This process can explain why certain organs are specifically targeted for GVHD and may provide specific therapy. For example, the T cells are driven to the gastrointestinal (GI) tract by α4β7 integrin which could be inhibited by vedolizumab.

▸ Phase 3: Cellular and Inflammatory Effector Phase

This phase is where the cytokines developed earlier amplify the cellular and inflammatory mediators causing T cells, neutrophils, macrophages, NK cells, and NK-T cells to damage tissues and organs.[14]

In this phase, there still continues to be secretion of many inflammatory cytokines especially TNFα which can also drive effector cells to target organs and directly cause tissue damage via apoptosis, which is generally reported on pathology review of biopsies; however, necrosis may also be present.

PHARMACOLOGIC THERAPY AND HCT TREATMENT PROCESS

The HCT process contains several steps as outlined in Figures 98–2 and 98–3 including HSC collection, preparative or conditioning chemotherapy, HSC infusion, engraftment period, early post engraftment and acute GVHD period (allogeneic HCT), late post engraftment and chronic GVHD period (allogeneic HCT), and long-term outcome period which each involve specific therapies and potential complications.

Hematopoietic Stem Cells: Sources and Collection

KEY CONCEPT There are three main sources for HSCs: BM, peripheral blood (PBSCs), and UCB.[1] Harvesting HSCs directly from the BM requires a surgical procedure and with the development of the hematopoietic growth factor (HGF), granulocyte colony-stimulating factor (filgrastim, Neupogen), has been largely replaced by PBSCs. Filgrastim is given daily for 5 to 7 days and causes mobilization of stem cells out of the marrow into the peripheral blood where they can be collected by apheresis making this a much safer and simpler procedure.[1] The goal is to collect at least 2 to 3×10^6 CD34+ cells/kg of the recipient. PBSCs are almost always used for autologous HCT. Sometimes, however in an autologous recipient, it may be difficult to mobilize enough cells into the peripheral blood due to marrow suppression from prior therapy such as chemotherapy or lenalidomide. If this is the case the combination of chemotherapy (ie, cyclophosphamide or etoposide) with an HGF enhances PBPC mobilization relative to HGF alone.[15] In addition to treating the underlying malignancy, this approach lowers the risk of tumor cell contamination and the number of apheresis collections required, but there is a greater risk of thrombocytopenia, neutropenia, and hospitalization for neutropenic fever.[15] The HGF is initiated after completion of chemotherapy and is continued until apheresis is complete. To avoid mobilizing with chemotherapy, plerixafor (Mozobil) was FDA approved in combination with HGF to mobilize stem cells for autologous transplants in MM and NHL patients.[16] HSCs are attached to the BM stroma by the chemokine receptor CXCR4,

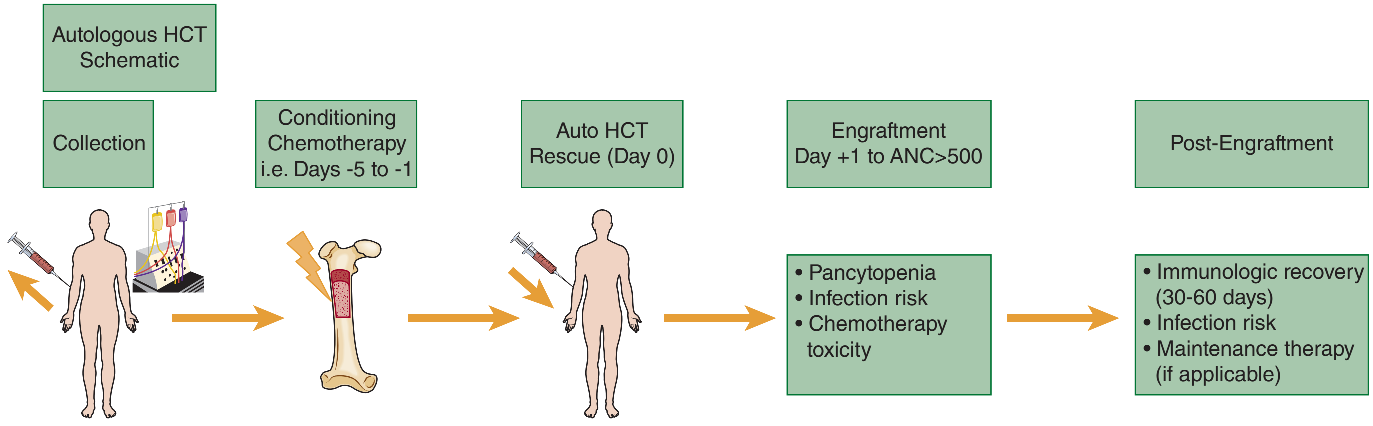
Autologous HCT Schematic
Collection
Conditioning Chemotherapy i.e. Days -5 to -1
Auto HCT Rescue (Day 0)
Engraftment Day +1 to ANC>500
Post-Engraftment
• Pancytopenia
• Infection risk
• Chemotherapy toxicity
• Immunologic recovery (30-60 days)
• Infection risk
• Maintenance therapy (if applicable)

FIGURE 98–2. Processes of autologous HCT.

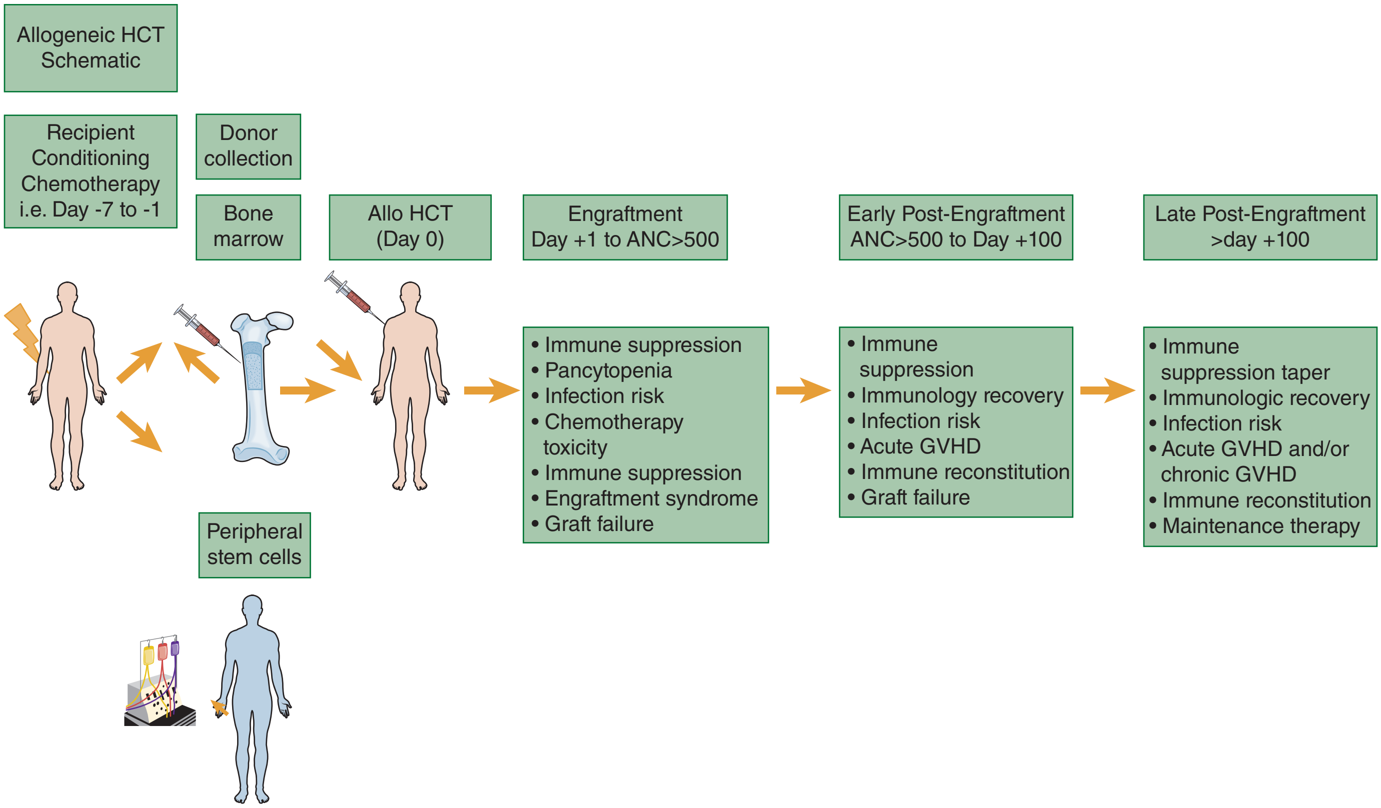
Allogeneic HCT Schematic
Recipient Conditioning Chemotherapy i.e. Day -7 to -1
Donor collection
Bone marrow
Allo HCT (Day 0)
Engraftment Day +1 to ANC>500
Early Post-Engraftment ANC>500 to Day +100
Late Post-Engraftment >day +100
• Immune suppression
• Pancytopenia
• Infection risk
• Chemotherapy toxicity
• Immune suppression
• Engraftment syndrome
• Graft failure
• Immune suppression
• Immunology recovery
• Infection risk
• Acute GVHD
• Immune reconstitution
• Graft failure
• Immune suppression taper
• Immunologic recovery
• Infection risk
• Acute GVHD and/or chronic GVHD
• Immune reconstitution
• Maintenance therapy
Peripheral stem cells

FIGURE 98–3. Processes of allogeneic HCT.

which is blocked by plerixafor, thus releasing cells into the peripheral blood for collection.

Cells for allogeneic HCT, except for UCB, are usually collected within 24 hours of the transplant and are given to the recipient without freezing. PBPCs are most commonly used for allogeneic HCT. The donor is given HGFs for 5 days, and then apheresis is used to collect the cells with the optimal number of CD34+ collected being 4 to 8 × 10^6 cells/kg of recipient body weight.[1] Allogeneic PBPC grafts contain approximately 10 times more T and B cells than BM grafts, and data has shown that allogeneic PBSCs may induce more chronic GVHD than cells from the BM, however, there was no difference in overall survival (OS), relapse, acute GVHD, or mortality at 2 years.[17] There has been an increasing trend, especially in related donors and pediatric transplants, to use BM cells.[4] The BM may need additional processing if the donor and recipient are ABO incompatible, which occurs in up to 30% of HCTs.[18] Red blood cells (RBCs) may need to be removed before infusion into the recipient to help prevent immune-mediated hemolytic anemia and thrombotic microangiopathic syndromes.

UCB offers an alternative stem-cell source to patients requiring an allogeneic transplant who do not have an acceptable matched related or URD.[7] The cord blood is obtained from a consenting donor in the delivery room after birth and delivery of the placenta. The UCB is processed, a sample is sent for HLA typing, and the cord blood is frozen and stored for future use. Numerous UCB registries exist, with the goal of providing alternative sources of allogeneic stem cells. UCB offers the advantage of being readily available, and has provided a stem-cell source to a more diverse patient population, in addition to a lower risk of GVHD.[19] Limitations include an increased risk of graft failure, delayed immune reconstitution leading to an increase in infections, and the inability to use donor-lymphocyte infusions in the event of relapse.[7] Cord blood has a limited number of CD34+ stem cells, thus limiting the size of the recipient so as to not risk failed engraftment. To overcome this and make this process even available in adults, the cells from two different umbilical cords can be given. While only one cord fully engrafts, the addition of the second cord significantly increases engraftment.[7]

▶ *T-Cell Depletion*

Immunocompetent T lymphocytes may be depleted from the donor BM *ex vivo* before infusion using physical (eg, density-gradient fractionation) and/or immunologic (eg, antithymocyte globulin [ATG] antibodies) methods.[20] It may also be done *in vivo* where ATG or alemtuzumab is given as part of the conditioning regimen to reduce the recipients T cells, but because of the long half-life of these antibodies, they can also deplete T cells that are infused with the transplant. This effect will be greater with higher doses of ATG or alemtuzumab and the closer to the transplant they are given.[21] T cell–depleted grafts decrease the risk of GVHD but also increase the risk of graft failure and of malignant disease relapse due to less GVT effects.[20] This may be a preferred option for nonmalignant transplants such as replacement of an immune dysfunction where there is no need for GVT effect. This process also will delay functional recovery of T cells in the recipient causing significantly increased risk of infections especially viral reactivation and of Epstein–Barr virus (EBV)–associated lymphoproliferative disorders. The use of donor lymphocyte infusion (DLI) in patients who relapse after receiving a T cell–depleted HCT is often required. DLI is a process where T-lymphocytes from the original stem-cell donor are infused after the transplant to augment an antitumor immune response or ensure that the donor stem cells remain engrafted, this can also increase the risk of developing GVHD. This clearly demonstrates the delicate balance between GVHD and GVT effects of T cells.

A newer version of T-cell depletion, developed with haploidentical HCT, is to give posttransplant cyclophosphamide at 50 mg/kg on days + 3 and + 4 after cell infusion and then calcineurin inhibitors and mycophenolate mofetil are started on day + 5.[22] The purpose of this is to allow the transplanted T cells to start to expand and possibly achieve tumor recognition and then destroy those alloreactive cells allowing immunologic tolerance and decreased GVHD. Stem cells should not be affected with cyclophosphamide due to low proliferation rate and the protection of high intracellular levels of aldehyde dehydrogenase. This approach has been shown to have overall comparable outcomes to matched related and matched unrelated transplants.[22]

Conditioning (or Preparative Regimen) for HCT

For both allogeneic and autologous transplants, HSCs are infused after the administration of chemotherapy and/or radiation, termed the conditioning or preparative regimen. There are two primary classifications of the preparative regimen. **KEY CONCEPT** A myeloablative preparative regimen involves the administration of chemotherapy which will cause full ablation to the recipient's BM. A nonmyeloablative preparative regimen utilizes a less intensive regimen to allow for better tolerability allowing older patients or those with some comorbidities to receive a transplant.[23] Other terminology often used is a "full intensity or reduced intensity" preparative regimen. Full intensity regimens are also usually myeloablative; however, reduced intensity may consist of a regimen that come close to being myeloablative but in some patients may not completely ablate the BM. Examples of commonly used preparative regimens are included in Table 98–3.

After an allogeneic HCT, it is possible to measure the percentage of donor cells versus the percentage of recipient CD3+ T cells and CD33+ myeloid cells in the blood and in the BM, which is called chimerism. After a myeloablative transplant, generally patients have 100% chimerism with all the cells being the donor. However, after a nonmyeloablative or reduced intensity transplant, it may take a few months before the donor fully engrafts and there will be a mixed chimerism (ie, donor 70% CD3+, and 50% CD33+, recipient 30% CD3+ and 50% CD33+) before this occurs. A mixed chimerism may also allow result in less early GVHD until more donor T cells take over, but here is also the risk of recipient taking over in which case DLI may be necessary.

▸ *Myeloablative Preparative Regimens*

Myeloablative conditioning refers to regimens of high-dose chemotherapy with or without radiation causing BM aplasia that would lead to death without stem-cell support. In both autologous and allogeneic HCT, infusion of stem cells circumvents this dose-limiting toxicity of myelosuppression, maximizing the potential value of the steep dose–response curve to alkylating agents and radiation, suppressing the host immune system, and creating space in the marrow compartment to facilitate engraftment. The preparative regimen is designed to eradicate immunologically active host tissues (lymphoid tissue and macrophages) and to prevent or minimize the development of host-versus-graft reactions. Most allogeneic preparative regimens for the treatment of hematologic malignancies contain cyclophosphamide, radiation, or both. The combination of cyclophosphamide and total-body irradiation (TBI) was one of the first preparative regimens developed and is still used widely today. Both cyclophosphamide and TBI are immunosuppressive and have inherent activity against hematologic malignancies (eg, leukemias and lymphomas), but hematopoietic stem cells are resistant to cyclophosphamide. TBI has the added advantage of being devoid of active metabolites that might interfere with the activity of donor hematopoietic cells. In addition, TBI eradicates residual malignant cells at sanctuary sites such as the central nervous system. Modifications of the cyclophosphamide–TBI preparative regimen include replacing TBI with other agents that are active against hematopoietic stem cells

Table 98–3

Commonly Used Preparative Regimens for HCT

Type of HCT	Preparative Regimen	Dose and Schedule for Adults
Allogeneic	Myeloablative CY-TBI	CY 60 mg/kg/day IV on 2 consecutive days before TBI 10–16 Gy fractionated over 1–7 days (varies)
Allogeneic, autologous	Myeloablative BU-CY	Busulfan 1 mg/kg per dose PO or 0.8 mg/kg per dose IV every 6 hours × 16 doses CY 60 mg/kg/day IV daily × 2 days after BU
Allogeneic	Myeloablative FLU-BU4[a]	Busulfan 3.6mg/kg IV daily × 4 days Fludarabine 40 mg/m^2 IV daily × 4 days
Autologous	Myeloablative BEAM (carmustine/ etoposide/-cytarabine/ melphalan)	Carmustine 300 mg/m^2 IV Etoposide 400–800 mg/m^2 IV given over 4 days Cytarabine 400–1600 mg/m^2 IV given over 4 days Melphalan 140 mg/m^2 IV
Allogeneic	Reduced intensity FLU-MEL	Fludarabine 25–30 mg/m^2 IV daily × 4–5 days Melphalan 100–180 mg/m^2 IV daily × 1 day
Allogeneic	Nonmyeloablative FLU-BU2	Busulfan 3.6 mg/kg IV daily × 2 days Fludarabine 40 mg/m^2 IV daily × 4 days
Allogeneic	Nonmyeloablative FLU-TBI	Fludarabine 25–30 mg/m^2/day IV daily × 3 days TBI 2 Gy × one dose

[a] Regimen may be considered myeloablative or reduced intensity dependent on busulfan AUC target.

BEAM, carmustine, etoposide, cytarabine, and melphalan; BU-CY, busulfan and cyclophosphamide; BU-FLU, busulfan and fludarabine; CY-TBI, cyclophosphamide–total-body irradiation; FLU-MEL, fludarabine and melphalan; IV, intravenous; PO, oral; TBI, total-body irradiation.

Data from Gyurkocza B, Sandeaier BM. Conditioning regimens for hematopoietic cell transplantation: one size does not fit all. Blood. 2014;124:344–353.

(eg, busulfan) or adding other chemotherapeutic or monoclonal agents to the existing regimen in hopes of minimizing long-term toxicities. In the case of a mismatched allogeneic HCT with a substantially increased chance of graft rejection, ATG also may be added to the preparative regimen to further immunosuppress the recipient through T-cell depletion.

The optimal myeloablative preparative regimen remains elusive as no clinical trial has definitively shown superiority of one regimen. Busulfan–cyclophosphamide (BU-CY) is a chemotherapy-only option used to avoid the toxicities associated with TBI. Furthermore, busulfan combined with the purine analog fludarabine (FLU-BU4) has even fewer toxicities compared to BU-CY with similar outcomes. Busulfan is an alkylating agent with activity in numerous hematologic malignancies. Intravenous busulfan with pharmacokinetic monitoring may improve outcomes when utilized with BU-CY and FLU-BU compared to CY-TBI in AML patients, although preparative regimens should be tailored to the primary disease and to the degree of HLA compatibility.[21]

At most HCT centers, age younger than 70 years and good renal, hepatic, pulmonary, and cardiac function as well as performance status are considered eligibility requirements for myeloablative allogeneic HCT.

▶ *Reduced Intensity and Nonmyeloablative Preparative Regimens*

A reduced intensity preparative regimen is composed of less toxic agents, lower doses of chemotherapy, and radiation, in the hope of being able to offer the benefit of an allogeneic HCT to more patients with less toxicity. In these cases, it is still critical to make sure the recipient's immune system is suppressed to hinder graft rejection, so these regimens often include fludarabine, a potent agent against T cells, or may include immune therapies such as ATG or alemtuzumab in the preparative regimen to assure host T-cell depletion; however, this comes with increased risk of infections and possibly higher relapse rates, especially if higher doses of ATG are used.[21] These regimens rely on the concept of a GVT effect as more residual disease remains due to the less intense conditioning.

Due to the severe regimen-related toxicity of a myeloablative preparative regimen, the use of HCT traditionally was limited to younger patients with minimal comorbidities. Most patients diagnosed with cancer are elderly; therefore, myeloablative HCT could not be offered to a substantial portion of cancer patients. The concept of donor immune response having a GVT effect gave rise to the theory of a strongly immunosuppressive, but not completely myeloablative, preparative regimen Reduced intensity is an intermediate category of reduced dose chemotherapy that may be considered myeloablative or nonmyeloablative, yet still require stem-cell rescue. Fludarabine, a purine analog, is commonly used due to potent immunosuppressive effects in combination with lower dose alkylating agents (eg, busulfan-half dose, melphalan) or TBI.

The nonmyeloablative preparative regimen does not completely eliminate host normal and malignant cells. Donor cells eradicate residual host hematopoiesis, and the GVT effects generally occur after the development of full donor T-cell chimerism. Thus, although transplant-related mortality is decreased due to reduced toxicity, there are higher rates of relapse.

▶ *Toxicities and Management of Preparative Regimens*

Myelosuppression is a frequent dose-limiting toxicity for antineoplastics when administered in the conventional doses used to treat cancer. However, because myelosuppression is circumvented with hematopoietic rescue in the case of patients receiving HCT, the dose-limiting toxicities of these myeloablative preparative regimens are nonhematologic and vary with the preparative regimen used. Most patients undergoing HCT experience toxicities commonly associated with chemotherapy (eg, alopecia, mucositis, nausea and vomiting, and infertility), albeit these toxicities are magnified in the HCT population.

Busulfan Seizures Seizures have been reported in both adult and pediatric patients receiving high-dose busulfan for HCT preparative regimens. Anticonvulsants are used to minimize the risk of seizures. Anticonvulsants are begun shortly before busulfan, with the loading dose, if necessary, completed at least 6 hours before the first busulfan dose. Phenytoin was the standard for many years and is the most studied. Oral loading and maintenance regimens generally are sufficient because target phenytoin concentrations of 10 to 20 mcg/mL (10–20 mg/L; 40–79 μmol/L) can be achieved by the peak time of seizure risk at 48 to 72 hours. Due to drug interactions and adverse effects, alternatives to phenytoin such as benzodiazepines or levetiracetam are preferred and have similar efficacy.[24] Antiseizure medications usually are discontinued 24 to 48 hours after administration of the last dose of busulfan. Seizures still can occur despite the use of prophylactic anticonvulsants and usually do not result in permanent neurologic deficits.

▶ *Adaptive Dosing of Busulfan*

The considerable interpatient variability in the pharmacokinetics of both oral and IV busulfan along with the identified concentration–effect relationships has led to the pharmacokinetic monitoring and adaptive dosing of busulfan.[25] Adjusting the busulfan dose to achieve a target concentration or exposure minimizes the toxicities of the BU-CY regimen, particularly hepatic sinusoidal obstruction syndrome (SOS; formerly referred to as veno-occlusive disease [VOD]) while improving engraftment and relapse rates.[25] Most transplant centers have adopted this practice and have internal therapeutic drug monitoring guidelines to adjust for a specified concentration at steady state or area under the curve.

HSC INFUSION (DAY 0)

Day 0 is designated as the day of infusion of the HSCs, this is often an emotional and celebratory day for patients and their families and is often deemed as a secondary birthday. The cells are given as an intravenous infusion and will track to the BM. If

Patient Encounter Part 2

The patient agrees to haploidentical transplant with PRPCs from his 35-year-old son who is a 7/10 (4/6) HLA match. The patient has blood type O and the son has type A. The preparative regimen is fludarabine and cyclophosphamide.

How is a haploidentical transplant different from a matched related sibling or a matched unrelated donor?

What nonhematologic toxicities are associated with the preparative regimen?

What type of preparative regimen is this patient receiving? How does this differ from other types of preparative regimens?

the cells were cryopreserved, they are thawed at the bedside and infused immediately. The DMSO in the cryopreserved product may cause nausea, emesis, or infusion-related reactions primarily from histamine release. Premedications of an antihistamine, an antiemetic, acetaminophen, and possibly a corticosteroid are common. Rarely DMSO can cause hypotension, neurologic symptoms, respiratory symptoms such as bronchospasm or an anaphylactic type reaction.[26] It is recommended that the maximum dose of DMSO delivered is 1 mL/kg/day, occasionally a patient may need to split the dose and receive the cells over 2 days. DMSO is partially cleared renally and fluids are given for hydration. DMSO is also cleared through the lungs and expired out into the air. This results in a pungent smell similar to garlic or creamed corn for 24 to 48 hours. Patients are given mints to block some of the bitter flavor the DMSO may cause as well as prevent nausea and vomiting.

For an allogeneic HCT it is important that immune suppression for prophylaxis of GVHD should be therapeutic before the cells are infused as this decreases severe GVHD incidence. Also if there is an ABO mismatch there is a risk of hemolysis with infusion. Prehydration, acetaminophen, antihistamine, and a steroid are common with ABO mismatch cell infusions. If there is a major ABO incompatibility the recipient may also receive plasma pheresis to remove antibodies before the cells are infused. Rituximab may be given to inhibit recipient B cells and decrease further antibody production before the donor cells engraft.[18]

Immune Suppression for Prevention of Acute GVHD in Allogeneic HCT

KEY CONCEPT Acute GVHD is a leading cause of morbidity and mortality after allogeneic HCT occurring in approximately 35% to 47% of patients, and thus, efforts have focused on utilizing immune suppression to prevent GVHD.[4] The donor graft and preparative regimen influence the prophylactic regimen for acute GVHD, with two primary approaches being most common. One approach involves T-cell depletion as discussed earlier and the second approach is to suppress T-cell function and expansion using a two-drug immunosuppressive therapy that typically consists of a calcineurin inhibitor (ie, cyclosporine or tacrolimus) with either low dose methotrexate on days + 1, + 3, + 6, and + 11 after myeloablative HCT or with mycophenolate mofetil for 28 days after a nonmyeloablative HCT.[1]

Since the calcineurin inhibitors (ie, cyclosporine and tacrolimus) inhibit both cytotoxic and helper T-cell proliferation and activation through inhibition of IL-2, they should be initiated 2 to 3 days before and have therapeutic levels before donor cell infusion. Studies comparing cyclosporine and tacrolimus in combination with methotrexate have shown that tacrolimus administration is associated with a lower incidence of grade II to IV acute GVHD and a similar incidence of chronic GVHD but variable effects on OS.

A newer version of T-cell depletion, developed with haploidentical HCT, is to give posttransplant cyclophosphamide at 50 mg/kg on days + 3 and + 4 after cell infusion and then calcineurin inhibitors and mycophenolate mofetil are started on day + 5.[22] The purpose of this is to allow the transplanted T cells to start to expand and possibly achieve tumor recognition and then destroy those alloreactive cells allowing immunologic tolerance and decreased GVHD. Stem cells should not be affected with cyclophosphamide due to low proliferation rate and the protection of high intracellular levels of aldehyde dehydrogenase. This approach has been shown to have overall comparable outcomes to matched related and matched unrelated transplants.[22]

Patient Encounter Part 3

It is transplant day (day 0) and the patient has several family members come for his "new birthday" celebration. The son has just finished the cell collection, and there were 5.5×10^6 cells per kg of the patient collected. The patient is excited to receive his new cells. The patient has blood type O and the son has type A.

Do the cells need to be processed before giving to the patient?

How are the cells given to the patient?

Will there be DMSO in the cells?

What type of prophylactic medications are given before the cells?

When will this patient's calcineurin inhibitor start and why? What monitoring parameters are necessary for this medication to ensure safety and efficacy?

Will this patient receive methotrexate or mycophenolate mofetil with the calcineurin inhibitor?

Will this patient receive any chemotherapy after the transplant, why?

▸ *Adaptive Dosing of the Calcineurin Inhibitors*

KEY CONCEPT The calcineurin inhibitors cyclosporine and tacrolimus are pharmacokinetically monitored and adjusted to target therapeutic concentration ranges. Cyclosporine and tacrolimus trough concentrations are associated with acute GVHD and nephrotoxicity. Cyclosporine trough concentrations usually are maintained between 150 and 400 ng/mL (125 and 333 nmol/L) in patients undergoing allogeneic HCT depending on the assay utilized with TDX having higher levels than HPLC.[27] Tacrolimus trough concentrations are often targeted to a range of 5 to 15 ng/mL (6.2–18.6 nmol/L).[28,29] Nephrotoxicity can occur despite low or normal concentrations of the calcineurin inhibitor and may be a consequence of other drug- or disease-related factors known to influence the development of nephrotoxicity (eg, genetic risk factors, concurrent use of other nephrotoxic agents, and sepsis). Careful monitoring for drug interactions via CYP 3A4 and P-glycoprotein is essential. The calcineurin inhibitor doses are adjusted based on serum drug levels and the calculated creatinine clearance. Common adverse effects to these agents include neurotoxicity, hypertension, hyperkalemia, hypomagnesemia, and/or nephrotoxicity (which may lead to an impaired clearance of methotrexate).

ENGRAFTMENT PERIOD (DAY + 1 TO DAY + 30)

This is one of the most acute times in the transplant process as the side effects from the conditioning regimen occur and patients are generally treated in the hospital for much of this time. The conditioning therapy will cause pancytopenia and the initial outcome desired from the HCT is to have the infused cells return to the BM and start to proliferate and mature and return to appropriate peripheral counts of neutrophils, erythrocytes and platelets. Engraftment is defined as the point at which the patient maintains a sustainable absolute neutrophil count (ANC) of greater than 500 cells/mm^3 (0.5×10^9/L) and a sustained platelet count of 20,000/mm^3 (20×10^9/L) lasting 3 or more consecutive days without transfusions. The median time to engraftment of neutrophils is approximately 10 to 16 days and engraftment of neutrophils is often the requirement for hospital discharge. Several factors may affect the timing including the source and quantity of stem cells, HGF use, infection, and engraftment syndrome. PBPCs tend to have the most rapid engraftment followed closely by BM; however, UCB tends to be the slowest, often taking 20 to 30 days. HGFs are recommended to hasten hematopoietic recovery during the period of aplasia after an autologous, haploidentical and UCB transplant starting between days 5 and 7 after transplant and continuing until ANC greater than 1000 to 2000 cells/mm^3 ($1–2 \times 10^9$/L) × 2 days.[30] It is controversial whether or not HGFs should be administered after allogeneic transplant as use may increase GVHD and mortality; however, they are used routinely at many centers.[31]

Chemotherapy-Induced Gastrointestinal Effects

The preparative regimen causes damage to the rapidly dividing epithelial cells lining the GI tract resulting in inflammation, apoptosis, and possible ulceration. Higher intensity myeloablative regimens are at especially high risk for severe GI toxicity, specifically mucositis or stomatitis that can happen throughout the entire GI system, this causes diarrhea as well as nausea and vomiting. Patients may also have delayed chemotherapy-induced nausea and vomiting (CINV) during this time. Prevention and treatment of CINV should be addressed accordingly as per published clinical practice guidelines and are further detailed in Chapter 99.[32] Olanzapine 5 to 10 mg daily has been shown to be effective both on the acute phase and the more delayed phase associated with transplant and should be considered for use until engraftment.[33]

Diarrhea occurs in the majority of patients beginning within the first week after the initiation of chemotherapy and/or radiation and may cause dehydration and severe electrolyte impairments, which should be monitored daily. During this early period, infections with *Clostridium difficile* are also common and must be evaluated before the administration of antidiarrheals. The breakdown in mucosal lining also allows for transit of bacteria and fungi from the GI tract, increasing the risk for infection.

Virtually all patients receiving a myeloablative preparative regimen experience oral mucositis resulting in severe pain and difficulty eating and swallowing. Routine oral care protocols are indicated to reduce the severity of mucositis, which may occur within the first week of HCT and persist for approximately 2 weeks.[34] Palifermin, a keratinocyte growth factor, may be considered for patients undergoing autologous HCT with myeloablative TBI-based preparative regimens. Patients may require parenteral opioid analgesics for pain relief owing to mucositis, and total parenteral nutrition may be necessary to prevent the development of nutritional deficiencies.

▶ *Infections and Neutropenic Fever*

KEY CONCEPT Fever and infection in these neutropenic patients are common and patients receive prophylaxis with broad spectrum antibiotics (ie, levofloxacin), antivirals (ie, acyclovir, letermovir), and antifungals (ie, fluconazole, echinocandins, or broad-spectrum azoles) at this early stage. Orders for blood and urine cultures and intravenous therapy with antibacterials covering pseudomonas and GI organisms should be readily available for activation when a fever over 38°C occurs.

▶ *Sinusoidal Obstruction Syndrome*

Hepatic SOS is a life-threatening complication that may occur secondary to preparative regimens or radiation. The pathogenesis of SOS is not completely understood but the key event appears to be sinusoidal endothelial damage caused by the preparative regimen which initiates the coagulation cascade, induces thrombosis of the hepatic venules, and eventually leads to fibrous obliteration of the affected venules.[35]

The clinical manifestations of SOS are hyperbilirubinemia, jaundice, fluid retention, weight gain, and right upper quadrant abdominal pain. To make a clinical diagnosis of SOS, these features must occur in the absence of other causes of posttransplant liver failure, including GVHD, viral hepatitis, fungal abscesses, or drug reactions. Most cases of SOS occur within 3 weeks of HCT, and the clinical diagnosis can be confirmed histologically via liver biopsy.

Patients with mild SOS have an excellent prognosis, but those with more severe disease (ie, bilirubin higher than 20 mg/dL [342 μmol/L] or weight gain greater than 15%) with renal impairment (SCr greater than 3 × baseline, GFR less than 40% baseline and/or oxygen saturation less than 90% on room air) have a high mortality rate. Pretransplant risk factors for SOS include a mismatched or unrelated graft, increased age, prior abdominal radiation or stem-cell transplant, exposure to inotuzumab or gemtuzumab ozogamicin, and increased transaminases before HCT.[35] Interpatient variability in the metabolism and clearance of the chemotherapy (ie, BU-CY) used within the preparative regimen also may be associated with a poor outcome, although the relationships vary within the various preparative regimens. The association of SOS with busulfan concentrations is discussed in the section on adaptive dosing of busulfan. Use of ursodiol, has been associated with a lower incidence of SOS in a limited number of small, randomized studies and may be recommended for SOS prophylaxis.[35]

The mainstay of treatment for established SOS is supportive care aimed at sodium restriction, increasing intravascular volume, decreasing extracellular fluid accumulation, and minimizing factors that contribute to or exacerbate hepatotoxicity and encephalopathy. Defibrotide, an oligonucleotide with antithrombotic, antiischemic, and anti-inflammatory activity, is FDA approved for the treatment of SOS in patients with renal or pulmonary dysfunction following HCT. In a phase III clinical trial, defibrotide improved day + 100 OS from 25% to 38.2% compared to placebo and was generally well tolerated.[35] Defibrotide has been evaluated for SOS prophylaxis with mixed results.

▶ *Engraftment Syndrome*

Around the time of neutrophil engraftment, a cytokine release may lead to a “Cytokine Storm or Engraftment Syndrome” characterized by fever, skin rash, and weight gain and may involve diarrhea, pulmonary edema, liver and renal dysfunction and encephalopathy. In allogeneic transplant this appears to be an early phase GVHD which increases the risk of later onset severe GVHD and mortality.[36] Engraftment syndrome can be severe and may lead to mortality if not recognized early and aggressive treatment with prednisone or methylprednisolone 1 to 2 mg/kg/day may be required with a taper after symptoms resolve.

▶ *Idiopathic Pulmonary Syndrome (IPS)*

Idiopathic pulmonary syndrome (IPS) is used to define a spectrum of noninfectious, diffuse lung injuries that include multilobar airspace opacities on chest imaging, absence of lower respiratory tract infection, and hypoxemia that occur following allogeneic HCT with most cases occurring in the first month.[37] The mortality rate is approximately 50% to 70%.[37] Risk factors include conditioning intensity, TBI dose, high-grade acute GVHD and advanced age; however, TBI more than 12 Gy may be the most important. Lung shielding is recommended when delivering high-dose TBI. Viral reactivation, including HHV6 which occurs commonly in the first 30 days, may confound the diagnosis or it may increase the risk of IPS.[37] Standard therapy has been methylprednisolone 2 mg/kg/day. TNF and IL-6 have been shown to be high in both serum and BAL fluid and TNF inhibition or IL-6 inhibition and addition of etanercept to methylprednisolone has been studied in pediatrics.[38]

▶ *Hemorrhagic Cystitis*

High-dose cyclophosphamide causes moderate to severe hemorrhagic cystitis; acrolein, a metabolite of cyclophosphamide, is the putative bladder toxin. Preventive measures to lower the risk of hemorrhagic cystitis include vigorous hydration, continuous bladder irrigation, or concomitant use of the uroprotectant 2-mercaptoethane sulfonate (mesna). The American Society of Clinical Oncology (ASCO) Guidelines for the Use of Chemotherapy and Radiotherapy Protectants recommends the use of mesna plus saline diuresis or forced saline diuresis to lower the incidence of urothelial toxicity with high-dose cyclophosphamide in the setting of HCT.[39] Hemorrhagic cystitis may also be caused by BK or adenovirus post HCT which should be evaluated by polymerase chain reaction copy number. These infections are treated with decreased immune suppression if possible and cidofovir which may cause significant renal toxicity that can be limited by using a low dose cidofovir.[40] Patients must be well hydrated and calcineurin inhibitor levels monitored carefully.

▶ *Graft Failure*

Graft failure is defined as the lack of functional hematopoiesis after HCT and can occur initially as a primary failure where initial hematopoietic recovery fails to take place or can occur later after 30 days as a secondary failure often in association with recurrence of the disease or reappearance of host cells after initial donor cell engraftment.[9] A delicate balance between host and donor effector cells in the BM is necessary to ensure adequate engraftment because residual host-versus-graft effects may lead to graft rejection. The incidence of graft rejection is higher in patients with aplastic anemia and those with HLA mismatched or T-cell–depleted marrow.[9] Graft rejection is uncommon in patients with leukemia receiving myeloablative preparative regimens with a histocompatible allogeneic donor.

Therapeutic options for the treatment of graft rejection or graft failure are limited and may include addition of sargramostim or use of thrombopoietin agonist (especially for poor platelet engraftment), which also stimulates stem cells.[41] A second HCT is the most definitive therapy, although the associated complications and toxicities may preclude its use.[42]

Patient Encounter Part 4

The patient starts to have some anxiety shortly after the transplant. He develops nausea and vomiting on day + 4, he becomes neutropenic on day + 5, and on day + 8, he starts granulocyte colony stimulating factor injections daily. He develops neutropenic fever and significant diarrhea on day + 9. On day + 15, his neutrophils are 0.5×10^9 cells/L, and he starts to have fever, rash, increased diarrheas, and shortness of breath requiring 4 L of oxygen. On day + 18, he engrafts with an absolute neutrophil count of 4.8×10^9 cells/L.

What antiemetic may be particularly helpful for this patient?

Are there risks to giving growth factor to this patient?

What infectious complications are of a concern for this patient during the early transplant period?

What work up should be done for his initial diarrhea?

What is likely causing his symptoms starting on day + 15 and how would you treat this?

EARLY POST ENGRAFTMENT PERIOD (DAY + 30 TO DAY + 100)

Acute Graft-Versus-Host Disease

While acute GVHD may happen before day + 30 or after day + 100 the most common occurrence is between this time period. **KEY CONCEPT** GVHD is caused by the activation of donor lymphocytes, leading to alloreactive immune damage to potentially any part of the recipient's body; however, it presents most commonly in the skin, GI system, and liver. Immune-mediated destruction of tissues, a hallmark of GVHD, disrupts the integrity of protective mucosal barriers and, thus, provides an environment that favors the establishment of opportunistic infections as discussed in the Infectious disease section. The combination of GVHD and infectious complications are leading causes of mortality for allogeneic HCT patients. GVHD is divided into acute and chronic categories based on clinical manifestations. Traditionally, the boundary between acute and chronic GVHD was set at 100 days after HCT; however, National Institute of Health (NIH) consensus criteria has refined the definition of both acute and chronic GVHD based on clinical symptoms and organs involved rather than the time of onset and also describe an overlap syndrome where there is a mix of acute and chronic GVHD symptoms.[43]

Acute GVHD is defined as classic aGVHD symptoms (erythema, maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea, ileus, or cholestatic liver disease) occurring within 100 days after transplantation or after DLI in a patient not meeting criteria for the diagnosis of chronic GVHD. Persistent, recurrent, or late onset acute GVHD is defined as features of classic acute GVHD occurring beyond 100 days post transplantation or after DLI in a patient not meeting criteria for the diagnosis of chronic GVHD (often seen during the taper or withdrawal of immune suppression). The term "overlap" refers to the presence of one or more acute GVHD manifestations in a patient with a diagnosis of chronic GVHD and can be present at initial diagnosis of chronic GVHD or can develop after the diagnosis of chronic GVHD and may recur with or without resolution of prior chronic GVHD manifestations.

Skin is the most affected organ with an erythematous, maculopapular rash. In severe cases the skin may blister and ulcerate and may lose many layers of skin, similar care to burn victims may be required. GI acute GVHD is often difficult to treat and may present as nausea, vomiting, anorexia, diarrhea, and/or abdominal pain. It may involve any or all of the intestine and/or stomach. Lower GI aGVHD generally results in secretory diarrhea which can be several liters a day and may cause significant bleeding because of mucosal ulceration. Liver acute GVHD is often difficult to distinguish from possible other causes, such as drug-related toxicities or viral infections, and often is assumed if other organs have GVHD but may only be confirmed with a liver biopsy. Generally, an increase in liver function enzymes and/or bilirubin are the initial signs followed by jaundice.

A few staging systems exist that are based on clinical criteria is used to grade acute GVHD. The severity of organ involvement is staged on an ordinal scale from 0 (no symptoms) to 4 (severe symptoms), and then an overall grade of 0 to IV is established

Table 98–4

Mount Sinai Acute GVHD International Consortium (MAGIC) Staging of Acute GVHD[44]

			GI/Gut (Stool Output per Day)	
Stage	**Skin**	**Liver (Bilirubin)**	**Adult**	**Child**
0	No GVHD rash	< 2 mg/dL	< 500 mL or < 3 episodes/day	< 10 mL/kg or < 4 episodes/day
1	Maculopapular rash < 25% BSA	2–3 mg/dL	500–999 mL or 3–4 episodes/day	10–19.9 mL/kg or 4–6 episodes/day; persistent nausea, vomiting, or anorexia, with a positive result from upper GI biopsy
2	Maculopapular rash 25%–50% BSA	3.1–6 mg/dL	1000–1500 mL or 5–7 episodes/day	20–30 mL/kg or 7–10 episodes/day
3	Maculopapular rash > 50% BSA	6.1–15 mg/dL	> 1500 mL or > 7 episodes/day	> 30 mL/kg or > 10 episodes/day
4	Generalized erythroderma plus bullous formation and desquamation > 5% BSA	> 15 mg/dL	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume)	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume)

From Harris AC, Young R, Devine S, et al. International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium. Biol Blood Marrow Transplant/ 2016;224–10.

based on the number and extent of involved organs as shown in Table 98–4 and Table 98-5. However, Upper GI GVHD is only classified as stage 0 if no or intermittent nausea, vomiting or anorexia or stage 1 if persistent nausea, vomiting or anorexia.[44]

▸ *Treatment of Acute GVHD*

First-Line Therapy of Acute GVHD For most grade II to IV aGVHD or any visceral involvement initial treatment is methylprednisolone 2 mg/kg/day or equivalent steroid and a calcineurin inhibitor.[14] Corticosteroids have several mechanisms including indirectly halting the progression of immune-mediated destruction of host tissues by blocking macrophage-derived IL-1 secretion. IL-1 is a primary stimulus for T helper cell–induced secretion of IL-2, which, in turn, is responsible for stimulating proliferation of cytotoxic T lymphocytes.

In certain cases with limited low grade acute GVHD, like grade I skin GVHD, systemic steroids can be initially spared with the use of topical steroids alone. For only upper GI GVHD, which is usually more responsive to steroids, methylprednisolone 1 mg/kg/day can be effective and oral budesonide solution may be added. Despite high-dose steroids being the standard for over 25 years, responses are poor with only 40% to 50% of grade II to IV achieving a complete or partial response.[14] To try and improve first-line response, a randomized phase III trial added mycophenolate mofetil to steroids and a CI as initial therapy without benefit compared to steroids and CI alone; thus, steroids remain first-line therapy.[45] Since the response to initial therapy correlates directly with posttransplant survival it is imperative to find more effective therapy first-line therapy and it is especially critical to have effective second-line therapy.

Table 98–5

Overall Clinical Grade (Based Upon Most Severe Target Organ Involvement)[44]

Grade 0	No stage 1–4 of any organ
Grade I	Stage 1–2 skin without liver, upper GI, or lower GI involvement
Grade II	Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI
Grade III	Stage 2–3 liver and/or stage 2–3 lower GI, with stage 0–3 skin and/or stage 0–1 upper GI
Grade IV	Stage 4 skin, liver or lower GI involvement, with stage 0–1 upper GI

In patients who do respond to corticosteroids, tapering should begin as soon as there is major improvement in the GVHD. Rapid tapers may increase the risk of GVHD exacerbation or recurrence while slow taper rates increase the risk of steroid-related complications including hypertension, hyperglycemia, edema, bone loss, muscular atrophy, cataracts and infections, especially fungal and viral. Generally, the dose is reduced by approximately 10% to 20% every 3 to 7 days depending on response and slowed when the prednisone dose is less than 30 mg/day.[46] Unfortunately recurrence or exacerbation of GVHD occurs approximately 35% to 50% of the time during steroid taper.

▸ *Second-Line Therapy of Acute GVHD*

There is only one FDA approved agent for second-line treatment of steroid refractory aGVHD, ruxolitinib. Ruxolitinib inhibits the Janus kinase 1 and 2 (JAK1/JAK2) tyrosine kinase resulting in the inhibition of several cytokines including TNF, IL-2, IL-6, and IFN-γ which utilize the JAK-STAT pathway for activation of cellular activity, thus blocking their critical roles in GVHD.[14] Ruxolitinib also impairs differentiation of $CD4^+$ T cells into IFN-γ- and IL-17A-producing cells, thus decreasing activity of GVHD while it increases regulatory T cells which are important in immunologic tolerance. The approval in patients 12 years of age and older was based on a prospective, open-label, single-cohort, multicenter study of ruxolitinib in 71 patients with grades II to IV SR aGVHD.[47]

▸ *Other Agents for Treatment of Steroid Refractory GVHD*

Tocilizumab IL-6 baseline and posttransplant levels are predictive of increased grade II to IV GVHD and OS.[50] Tocilizumab, the humanized anti-IL-6 receptor monoclonal antibody has been evaluated in small trials and has demonstrated a 63% complete response with GI GVHD as second line; however, another reported an ORR of 44% that was not durable in grade III to IV GVHD when used as third or fourth-line therapy.[51]

Anti-TNFα Agents One of the earliest targeted biologic therapies for GVHD were TNFα inhibitors and most reports are with infliximab, the chimeric monoclonal antibody which binds to either membrane bound or unbound TNFα, or etanercept, the soluble dimeric TNFα receptor 2 that only effects unbound TNFα. Infliximab has more inhibition of macrophages and is associated with higher rates of fungal infections, especially aspergillus. It is critical that with many of these biologic therapies appropriate antifungal prophylaxis is a standard part of the regimen.

While inhibition of TNFα is a common therapeutic strategy, the data are not convincing that this is a highly effective therapy in grade II to IV GVHD and may have higher responses when used for GI GVHD.[52] In a phase III randomized trial of high-dose corticosteroids with or without infliximab including 63 newly diagnosed GVHD patients, no statistically significant difference was found in GVHD-related mortality, nonrelapse mortality, or OS.

Anti-IL-2 Receptor Antibodies Basiliximab, a monoclonal antibody that inhibits IL-2 receptor has been evaluated in a few small studies and is used off-label for chronic graft versus host disease.

Sirolimus Sirolimus, a mammalian-target-of-rapamycin (mTOR) inhibitor, has an advantage of having no inhibitory effect on Treg cells, thus potentially helping to increase tolerance. The majority of studies for GVHD have combined sirolimus with steroids and a calcineurin inhibitor which will decrease Tregs, taking away one of the advantages of sirolimus.[52] Toxicities make sirolimus often difficult to use in patients with GVHD, especially with steroids. While hyperlipidemia and hypertriglyceridemia are very common effects, it is thrombotic microangiopathy that is generally most concerning and may be easily overlooked until severe. A case of severe life threatening hypertriglyceridemia with the combination of sirolimus and ruxolitinib has been reported.[53] There is also concern of longer term cardiac issues in these patients and potentially the increased cholesterol could lead to worsening of GVHD.[54] In addition, the risk of inflammatory pulmonary toxicity is worrisome especially if the patient has any active lung GVHD.

Alemtuzumab Alemtuzumab is a humanized monoclonal antibody to CD52 which is expressed on B cells, T cells, NK cells and dendritic cells causing extreme lymphopenia. While it would be expected that this should resolve active GVHD, the results tend to show about 50% to 60% overall response, however with an extremely high infection risk and mortality.[52] This demonstrates the delicate balance of immunosuppression that makes treating GVHD so difficult. While alemtuzumab does have efficacy it is important that mortality appears to increase significantly due to infection and these patients should have broad spectrum prophylaxis with a strong consideration for letermovir in patients at risk for cytomegalovirus (CMV). A risk adapted approach using lower doses needs to be further studied to determine if this would be a more feasible strategy to limit toxicities.[55-58]

Antithymocyte Globulin (ATG) Multiple retrospective studies have shown some benefit of ATG in SR disease.[52] Historically ATG increases the risk of developing posttransplant lymphoproliferative disorder so EBV copy numbers should be monitored routinely in patients receiving this therapy.

Mesenchymal Stem Cells Remestemcel-L is a frozen and cryopreserved allogeneic cell product that comprises *ex vivo* cultured adult human mesenchymal stromal cells (MSCs) from healthy adult donors. While still investigational it is very promising in steroid refractory aGVHD with 70% ORR and 70% Day 180 survival. MSCs are a rare population of multi potent nonhematopoietic progenitor cells that express low levels of MHC class I and an absence of the MHC class II molecule, HLA-DR, thus making these cells a hypo-immunogeneic phenotype.[48] MSCs are stimulated by TNFα binding to TNFR1 receptors on the MSCs and cause release of paracrine factors, such as PGE2, which then change naïve and effector T cells, dendritic cells, and NK cells toward anti-inflammatory phenotypes, also resulting in decreased secretion of proinflammatory cytokines, and increased regulatory T cells.[49]

GI Specific Therapies for GVHD Gastrointestinal GVHD occurs in up to 60% of transplants and may cause anorexia, malnutrition, severe diarrhea and GI bleeding. It is often steroid refractory and grade III to IV GVHD may cause mortality in over 70% of patients.[14] Oral budesonide (Entocort), approved for use in Crohn disease, is enteric coated, dissolving at high pH allowing delivery to the intestines. Budesonide is available in 3 mg capsules and is generally dosed as 3 mg daily to three times daily for GVHD. A newer product, budesonide extended release tablets (Uceris), is enteric coated and has delayed release beads potentially allowing for more drug to reach lower into the intestines and colon where GVHD may be more prevalent. It is only available in 9-mg capsules, so is generally dosed as 9 mg daily. While budesonide has not been evaluated in randomized trials, a similar agent, beclomethasone, has been assessed. A phase III trial compared immediate-release and sustained-release beclomethasone at 2 mg every 6 hours with prednisone to prednisone with improved response and mortality in the beclomethasone arm.[59] Beclomethasone also resulted in a faster prednisone taper. Budesonide plus beclomethasone has been shown to be effective also in upper GI GVHD.[60] While budesonide is often described as a "nonabsorbable" steroid it is actually greatly absorbed but undergoes extensive first pass metabolism primarily by CYP3A4 and thus has poor bioavailability. If patients are on an inhibitor of CYP3A4, such as voriconazole or posaconazole, the bioavailability will increase substantially, potentially to 100%. It is possible to monitor budesonide levels which may be important since it is a highly potent steroid.

Donor T lymphocytes which express α4β7 integrin will migrate to lymphoid tissues of the GI mucosa and this trafficking may be inhibited by blocking the α4β7 integrin with vedolizumab, a monoclonal antibody directed against α4β7 integrin. In a patient with only active GI GVHD, it would be ideal to specifically cause local immunosuppression, thus limiting potential complications of systemic suppression. Retrospective data from multiple centers evaluated the use of vedolizumab in steroid refractory acute GI GVHD patients with most having stages 2 to 4 disease.[61] A median of 3 weekly doses of 300 mg were given with 64% overall response at 6 to 10 weeks and OS 54% over 6 months. Several infections were still reported including eight nonserious infections and one serious infection with confirmed GI origin in eight patients. While larger trials would be beneficial, this is an intriguing therapy to help treat localized GI GVHD.

MAINTENANCE THERAPY AFTER TRANSPLANT

Relapse remains a primary cause of mortality after HCT. New strategies to use maintenance therapy after HCT have shown significant benefit in certain disease states.

Autologous HCT

After an autologous HCT, primary disease relapse is the most commonly reported cause of death, representing 37% of deaths in the first 100 days and 78% of deaths after 100 days. Autologous transplants for MM are not curative but are used to increase progression-free survival (PFS). Lenalidomide maintenance, generally with a dose of 10 mg daily, starting approximately day + 60 has become a standard for most patients.[62-64] A meta-analysis comparing lenalidomide to placebo demonstrate improved PFS but not survival with lenalidomide.[65] It should be noted that up to 27% of patients discontinued the drug due to adverse events and a small increase in secondary malignancies was reported in the lenalidomide group. It is often recommended that maintenance therapy continues until progressive disease as it appears that PFS after stopping therapy is approximately 10 months.[66] Other strategies in especially high-risk patients or patients refractory to lenalidomide have been to use proteasome inhibitors such as bortezomib.

Rituximab maintenance of 375 mg/m^2 every 2 months for 3 years after autologous HCT for mantle-cell lymphoma has demonstrated significantly better PFS than observation at 4 years.[67]

Allogeneic Transplants

Within the first 100 days, relapse of primary disease accounts for 34% of deaths in HLA-matched sibling transplant recipients and 51% of deaths in URD allogeneic HCT.[4] This is an especially vulnerable time for relapse due to immune suppression and especially high risk if there was any disease present before the transplant, including minimal residual disease, high-risk cytogenetics, or the use of reduced intensity conditioning therapy. Early, small trials have shown that giving maintenance therapy after allogeneic transplant appears to be beneficial in the setting of AML using targeted therapies for FLT3+ disease. A randomized phase II study comparing sorafenib, a raf tyrosine kinase inhibitor that has flt3 inhibition, to placebo demonstrated a 60% improvement in relapse-free survival (RFS), however no significant improvement in OS.[68] A second trial randomizing patients to the flt3 tyrosine kinase inhibitor midostaurin or standard of care demonstrated a 40% reduction in relapse risk and 42% reduction in death with midostaurin; however, these were not statistically significant.[69] Several questions remain with this approach including which is the most effective agent to use, if certain populations are best candidates and what is the optimal dose and duration of therapy. Another approach has been to use epigenetic modifiers such as DNA hypomethylating agents which have shown promising results but do have significant toxicity.[69] Prophylactic DLI, especially after a reduced intensity regimen, provides the rationale of increasing GVT effect.[70] A retrospective matched-pair analysis resulted in 69% improved 5-year RFS in high-risk AML, but no difference in standard risk AML; however, there was a trend toward more chronic GVHD. While many centers have readily adopted maintenance therapy in certain high-risk patients already, larger randomized trials are ongoing to better define the role of maintenance therapy including in the setting of minimal residual disease or not.

Patient Encounter Part 5

The patient was treated with methylprednisolone 2 mg/kg for 5 days and his engraftment syndrome resolved. He was then tapered to 1 mg/kg for another 5 days without any recurrence of symptoms, so he was discharged on 0.5 mg/kg for 3 days and 0.1 mg/kg for 3 days and stopped. On day + 45 he presents to the transplant clinic complaining of a skin rash covering 50% of his body surface including on her palms, arms, soles, and trunk. He also reports being persistently nauseous and having 5 to 6 stools throughout the day. He has an endoscopy and colonoscopy and a skin biopsy will all show areas of apoptotic cells representing GVHD. He is started back on methylprednisolone 2 mg/kg/day and in 5 days his skin is less red but is now on 70% of his body and his diarrhea is no better with 1.4 L output per day.

What grade of GVHD is did this patient present with?

Are steroids alone the appropriate option for first-line treatment?

How should this patient be monitored for progression of GVHD?

Is this patient steroid refractory?

What is approved for second-line therapy of GVHD?

Late Post Engraftment and Chronic GVHD Period (After Day + 100)

▶ *Taper of Immune Suppression*

Tapering schedules for the calcineurin inhibitors after myeloablative HCT vary widely. In patients without acute GVHD, the calcineurin inhibitor levels are maintained therapeutic for the first 3 months after HCT and then are tapered slowly with the intent of discontinuing all immunosuppressive agents by 6 to 9 months after HCT. By this time, immunologic tolerance may develop and patients may no longer require immunosuppressive therapy. There is a paucity of information regarding the optimal duration of GVHD prophylaxis after nonmyeloablative HCT and immunosuppression taper schedules may be individualized based on GVHD and disease-specific factors.[28] It is not uncommon that acute GVHD may occur or flare with the decreased immune suppression.

▶ *Chronic GVHD*

Chronic GVHD is a major cause of non-relapse mortality and morbidity in allogeneic HCT recipients with up to 40% of patients requiring systemic therapy within 2 years of HCT.[71] The clinical course of chronic GVHD is multifaceted, involving almost any organ in the body and symptoms resemble autoimmune and immunologic disorders (eg, scleroderma, sicca syndrome). Chronic GVHD symptoms usually present within 1 year after allogeneic HCT and often are preceded by acute GVHD, although up to 10% of cases present later.[71] A consensus document regarding the diagnosis and scoring of chronic GVHD has been published that proposes a clinical scoring system to describe chronic GVHD as opposed to historical descriptions of chronic GVHD, which described the phenomenon as being "limited" versus "extensive" in nature.[72] The diagnosis of chronic GVHD requires distinction from acute GVHD; the presence of at least one diagnostic clinical sign of chronic GVHD or presence of at least one distinctive manifestation confirmed by pertinent biopsy or other relevant tests; and exclusion of other possible diagnoses.

▶ *Prevention and Treatment of Chronic GVHD*

Chronic GVHD is not a continuation of acute GVHD, and separate approaches are needed for its prevention and management. Prevention of chronic GVHD through prolonged use of immunosuppressive medications has been unsuccessful.[12] Thus, its prevention is focused on minimization of factors associated with higher rates of chronic GVHD. Several recipient, donor, and transplant factors are relevant. Recipient risk factors that are not modifiable include older age, certain diagnoses (eg, chronic myeloid leukemia), and lack of an HLA-matched donor. Modifiable factors that may lower the risk of chronic GVHD include selection of a younger donor, avoidance of a multiparous female donor, use of UCB or BM grafts rather than PBPCs, and limitation of CD34+ and T-cell dose infused.[12] Development of acute GVHD is a major predictor for chronic GVHD, with 70% to 80% of those with grade II to IV acute GVHD developing chronic GVHD.[1]

Relative to no treatment, survival in those with chronic GVHD is improved by extended corticosteroid therapy; however, multiple long-term adverse effects are associated with corticosteroid use. The prednisone dosage is 1 mg/kg/day administered orally in divided doses for 30 days and then slowly converted to an alternate-day therapy. One to two months may pass before an improvement in clinical symptoms is noted, and therapy is usually continued for 9 to 12 months. Therapy can be tapered slowly after resolution of signs and symptoms of chronic GVHD. If a flare of chronic GVHD occurs during the tapering schedule or after therapy is discontinued, immunosuppressive therapy is restarted. Ibrutinib (Imbruvica), a Bruton tyrosine kinase (BTK) and IL-2–inducible T-cell kinase (ITK) inhibitor, has been approved for treatment of cGVHD after failure of at least one treatment option based on an open-label, multicenter, single-arm trial of 42 patients with cGVHD.[73] Dosed at 420 mg daily, ORR was 67% with 21% demonstrating a complete response. Adverse events including arrhythmias and myelosuppression resulted in approximately 30% of patients decreasing the dose and 30% stopping therapy. Other potential approaches for patients who are refractory to initial therapy include etanercept (Enbrel), infliximab (Remicade), mycophenolate mofetil (Cellcept), rituximab (Rituxan), extended use of calcineurin inhibitors, or extracorporeal photopheresis (ECP).[74] When immunosuppressive therapy is administered for long periods, the patient must be monitored closely for chronic toxicity. Cushingoid effects, osteoporosis, aseptic necrosis of the joints, and diabetes can develop with long-term corticosteroid use. Other severe complications include a high incidence of infection with encapsulated organisms and atypical pathogens such as *Pneumocystis jiroveci*, CMV, and varicella zoster virus (VZV).

► *Infectious Complications*

Recipients of HCT are at higher risk of bacterial, viral, and fungal infections and usually receive a prophylactic or preemptive regimen to minimize the morbidity and mortality associated with infectious complications. There are three periods of infectious risks, pre-engraftment (from 15 days prior and to 30 days after HCT), post-engraftment (engraftment to day 100 post-engraftment), and late (100 days after engraftment). From days 0 to 30 after HCT, particularly for patients undergoing myeloablative HCT, the primary pathogens are aerobic bacteria, *Candida* spp., and herpes simplex virus (HSV). Early infections are due to damage to the GI tract that results in translocation of gut microorganisms (Gram-negative, *Candida* spp., for example). Respiratory viruses such as respiratory syncytial virus (RSV), influenza, adenovirus, and parainfluenza virus are recognized increasingly as pathogens causing pneumonia, particularly during community outbreaks of infection with these organisms. Because of the need to administer chemotherapy, blood products, antibiotics, and other adjunctive medications, the placement of a semipermanent double- or triple-lumen central venous catheter is necessary before HCT. However, the indwelling IV central catheters put HCT recipients at increased risk for *Staphylococcus* infections.

The second period of infectious risk occurs after engraftment to post-transplant day 100. Bacterial infections are still of concern, but pathogens such as CMV, adenovirus, and *Aspergillus* spp. are common. A common manifestation of infection is interstitial pneumonitis (IP), which can be caused by CMV, adenovirus, *Aspergillus,* and *P. jiroveci*. Suppression of the immune system from acute GVHD and corticosteroids primarily targets T cells and contributes to the risk of such infections during this period.[75]

During the late period (100 days after engraftment), the predominant organisms are the encapsulated bacteria (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*), fungi, and VZV. The encapsulated organisms commonly cause sinopulmonary infections. The risk of infection during this late period is increased in patients with chronic GVHD as a result of prolonged immunosuppression.

Prevention and Treatment of Bacterial, Viral, and Fungal Infections Between the time of administration of the preparative regimen and successful engraftment, allogeneic myeloablative HCT patients undergo a period of pancytopenia that can last from 2 to 6 weeks. The risk of infection is reduced by aggressive use of antibacterial, antifungal, and antiviral therapy both prophylactically and for the treatment of documented infection. The antibacterial prophylactic regimens vary substantially among HCT centers. Some HCT centers use a prophylactic fluoroquinolone (eg, levofloxacin) on admission for HCT and then switch to a broad-spectrum IV antibiotic (eg, cefepime) when the patient experiences his or her first neutropenic fever. Although fluoroquinolones reduce the incidence of Gram-negative bacteremia, they have not been shown to affect mortality; the possibility of developing *Clostridium difficile*-associated diarrhea exists with fluoroquinolone use and infectious causes should be ruled out if diarrhea occurs. Concerns with fluoroquinolone use in the prophylactic setting during HCT include the emergence of resistant organisms and an increased risk for streptococcal infection. Broad-spectrum antipseudomonal IV antibiotics should be initiated immediately at the time of the first neutropenic fever under the treatment guidelines endorsed by the Infectious Disease Society of America for management of fever of unknown origin in the neutropenic host.[76]

Prevention of HSV and VZV Recipients who are HSV antibody seropositive before HCT are at high risk for reactivation of their HSV infection. Acyclovir is highly effective in preventing HSV reactivation, and thus, prophylactic acyclovir is standard in HSV-seropositive patients who are undergoing an allogeneic or autologous HCT. In the setting of HSV prophylaxis, dosing regimens for prophylactic acyclovir vary widely, from 400 mg twice daily to 800 mg three times daily.[77] Valacyclovir (Valtrex), a prodrug of acyclovir with improved bioavailability, may allow for adequate serum concentrations to prevent HSV in patients undergoing HCT as well.

In those with a history of VZV infection, VZV disease occurs in 30% of allogeneic HCT recipients.[77] The appropriate duration of VZV prophylaxis is controversial. Although VZV infections are reduced by prophylactic acyclovir administered from 1 to 2 months until 1 year after HCT, the risk of VZV persists in those on continued immunosuppression.[75]

Prevention and Preemptive Therapy of CMV Disease After allogeneic HCT, CMV disease is common and has high morbidity and mortality rates. Allogeneic patients are at greater risk than autologous recipients primarily because the latter more efficiently reconstitute their immune system after transplantation. Infection caused by CMV is usually asymptomatic and develops when CMV replication occurs. Replication occurs primarily in body fluids such as the blood (viremia), bronchoalveolar fluid, or urine (viruria). CMV disease occurs when the virus invades an organ or tissue. Pneumonia and gastroenteritis/colitis are the most common types of CMV disease after allogeneic HCT. The presence of a CMV viremia substantially increases the risk for developing invasive CMV disease. Strategies to prevent CMV infection have resulted in dramatic reductions in the incidence of CMV disease.

Primary CMV infection after transplant is rare and can be prevented with CMV seromatching, which includes transplanting PBPCs or BM from CMV-seronegative donors and infusing CMV-negative blood products to CMV-negative recipients. Antivirals are important in those who are CMV seropositive or have a CMV-seropositive graft, with three available approaches to minimize the morbidity associated with CMV. The first is universal prophylaxis, in which ganciclovir is begun at the time of engraftment and is continued until approximately day + 100; however, due to BM suppression, it is often difficult to start or to maintain appropriate doing. The second approach is preemptive therapy in which CMV titers in the blood by PCR are monitored weekly and therapy is started above a threshold level developed at the institution. The third approach utilizes the novel antiviral agent letermovir. By inhibiting the DNA terminase complex of CMV, letermovir selectively inhibits viral replication with minimal toxicity to human cells. A phase 3 placebo controlled study in CMV positive recipients utilizing letermovir 480 mg daily (or 240 mg if on cyclosporine) through week 14 after transplant demonstrated the incidence of clinically significant CMV infection, the primary endpoint, by week 24 was significantly reduced with letermovir.[78] However, all-cause mortality was significantly lower at week 24 in the letermovir group but not reduced at week 48.[79]

Fungal Infections

▶ *Prevention of Fungal Infections*

The widespread use of fluconazole prophylaxis since the early 1990s has led to a significant decline in the morbidity and mortality associated with invasive candidiasis in HCT recipients. However, invasive aspergillosis (IA), zygomycetes, and fluconazole-resistant *Candida* spp., such as *Candida krusei* and *Candida glabrata*, have increased markedly in incidence.[80] Itraconazole, another azole antifungal agent, has better *in vitro* activity against fluconazole-resistant fungi (eg, *Aspergillus* and some *Candida* spp.) and is more effective than fluconazole for long-term prophylaxis of invasive fungal infections after allogeneic HCT; however, itraconazole is used less often because of frequent GI side effects and concern for potential drug interactions. Posaconazole (Noxafil) is a triazole antifungal that has been approved by the FDA for prophylaxis in HCT patients with GVHD and is now the recommended prophylactic agent for this subset of HCT patients on immunosuppression.[80] Posaconazole oral suspension should be given with food to increase absorption but is still poorly absorbed in most patients and levels should be monitored to assure adequate absorption. The posaconazole extended release tablet can be administered without regard to food and has good bioavailability. Micafungin (Mycamine), an echinocandin, has been FDA approved for prophylaxis of *Candida* infections in patients undergoing HCT.

▶ *Risk Factors for Invasive Mold Infections*

Invasive mold infections (eg, *Aspergillus* spp., *Fusarium* spp., *Zygomycetes*, and *Scedosporium* spp.) are an increasing cause of morbidity and death after allogeneic and autologous HCT. It has been estimated that up to one-third of febrile neutropenic patients who do not respond to antibiotic therapy after 1 week are harboring a fungal infection. In HCT recipients, risk factors for invasive fungal infections include previous history of invasive infection; recipient factors, including older age, CMV seropositivity, and type of stem-cell transplant, treatment factors (eg, a fludarabine-based preparative regimen), transplant complications (eg, prolonged neutropenia, graft failure, and higher grade GVHD), and host factors (eg, diabetes, iron overload).[81] Infections with *Aspergillus* spp. remain the most common mold infections diagnosed in the HCT population and optimal treatment must be promptly initiated if indicated.

▶ *Treatment of Invasive Aspergillosis*

Early diagnosis and initiation of appropriate therapy may reduce the high mortality rate of IA. Outcomes also depend on recovery of the recipient's immune system and reduction of immunosuppression. Diagnosis is difficult with the use of computed tomography scans and cultures. Research is ongoing to evaluate the benefit of using nonculture-based methods, such as galactomannan and (1,3)-β-ᴅ-glucan antigen detection, which are components of the fungal cell wall that can be detected by commercially available assays.

Practice guidelines are available for the treatment of invasive *Aspergillus* infections in immunocompromised patients.[80] Available mold-active agents include triazole antifungals (itraconazole, voriconazole, posaconazole, and isavuconazole), echinocandins (caspofungin, micafungin, and anidulafungin), and amphotericin B formulations. The Infectious Disease Society of America Guidelines recommend early initiation of therapy with suspected infection. First-line therapy recommendation is voriconazole with alternatives being liposomal amphotericin or isavuconazole. Trough levels of the triazoles should be monitored at steady state. Many HCT patients are on prophylaxis with voriconazole, posaconazole, or isavuconazole, if aspergillosis occurs while on one of these agents then liposomal amphotericin would be recommended with careful monitoring of renal function and electrolytes. Also liposomal amphotericin plus an echinocandin could be considered.

The optimal duration of appropriate antifungal therapy for treating IA is individualized to the reconstitution of the patient's immune system and his or her response to antifungal treatment. Most clinicians continue aggressive antifungal therapy until the infection has stabilized radiographically and may continue with less aggressive "maintenance" therapy (eg, oral voriconazole) until immunosuppression is lessened or completed. In general, it is common to require several months of antifungal therapy to treat IA.

▶ *Pneumocystis Jiroveci*

After allogeneic HCT, prophylaxis for *P. jiroveci* (formerly *P. carinii*) pneumonia (PJP) is used because *Pneumocystis* is a serious infection with a high mortality rate if left untreated. Most centers use sulfamethoxazole/trimethoprim for 6 to 12 months after HCT; aerosolized or IV pentamidine, oral dapsone, and oral atovaquone are alternatives for patients who are allergic to sulfa drugs or who do not tolerate sulfamethoxazole/trimethoprim.[75] Because PJP most often occurs after engraftment, sulfamethoxazole/trimethoprim usually is begun after neutrophil recovery because of its myelosuppressive effects. Patients receiving prophylactic sulfamethoxazole/trimethoprim should be monitored closely for rash and unexplained neutropenia or thrombocytopenia. Autologous HCT patients do not receive posttransplant immunosuppression, and the risk of developing PJP is significantly lower; however, prophylaxis is still used often used for several months.

Patient Encounter Part 6

The patient was treated with methylprednisolone and ruxolitinib in conjunction with his tacrolimus which fully resolved his skin GVHD and significantly decreased his GI GVHD. He was requiring high doses of insulin, and he became so weak he had to use a wheelchair. Vedolizumab was added and after 3 weeks he also has resolution of his GI GVHD. He was then discharged from the hospital. On day + 130, he presented to clinic with extremely dry eyes and mouth and skin stiffening around his waist and arms where his acute GVHD was the worst. He also presented with progressive shortness of breath over the past 2 weeks, a CT was done revealing several nodules with a "halo" of ground glass attenuation, a bronchiolar lavage revealed aspergillus.

Is this patient experiencing chronic GVHD, what are his symptoms?

Are steroids alone the appropriate option for treatment?

How should his aspergillus be treated?

Should he be started on maintenance therapy for the AML?

Nonpharmacologic Therapy

▶ *Psychologic Support*

Patients and their caregivers may experience emotional and psychological distress during and for sometimes long after the HCT.[82] This may have negative impacts on recovery, increase GVHD, and even effect mortality. HCT may cause significant financial hardships, cause patients to move near a transplant center for a period of time, limit social contacts, and limit activities for a long period of time. Patients may experience long hospitalizations or GVHD with multiple readmissions and then face new long-term challenges with chronic GVHD. It is critical that patients are evaluated and monitored and behavioral therapies are implemented for both patients and caregivers to ease emotional burdens as much as possible through this process.

▶ *Graft-Versus-Tumor Effect*

A GVT effect caused by the donor lymphocytes occurs after transplant. This results in lower relapse rates in patients with GVHD relative to those who did not have GVHD; a higher rate of leukemia relapse after T-cell–depleted, autologous, or syngeneic HCT; and the effectiveness of DLIs in reinducing a remission in patients who relapsed after allogeneic HCT. Rapid taper of immunosuppression in patients with residual disease may induce a GVT effect. In DLI, lymphocytes are collected from the peripheral blood of the donor and administered to the recipient. Eradication of the recurrent malignancy is caused by either specific targeting of the tumor antigens or GVHD, which may affect cancer cells preferentially. Patients with hematologic malignancies (eg, CML and AML) and certain solid tumors (eg, renal cell carcinoma) appear to benefit from a GVT effect. These data gave rise to the use of nonmyeloablative preparative regimens.

LONG-TERM SURVIVORSHIP ISSUES AFTER HCT

The number of long-term HCT survivors is increasing as 5-year disease-free survival rates improve. HCT recipients—with either an autologous or an allogeneic graft—have a higher mortality rate than the general population.[5,83] **KEY CONCEPT** Long-term survivors of HCT should be monitored closely for many potential complications including cardiac, renal, hepatic, endocrine, and pulmonary toxicities as well as poor bone health, dental health, infections, and secondary malignancies.[5]

Survivors of HCT are at higher risk for secondary malignancies from the chemotherapy, TBI, immune suppression or from cytogenetic changes. Skin cancers are most prevalent and patients should assessed annually for new skin cancers. Long-term impairment of end-organ function of the kidneys, liver, and lungs, may be caused by the preparative regimen, infectious complications, posttransplant immunosuppression and/or from complications of GVHD. Many HCT recipients experience endocrine dysfunction, such as hypothyroidism from TBI, adrenal insufficiency from long-term corticosteroids to treat GVHD, thyroid dysfunction from GVHD, diabetes from GVHD and corticosteroids or TBI, and infertility from radiation and/or high doses of alkylating agents in myeloablative preparative regimens. Osteopenia has been found in more than half of HCT recipients, likely from gonadal dysfunction, corticosteroids, endocrine dysfunction, and vitamin deficiencies. Appropriate treatment and prevention, often with bisphosphonates, is important to help prevent fractures and osteoporosis.

Close monitoring of HCT recipients for infections is necessary because recovery of immune function is slow, sometimes requiring more than 2 years, even in the absence of immunosuppressants.[84] Fevers should be assessed and treated rapidly to minimize the likelihood of a fatal infection. HCT recipients—both autologous and allogeneic—lose memory B cells and thus lose the protective antibodies to vaccine-preventable diseases requiring reimmunization of HCT recipients.[85]

All survivors of HCT should be monitored routinely for signs of relapse. Allogeneic recipients must also always be monitored for chronic GVHD. They should be advised regarding revaccination and obtaining prompt medical care for fevers or signs of infection. Routine evaluations of organ function (ie, renal, hepatic, thyroid, and ovarian) and osteopenia/osteoporosis with bone density scans should occur and the appropriate management strategies initiated if necessary.

OUTCOME EVALUATION

The overall desired outcome with HCT is to cure the patient of his or her underlying disease while minimizing the short- and long-term morbidity associated with HCT. Early intense monitoring for nonhematologic toxicity of the preparative regimen during its administration and at least daily, with more frequent monitoring if the patient is experiencing these nonhematologic effects. Monitoring immune suppression and calcineurin levels are important for decreasing GVHD and nephrotoxicity. Monitoring for chimerism in allogeneic patients is important until full chimerism occurs. Patients should be assessed for infections throughout all phases of the transplant process. Monitoring for symptoms of GVHD are critical, especially to start therapy early in the process. Patients should be monitored for symptoms and signs of the disease that is being treated by HCT to assess the effectiveness of the HCT; for example, monitoring radiologic scans for lymphoma patients or appropriate biologic markers for myeloma patients. If a molecular target is present such as *BCR-ABL* positive ALL would be to monitor disease response by PCR of the *BCR-ABL* transcript. The actual clinical outcome monitored, along with the frequency of monitoring, is based on the underlying disease. If there is a targeted mutation and maintenance therapy was not given, then therapy should be considered with positive PCR.

Finally long-term monitoring of chronic GVHD symptoms and organ function and bone density is critical in providing successful outcomes.

Abbreviations Introduced in This Chapter

aGVHD	Acute graft-versus-host disease
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
ATG	Antithymocyte globulin
BMT	Bone marrow transplantation
BU-CY	Busulfan–cyclophosphamide
CD	Cluster of differentiation
CINV	Chemotherapy-induced nausea and vomiting
cGVHD	Chronic graft-versus-host disease
CML	Chronic myelogenous leukemia
CMV	Cytomegalovirus
CY-TBI	Cyclophosphamide–total-body irradiation
DMSO	Dimethyl sulfoxide
GVHD	Graft-versus-host disease
HGF	Hematopoietic growth factors
HLA	Human leukocyte antigen
HCT	Hematopoietic stem-cell transplant
IA	Invasive aspergillosis
IL	Interleukin
Mesna	2-mercaptoethane sulfonate sodium
MHC	Minor histocompatibility complex
MM	Multiple myeloma
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NMDP	National Marrow Donor Program
PBPC	Peripheral blood progenitor cells
PJP	Pneumocystis pneumonia
SOS	Sinusoidal obstruction syndrome
SCr	Serum creatinine
TNF	Tumor Necrosis Factor
TBI	Total-body irradiation
UCB	Umbilical cord blood
VOD	Venoocclusive disease
VZV	Varicella zoster virus

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Supportive Care in Oncology

Alexandre Chan and Lee Nguyen

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Describe the impact of various supportive care interventions on the prognosis of patients with cancer.
2. Discuss the scientific basis for providing various supportive care interventions in the oncology patient population.
3. Identify patient-related and disease-related risk factors in defining a population for whom supportive care interventions would be of benefit.
4. Recognize typical presenting signs and symptoms of common complications and emergencies that require supportive care interventions.
5. Outline appropriate prevention and management strategies for various supportive care interventions.
6. Prepare a monitoring plan to evaluate the efficacy and toxicity of pharmacotherapy interventions for supportive care problems.

INTRODUCTION

Patients with cancer are at risk for serious adverse events that result from their treatment, the cancer, or both. The management of these complications is generally referred to as supportive care or symptom management. Examples of treatment-related complications include chemotherapy-induced nausea and vomiting (CINV), myelosuppression, febrile neutropenia (FN), hemorrhagic cystitis, mucositis, tumor lysis syndrome (TLS), and immunotherapy-related toxicities. Tumor or cancer-related complications include superior vena cava (SVC) obstruction, spinal cord compression, hypercalcemia, and brain metastases. In some cases, these events can be life threatening. SVC obstruction, spinal cord compression, TLS, and hypercalcemia have traditionally been defined as oncologic emergencies. Treatment- and disease-related complications in the cancer patients require rapid assessment and supportive care interventions. The onset of oncologic emergencies may herald the onset of an undiagnosed malignancy or progression or relapse of a preexisting malignancy. Optimal management of patients with various oncologic emergencies and complications requiring supportive care interventions can significantly decrease morbidity and mortality in patients with cancer. This chapter provides an overview of these issues.

CHEMOTHERAPY-INDUCED TOXICITIES: NAUSEA/VOMITING

Nausea and vomiting were once the most common feared toxicities by patients undergoing treatment. However, with the advent of supportive care, CINV is largely manageable with prophylactic usage of antiemetics.[1] KEY CONCEPT The optimal method of managing CINV is to provide adequate pharmacologic prophylaxis given a patient's risk level for emesis. Insufficient control during the first cycle of chemotherapy leads to more difficulty in controlling emesis for subsequent cycles.[2]

EPIDEMIOLOGY AND ETIOLOGY

Although it is widely known that chemotherapy causes nausea and vomiting, the rate of emesis varies depending on individual patient risk factors and drug therapy regimen. Therefore, cancer treatments are stratified into varying risk levels: high, moderate, low, and minimal. Agents with a "high" emetic risk cause emesis in more than 90% of cases if not given any prophylaxis. The rates of emesis for "moderate," "low," and "minimal" are 30% to 90%, 10% to 30%, and less than 10%, respectively. Table 99–1 lists the individual agents and their risk category.[3]

PATHOPHYSIOLOGY

The pathophysiology of nausea and vomiting is described in Chapter 20. Specific to CINV, the key receptors include serotonin (5-HT_3) receptors (located in the chemoreceptor trigger zone, emetic center of the medulla, and gastrointestinal [GI] tract) and neurokinin-1 (NK1) receptors (located in the emetic center of the medulla). Serotonin plays an important role in the genesis of acute vomiting, occurring within the first 24 hours of chemotherapy, because some cancer drug therapies can stimulate a release of serotonin from enterochromaffin cells in the GI tract. Serotonin then activates the emetic response by binding to $5HT_3$ receptors in the emetic center. This short-lived release of serotonin likely explains why serotonin antagonists are more beneficial for preventing acute versus delayed vomiting. Other sites that are targeted by antiemetics include dopamine, muscarinic (acetylcholine), histamine, and cannabinoid receptors.[1]

CLINICAL PRESENTATION AND DIAGNOSIS

CINV, although frequently discussed as one syndrome, includes two distinct clinical entities, including both nausea and vomiting. Nauseous patients may present with general GI upset and reflux and may report a sensation or desire to vomit

Table 99–1

Emetogenic Potential of Selected Chemotherapy

Risk	Agent
High emetic risk (> 90% of patients will vomit without appropriate antiemetics)	AC combination (doxorubicin or epirubicin and cyclophosphamide) Carmustine > 250 mg/m^2 Carboplatin AUC ≥ 4 Cisplatin Cyclophosphamide > 1500 mg/m^2 Dacarbazine Doxorubicin ≥ 60 mg/m^2 Epirubicin > 90 mg/m^2
Moderate emetic risk (30%–90%)	Amifostine > 300 mg/m^2 Arsenic trioxide Azacitidine Bendamustine Busulfan > 4 mg/m^2 Carboplatin AUC < 4 Carmustine ≤ 250 mg/m^2 Cyclophosphamide ≤ 1500 mg/m^2 Cytarabine > 200 mg/m^2 Daunorubicin Doxorubicin < 60 mg/m^2 Epirubicin < 90 mg/m^2 Idarubicin Ifosfamide < 2 g/m^2 Irinotecan Methotrexate > 250 mg/m^2 Oxaliplatin
Low emetic risk (10%–30%)	Ado-trastuzumab emtansine Afatinib (oral) Amifostine < 300 mg/m^2 Bexarotene Brentuximab Cabazitaxel Carfilzomib Capecitabine (oral) Dasatinib (oral) Docetaxel Doxorubicin (liposomal) Eribulin Erlotinib (oral) Etoposide 5-Fluorouracil Gemcitabine Ixabepilone Methotrexate > 50 mg/m^2 and < 250 mg/m^2 Mitomycin Mitoxantrone Paclitaxel Palbociclib (oral) Pemetrexed Sunitinib (oral) Topotecan Vorinostat
Minimal risk (< 10%)	Most other agents

Data from National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Antiemetic v.2.2020.

without being able to do so. In all cases, it is important that other etiologies of nausea and vomiting are ruled out before diagnosing chemotherapy as the cause. Other causes of nausea and vomiting may include bowel obstruction, opioid intolerance, electrolyte imbalances, brain metastases, and vestibular dysfunction.[4]

TREATMENT

Desired Outcomes

The desired outcome is to completely prevent or minimize the severity of nausea, vomiting, and the use of breakthrough antiemetic medications. In clinical trials, a common end point is "complete response," defined as having no emesis and no breakthrough medication use within a defined period of time.[5] If patients experience nausea or emesis, the goal is to quickly relieve the episode and prevent future nausea or vomiting, whether in the next few days or for the next cycle of chemotherapy.[4]

General Approach to Treatment

Treatment-related factors and patient-related factors can help define a patient population at risk for developing CINV.[2] Treatment-related factors include those chemotherapy agents with high and moderate levels of emetogenicity, dose, and schedule (see Table 99–1 for a complete listing).[3] CINV is typically a cyclical occurrence. Although this section focuses on CINV, it can be helpful for practitioners to remember that patients undergoing concomitant radiation therapy and chemotherapy are at risk for more severe nausea and vomiting. Radiation (particularly total-body irradiation as part of a conditioning regimen for stem-cell transplant) can cause a more cumulative (versus cyclical) nausea/vomiting phenomenon.[3]

Specific patient-related factors such as female gender, age less than 50, history of motion sickness, pregnancy-induced nausea or vomiting, anxiety, low alcohol consumption, and poor emetic control in previous chemotherapy cycles increase the risk of emesis.[6] It is important to design an antiemetic regimen with consideration of these patient-specific risk factors.[4] A well-designed regimen includes a prophylactic regimen targeting various phases of nausea/vomiting and a breakthrough antiemetic drug "as needed." Although many drugs are recommended as "breakthrough" drugs, choose a drug with a different mechanism of action compared with the drugs used for prophylaxis.[4]

▶ *Nonpharmacologic Therapy*

Nonpharmacologic therapies for nausea and vomiting can be useful adjuncts to drug therapy, particularly in the setting of anticipatory nausea and vomiting. Behavior therapies such as relaxation, guided imagery, and music therapy as well as acupuncture or acupressure may be useful in this setting. Mixed benefits have been observed with the use of ginger extract. Other general measures that can be taken include ensuring adequate sleep before treatment, eating smaller meals, and avoiding spicy and greasy foods and foods with strong odors.[4]

Clinical Presentation and Diagnosis of CINV

Acute Nausea/Vomiting

- Occurs within the first 24 hours after chemotherapy administration

Delayed Nausea/Vomiting

- Occurs between 24 hours and 5 days after chemotherapy administration

Anticipatory Nausea/Vomiting

- A learned, conditioned reflex response to a stimulus (sight, sound, smell) often associated with poor emetic control in a previous cycle of chemotherapy

Breakthrough Nausea/Vomiting

- Occurs despite prophylaxis with an appropriate antiemetic regimen

Differential Diagnosis

- Surgery, radiation
- Brain metastases
- Gastric outlet or bowel obstruction, constipation
- Hypercalcemia, hyperglycemia, hyponatremia, uremia
- Food poisoning or intolerance
- Other drugs (opioids)

Table 99–2

Recommended Therapy by Emetic Risk

Emetic Risk Category (Incidence of Emesis Without Antiemetics)	Antiemetic Regimens and Schedules
High: Cisplatin and other agents, (>90%)	5-HT_3 receptor antagonist: day 1[a] Dexamethasone: days 1–4 NK-1 receptor antagonist: day 1 only (except oral aprepitant: days 1–3) Olanzapine: days 1–4
High: Anthracycline combined with cyclophosphamide (>90%)	5-HT_3 receptor antagonist: day 1 Dexamethasone: day 1 NK-1 receptor antagonist: day 1 only (except oral aprepitant: days 1–3) Olanzapine: days 1–4
Moderate (30%–90%)	5-HT_3 receptor antagonist: day 1 Dexamethasone: day 1 *Or* 5-HT_3 receptor antagonist: day 1 Dexamethasone: days 1–3 for regimens with drugs known to cause delayed nausea/vomiting
Low (10%–30%)	Dexamethasone: day 1 *Or* 5-HT_3 receptor antagonist: day 1
Minimal (< 10%)	No routine prophylaxis. 5-HT3 receptor antagonists, others as needed

Data from Antiemetics, ASCO Guideline Update, 2020 and National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Antiemetics v.2.2020.

[a] If netupitant-palonosetron or fosnetupitant-palonosetron is used, no additional 5-HT3 receptor antagonist is needed.

▶ *Pharmacologic Therapy*

Nonprescription medications such as antacids, histamine-2 receptor blockers, and proton pump inhibitors can be helpful in reducing gastroesophageal reflux associated with some cancer treatments that may trigger or exacerbate CINV.[4] Nonprescription antihistamines marketed for nausea associated with motion sickness are not usually helpful in managing CINV.

Four drug classes are highly effective in preventing CINV: corticosteroids (dexamethasone), serotonin (5-HT3) receptor antagonists, NK1 receptor antagonists, and the thienobenzodiazepine, olanzapine.[3] Drugs with differing mechanisms of action are combined, depending on the emetic risk level of the chemotherapy regimen (Table 99–2).

Intravenous (IV) antiemetics are usually administered 30 minutes before chemotherapy, and oral antiemetics are administered 60 minutes before chemotherapy. Dexamethasone is the preferred agent to prevent CINV in the delayed setting (days 2–4 after chemotherapy administration) and given at dose of 8 mg once daily for 3 to 4 days.[3,4] The use of multiday dexamethasone should only be limited to highly emetogenic risk chemotherapy and only for those moderately emetogenic regimens known to cause delayed nausea and vomiting (such as cyclophosphamide, doxorubicin, and oxaliplatin) due to concerns for toxicities related to dexamethasone. In some cases, the serotonin antagonists may also be continued orally for 2 to 3 days after chemotherapy or be used in place of dexamethasone, though practice guidelines differ in their recommendations.[3,4] In view of the ability to decrease the persistence of CAR T-cell population, dexamethasone should be avoided for 3 to 5 days before and 90 days after CAR T-cell therapies. Several NK1 receptor antagonists are currently available, and these agents should be given on day 1 of the chemotherapy cycle, with the exception of oral aprepitant which should be continued on days 2 and 3 of the chemotherapy cycle. Netupitant and fosnetupitant are available as fixed combination products with palonosetron, which is a long-acting 5-HT$_3$ receptor.

Olanzapine is now a standard component of the antiemetic regimens for high emetic-risk chemotherapy at 10 mg by mouth once daily (5 mg by mouth once daily for elderly patients) for 4 days starting the day of chemotherapy and as an option to add to the antiemetic regimen for moderately emetogenic chemotherapy.[3,4] Olanzapine can be substituted for dexamethasone if patients are unable to tolerate dexamethasone (eg, diabetics).[4] Concerns of QT prolongation have resulted in the IV formulation of dolasetron to be removed from the market and dosing of ondansetron has been reduced to 16 mg IV as the 32 mg IV was reported to extend the QT interval.[7]

The other classes of antiemetics are usually prescribed “as needed” for breakthrough nausea or vomiting. The dopamine antagonists prochlorperazine and metoclopramide are usually recommended because they antagonize a different receptor than the drugs already given for prophylaxis. Other medications, including serotonin receptor antagonists, cannabinoids, dexamethasone, scopolamine, or olanzapine, may be used as alternatives to dopamine antagonists for breakthrough nausea and vomiting.[3,4] For those in any risk group who experience anticipatory nausea and vomiting, the addition of lorazepam for prophylaxis and breakthrough to behavioral therapy is recommended for its antiemetic and antianxiety properties, but not as a single-agent to prevent CINV.[3,4] Table 99–3 lists the doses of the antiemetic agents for prophylaxis and breakthrough use.

Table 99–3

Antiemetic Dosing

Antiemetic	Single Dose Administered Before Chemotherapy	Daily Schedule
5-HT$_3$ Receptor Antagonists		
Dolasetron	By mouth: 100 mg	100 mg by mouth daily
Granisetron	By mouth: 2 mg IV: 1 mg or 0.01 mg/kg Topical: 34.3-mg patch (apply 24–48 hours before chemotherapy, leave on for 7 days)	1–2 mg by mouth daily or 1 mg by mouth two times a day
Ondansetron	By mouth: 16–24 mg IV: 8–16 mg	8 mg by mouth two times a day or 16 mg by mouth daily
Palonosetron	IV: 0.25 mg	None
NK-1 Receptor Antagonists		
Aprepitant	By mouth: 125 mg IV emulsion: 130 mg	If oral on day 1, 80 mg by mouth days 2 and 3
Fosaprepitant	IV: 150 mg × 1	None
Netupitant/palonosetron combination	By mouth: netupitant 300 mg/palonosetron 0.5 mg IV: fosnetupitant 235 mg/palonosetron 0.25 mg	None
Rolapitant	By mouth: 180 mg	None
Others		
Dexamethasone	By mouth or IV: 12 mg	8 mg by mouth days 2–4
Olanzapine	5–10 mg by mouth daily	5–10 mg by mouth days 2–4

Data from Antiemetics, ASCO Guideline Update, 2020 and National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Antiemetics v.2.2020.

A prophylactic antiemetic regimen for high emetic risk levels of IV chemotherapy should be with a four-drug combination using dexamethasone, olanzapine, NK1 receptor antagonist, and 5-HT$_3$ antagonist to prevent both acute and delayed emesis.[3,4] Dexamethasone and olanzapine should be continued until day 4, and oral aprepitant is also administered on days 2 and 3 if oral aprepitant is used. In a phase 3 randomized trial, olanzapine versus placebo were added to aprepitant or fosaprepitant, a 5-HT$_3$ receptor antagonist and dexamethasone for patients receiving highly emetogenic chemotherapy. The four-drug combination with olanzapine substantially increased the response rate compared with placebo for acute, delayed, and overall control of CINV.[8] Currently, guidelines recommend the use of a four-drug combination as prophylactic antiemetics for high emetic risk chemotherapy regimens.

Patient Encounter 1: CINV

Your patient is receiving her second cycle of chemotherapy today. She had intractable nausea and vomiting after her last cycle of treatment. On interview with her pharmacist today, she is very anxious about her treatment, and she is experiencing severe nausea and retching symptoms.

What type of nausea is this patient manifesting?

What do you recommend for manage the nausea and vomiting in this patient?

For moderately emetogenic regimens, acute emesis is still of major concern, but the incidence of delayed emesis is less. Therefore, dexamethasone plus a 5-HT$_3$ antagonist should be given on day 1. On days 2 to 3, either the dexamethasone or the 5-HT$_3$ antagonist (dexamethasone preferred for regimens known to cause delayed CINV) is continued, though one exception is when palonosetron is given as the 5-HT$_3$ antagonist on day 1. Because its half-life is long, no redosing is necessary on subsequent days. While NK1 receptor antagonist is not routinely used for moderately emetogenic chemotherapy, if patients have clinical risk factors or if they experienced uncontrolled emesis with previous chemotherapy cycles, follow the suggest guidelines for "high" emetogenic risk level.[4]

For low emetic risk IV chemotherapy regimens, single-agent antiemetic prophylaxis with either dexamethasone or 5HT$_3$ antagonist is recommended 30 minutes before chemotherapy.[3,4] For minimal emetic risk groups, guidelines do not recommend routine prophylaxis with antiemetics; instead, patients should be provided with a drug to take as needed for nausea and vomiting.[3,4] Table 99–2 summarizes regimens for antiemetic prophylaxis for the different risk levels of IV chemotherapy.

Many oral anticancer agents are now available and are typically administered daily. For highly and moderately emetogenic oral anticancer therapy, an oral 5HT$_3$-antagonist is administered 60 minutes before each chemotherapy dose. For low–minimal risk oral anticancer agents, an "as needed" antiemetic agent may be given for any breakthrough nausea/vomiting.[4]

OUTCOME EVALUATION

Evaluating patients' nausea and vomiting when chemotherapy is given in the outpatient setting is challenging, as patients return home after drug administration and may or may not report inadequate control of nausea or emesis. Subsequent chemotherapy cycles may be poorly controlled, especially if patients do not state their experience with the previous cycle. To ameliorate this problem, patients' experiences with CINV should be assessed, particularly after the first and second cycles of chemotherapy. Patients should be asked about their previous emesis control with subsequent cycles of chemotherapy, and the prophylactic regimen may need to be adjusted. Patients should also be encouraged to self-report symptoms of nausea and vomiting while at home. Patients should be educated on appropriate usage of antiemetics at home, and side effects of the antiemetic regimen should be routinely assessed and reported.

MUCOSITIS

Mucositis is the inflammation of the mucosal lining in the oral cavity and GI tract caused by damage from radiation or cytotoxic chemotherapy, often leading to ulcers. Stomatitis is a related term that is specific to inflammation in the oral cavity and associated with mammalian target of rapamycin (mTOR) inhibitors, such as everolimus. Both mucositis and stomatitis are common supportive care issues that deserve attention and are associated with many negative health consequences, including pain, inadequate nutritional intake, and risk for infection. Diagnosis is based on symptoms of pain, vomiting, diarrhea, and impact on appetite, all of which are surrogates for the inflammation and damage to the mucosal lining due to the impractical nature of a definitive diagnosis by invasive endoscopic biopsy. Patients with mucositis often require parenteral analgesics, nutrition supplementation, and anti-infectives to treat concomitant bacterial, fungal, or viral infections. Furthermore, mucositis is associated with economic consequences, primarily increased length of hospital stay, nutrition support, pain management, and infection management. The use of evidence-based practice for prevention and treatment of mucositis can help improve patient outcomes.[9,10]

EPIDEMIOLOGY AND ETIOLOGY

The incidence of chemotherapy or radiation-induced mucositis depends mostly on the type of chemotherapy, the type and area of radiation, and the specific cancer. Studies have reported an incidence of about 85% in head and neck cancer patients receiving chemoradiation.[10] The World Health Organization estimates that approximately 75% of patients who are treated with high-dose chemotherapy for stem-cell transplantation developed oral mucositis.[10] Specific chemotherapy agents associated with moderate to severe mucositis include taxanes, anthracyclines, platinum analogues, methotrexate, and the fluoropyrimidines. Everolimus-associated stomatitis can appear within 8 weeks of initiating therapy.[11]

PATHOPHYSIOLOGY

The classical concept of mucositis pathophysiology asserts that direct cytotoxicity from chemotherapy or radiation to basal epithelial cells results in ulcerative lesions caused by a lack of regeneration. These lesions are further complicated by trauma or microorganism growth. However, the most recent theory of mucositis pathophysiology is more detailed and involves a multistage, dynamic process that builds upon the historical model.[9] According to this theory, there are five stages of mucositis: initiation, primary damage response, signal amplification, ulceration, and healing. It is important to note that these stages do not occur sequentially and may be influenced by both the oral and gut microbiome as well as genetic polymorphisms in individual patients. Prevention of mucositis or treatment in early stages results in the best outcomes for patients. mTOR inhibitors, on the other hand, cause injury to oral mucosa through the inflammatory cascade, causing loss of epithelial barrier function, impairing angiogenesis and vascular cell proliferation, and causing problems with wound healing.[12]

CLINICAL PRESENTATION AND DIAGNOSIS

Patients experiencing chemotherapy-induced mucositis may present along a continuum of mild, painless, erythematous ulcers to those that are painful and/or bleeding. Stomatitis associated with mTOR inhibitors are typically presented as discrete aphthous-like lesions, rather than diffuse inflammation, in the oral cavity. In both cases, patients will experience difficulty eating and swallowing or that may require treatment with hydration, antibiotics, and/or parenteral nutrition or opioid therapy in its most severe forms.[9,10]

Clinical Presentation and Diagnosis of Mucositis

- Chemotherapy-induced mucositis generally present with painful, erythematous ulcers develop on the lips, buccal mucosa, soft palate, floor of mouth, and throughout the entire gastrointestinal (GI) tract. Symptoms appear within 5 to 7 days after chemotherapy and resolve in 2 to 3 weeks.
- Oral lesions associated with mTOR inhibitors are typically shallow, nonconfluent ulcerations, well demarcated with intense erythematous margins, and involves nonkeratinized oral mucosa.
- Pain may affect ability to swallow and eat.
- The patient may have concomitant localized or systemic infection.
- Diarrhea is a symptom of mucositis in the lower GI tract; can lead to electrolyte imbalances.

TREATMENT

Nonpharmacologic Treatment

The goal of nonpharmacologic measures to prevent mucositis is to reduce the bacterial load. **KEY CONCEPT** A multiagent approach is important, with the fundamental approach to lessen the severity of mucositis begins with basic, good oral hygiene (brushing with a soft-bristled toothbrush at least twice daily, flossing, bland rinses, and saliva substitutes) and maintaining optimal nutritional support. Cryotherapy with ice chips is also helpful for patients at risk for mucositis who are receiving 5-FU–based chemotherapy or undergoing autologous stem-cell transplantation. Photobiomodulation, which includes low-level laser therapy, is helpful to prevent mucositis in the hematopoietic cell transplant (HCT) setting and patients with head and neck cancer receiving radiation with or without chemotherapy.[9]

Pharmacologic Treatment

In the setting of radiation therapy, amifostine, a free radical scavenger, at doses equal to or greater than 340 mg/m^2 intrarectal before each dose of radiation therapy for rectal cancer may be considered to prevent GI mucositis. Among all anti-inflammatory agents, benzydamine mouthwash is the only anti-inflammatory agent that is recommended for prevention of mucositis. Gelclair, Caphosol, and Biotene are gels that provide a protective barrier between damaged oral mucosa and the environment, lessening pain and irritation and are also sometimes used as part of the overall treatment of patients with mucositis. Other antimicrobial mouth washes and lozenges, sucralfate and chlorhexidine rinses, and "magic-mouthwash" compounded rinses are not generally recommended by clinical practice guidelines for mucositis prevention even though they are frequently used in practice. H_2-antagonists or omeprazole orally are recommended to prevent pain associated with mucositis and reflux following offending chemotherapy. Additionally, octreotide at a dose of at least 100 mcg subcutaneously twice daily is recommended to treat mucositis-related diarrhea associated with high-dose stem-cell transplantation if loperamide is ineffective. Probiotics containing *Lactobacillus* spp. may be beneficial for prevention of chemoradiotherapy- and radiotherapy-induced diarrhea in patients with pelvic malignancy.[9] Prophylactic use of a steroid containing mouth rinse (such as dexamethasone) can reduce the onset and severity of mTOR associated stomatitis.[11]

Unfortunately, little evidence is available to recommend specific treatments for mucositis. Pain assessment and appropriate management are important. Pain management may be achieved with oral or intravenous opioids, topical anesthetic products, and compounded rinses that incorporate lidocaine. In more severe cases in which infection of the oral mucosa is suspected, appropriate antimicrobial therapy is necessary to prevent systemic infection.[9,10]

Palifermin is FDA-approved for the prevention and treatment of mucositis in patients receiving high-dose chemotherapy as part of stem-cell transplant or induction regimens for leukemia. Palifermin is administered as an IV bolus injection at a dosage of 60 mcg/kg/day for 3 consecutive days before and 3 consecutive days after myelotoxic therapy for a total of six doses. Administering palifermin within 24 hours of chemotherapy can result in an increased sensitivity of rapidly dividing epithelial cells to the cytotoxic agent. For this reason, palifermin should not be administered for 24 hours before, 24 hours after, or during the infusion of myelotoxic chemotherapy to avoid increasing the severity and the duration of oral mucositis.[9,10]

OUTCOME EVALUATION

The goal of therapy is to prevent or decrease the severity and duration of mucositis. Outcomes measured in clinical trials often assess the incidence, duration, and severity of mucositis with a given intervention intended to prevent or treat mucositis. Agents that are intended to palliate the symptoms of mucositis are usually assessed by measures in pain scales and the ability to eat or drink.

HEMATOLOGIC COMPLICATIONS: FEBRILE NEUTROPENIA (FN)

INTRODUCTION

FN is a common adverse effect after administration of cytotoxic chemotherapy. The mortality rate in neutropenic patients caused by infectious complications can be as low as 2.8% but can exceed 50% mortality depending on resistant bacterial type, effective antimicrobial therapy, and patient comorbidities. Therefore, FN is considered a true oncologic emergency. Patients frequently require hospitalization for prompt administration of broad-spectrum antibiotics that are critical to avoid morbidity and mortality.

EPIDEMIOLOGY AND ETIOLOGY

The microorganisms responsible for infections in neutropenic patients have changed significantly in the last 50 years. From the 1960s through the mid-1980s, gram-negative organisms were the most common bacteria isolated. This pattern shifted to the gram-positive organisms in the late 1980s, which remain the most common isolates. Recent data indicate that incidence of gram-positive to gram-negative organisms isolated in bloodstream infections (BSI) in cancer patients were 60% to 40%.[13] The organism with highest prevalence was associated with skin pathogens, coagulase-negative staphylococci followed by the class of Enterbacteriales. The previous shift from gram-negative to gram-positive organism as the cause of BSIs were likely attributed to the widespread use of central venous catheters (CVC) and more aggressive chemotherapy regimens as well as the use of prophylactic antibiotics with relatively poor gram-positive coverage (quinolones). The decline in CVC used and reduced presence of severe mucositis may have contributed to the reduction of gram-positive organisms as a causative pathogen in BSIs.[14] Commonly isolated pathogens are shown in Table 99–4. Although gram-negative infections are less common, they cause the majority of infections in sites other than the blood and are particularly virulent.[15] It should be noted that isolates vary considerably among institutions; thus, attention to institutional isolation patterns is prudent.

Table 99–4

Commonly Isolated Pathogens in Patients with FN

Type of Organism	Comments
Bacteria	
Gram-positive organisms	Most common isolates in FN
Coagulase-negative *staphylococci* (ie, *Staphylococcus epidermidis*)	Between 70% and 90% resistant to methicillin; indolent course with low mortality
Staphylococcus aureus	Some centers report > 50% resistance to methicillin
Enterococcus spp.	Resistance to vancomycin ≥ 30%
Viridans streptococci	Increasing resistance to penicillin; result of fluoroquinolone prophylaxis; associated with mucositis
Gram-negative organisms	
Pseudomonas aeruginosa	Infections rapidly fatal
Escherichia coli	High mortality rate; increasing resistance to quinolones
Klebsiella spp.	Increased incidence of β-lactamase–producing strains
Enterobacter spp.	Increased incidence of β-lactamase–producing strains
Fungi	Occur primarily after prolonged neutropenia (> 1 week)
Yeasts	
Candida albicans	Increasing incidence (~10%); high mortality rate
Non-*albicans Candida* (*Candida krusei, Candida glabrata*)	Resistant to fluconazole; high mortality rate
Molds	Resistant to fluconazole; high mortality
Aspergillus spp.	Pulmonary infection common
Fusarium spp.	Emerging pathogen
Scedosporium spp.	Emerging pathogen

FN, febrile neutropenia.

Fungal infections caused by *Candida* spp. (especially *Candida albicans*) have emerged as significant pathogens, especially in patients with hematologic malignancies and those undergoing bone marrow transplantation (BMT). In addition, *Aspergillus* spp. are important pathogens in patients with prolonged and severe neutropenia.[15]

PATHOPHYSIOLOGY

The neutrophils are the primary defense mechanism against bacterial and fungal infection. Most infections in neutropenic patients are a result of organisms contained in endogenous flora, both on the skin and within the GI tract. These organisms are provided access to the bloodstream through

Patient Encounter 2: FN

A 66-year-old woman with HIV who received treatment for metastatic breast cancer presents today, 8 days after chemotherapy, for follow-up and laboratory check. Relevant laboratory study results include WBC count, 0.6 × 10^3/mL (0.6 × 10^9/L); HgB 9.0 g/dL (90 g/L; 5.59 mmol/L)); HCT 26.6% (0.266); PLT, 5 × 10^3/mL (5 × 10^9/L), CD4 count 250 cells/mm^3; serum chemistries within normal limits except; SCr, 1.3 mg/dL (115 μmol/L); and estimated GFR 44 mL/min/1.73m^2. Vitals: T 98.2°F (36.8°C); P 68 beats/min; RR 18 breaths/min; BP 110/74 mm Hg. The patient has no known drug allergies.

What risk factors for FN does this patient have?

How would you approach this patient?

breakdowns in host defense barriers (mucositis, use of central venous catheters).

Neutropenia is defined as an absolute neutrophil count (ANC) less than 500/μL (0.50 × 10^9/L) cells or an ANC less than 1000/μL (1.00 × 10^9/L) cells with a predicted decrease to less than 500/μL (0.50 × 10^9/L) cells over the next 48 hours. The ANC is calculated by multiplying the total WBC by the percentage of neutrophils (segmented neutrophils plus "bands"). Fever is defined as a single oral temperature greater than or equal to 38.3°C (101°F) or a temperature greater than or equal to 38.0°C (100.4°F) for at least 1 hour. The combination of these two factors defines FN.[16-18] The risk of infection during the period of neutropenia depends primarily on two factors:

- The duration of the neutropenia (time period of ANC < 500/μL [0.50 × 10^9/L] cells)
- The severity of the neutropenia (lowest ANC level reached [nadir])

A multitude of other risk factors for FN have been identified (Table 99–5).[19] Many of these are also risk factors for poor outcome in patients who experience FN. Cancer drug therapy regimens are also categorized as being high risk (more than 20% incidence of FN reported in clinical trials) or intermediate risk (10%–20% risk of FN reported in clinical trials). Similar to the approach to the prevention of CINV, it is important to consider both the regimen and patient-specific risk factors when determining whether a patient should receive prophylactic therapy for FN.

It is clear that patients with FN represent a heterogeneous group. Some patients are at lower risk and could potentially be treated as outpatients, thereby avoiding the risk and cost of hospitalization. The Multinational Association for Supportive Care in Cancer (MASCC) has validated a risk assessment tool that assigns a risk score to patients presenting with FN (Table 99–6).[19] Patients with a risk-index score greater than or equal to 21 are identified as low risk and candidates for outpatient therapy (discussed under section Treatment).

PREVENTION

Three primary modalities for preventing infection in patients who are expected to become neutropenic have been utilized, the first of which is the least expensive and simplest:

- Vigilant hand hygiene
- Prophylactic antibiotics
- Colony-stimulating factors (CSFs)

Table 99–5

Risk Factors for FN

Patient Related	Therapy Related
Age >65 years receiving full chemotherapy dose intensity	Disease, cancer type, and burden
Baseline low neutrophil or lymphocyte counts	History of extensive chemotherapy
Bone marrow involvement by tumor	Chemotherapy regimen • High-dose therapy (ie, stem-cell transplant) • Dose-dense therapy
Decreased hemoglobin or albumin level	Treatment intent (curative vs. palliative)
Elevated LDH	> 20% incidence of FN reported in clinical trials with treatment regimen
HIV infection	10%–20% incidence of FN reported in clinical trials with treatment regimen plus presence of patient-specific risk factors
Liver dysfunction (bilirubin >2.0 mg/dL)	
MASCC Risk Index Score < 21	
Poor performance status	
Prior chemotherapy or radiation therapy	
Persistent neutropenia	
Recent surgery and/or open wounds	
Renal dysfunction (creatinine clearance <50 ml/min)	

FN, febrile neutropenia; LDH, lactate dehydrogenase; MASCC, Multinational Association for Supportive Care in Cancer.

Data from The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections. V.2.2020. Available from: https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf. Accessed August 17, 2020.

The advantages and disadvantages of these strategies are discussed individually in the following sections.

Hand Hygiene

As previously discussed, most infections in neutropenic patients are a result of endogenous flora; however, prevention of further acquisition of environmental pathogens is also important. Patients who are or will become neutropenic should practice careful handwashing and avoid contact with people who neglect hand hygiene. Although practice guidelines do not advocate for a "neutropenic diet" (avoiding ingestion of certain fresh fruits and vegetables as well as unprocessed dairy products), this is a common clinical advice given to patients despite the lack of strong evidence that following such a diet will reduce the risk of infection-related morbidity and mortality.[18] Evidence suggests that following a "neutropenic diet" does not have a lower incidence of infection.[20] Therefore, the focus should be on adherence to safe food handling, preparation, and storage guidelines set by the US Food and Drug Administration (FDA) to reduce food-borne infections. Practitioners should also engage in vigilant hand hygiene after each patient encounter to limit the spread of infections between patients.[17]

Prophylactic Antibiotics

Routine antibacterial prophylaxis is controversial and has been attempted primarily with sulfamethoxazole–trimethoprim (SMZ-TMP) and quinolones. SMZ-TMP offers improved prophylaxis against gram-positive organisms compared to the majority of

Table 99–6

MASCC Risk-Index for Identifying Low-Risk Patients with FN[a]

Characteristic	Score
Burden of FN with no or mild symptoms[b]	5
No hypotension (ie, systolic blood pressure > 90 mmHg)	5
No chronic obstructive pulmonary disease[d]	4
Solid tumor or hematologic malignancy without fungal infection[e]	4
No dehydration requiring parenteral fluids	3
Burden of FN with moderate symptoms[b]	3
Outpatient status	3
Age < 60 years[c]	2

[a] Note: Maximum score is 26. A risk-index score of ≥ 21 indicates that the patient is likely to be at low risk for complications and morbidity.

[b] Burden of febrile neutropenia refers to the general clinical status of the patient as influenced by the febrile neutropenic episode. It should be evaluated on the following scale: no or mild symptoms (score, 5), moderate symptoms (score, 3), and severe symptoms or moribund (score, 0). Scores of 3 and 5 are not cumulative.

[c] Does not apply to patients aged ≤ 16 years.

[d] Chronic obstructive pulmonary disease means active chronic bronchitis, emphysema, decrease in forced expiratory volumes, or need for oxygen therapy and/or steroids and/or bronchodilators requiring treatment at the presentation of the febrile neutropenic episode.

[e] Previous fungal infection means demonstrated fungal infection or empirically treated suspected fungal infection.

FN, febrile neutropenia; MASCC, Multinational Association for Supportive Care in Cancer.

From Klastersky J, Paesmans M. The Multinational Association for Supportive Care in Cancer (MASCC) risk index score: 10 years of use for identifying low-risk febrile neutropenic cancer patients. Support Care Cancer. 2013;21(5):1487–1495.

Clinical Presentation and Diagnosis of FN[16,17]

General

- Only 50% of patients with FN have a clinically documented infection.
- Only 25% of patients with FN have a microbiologically documented infection.

Signs and Symptoms

- Fever is typically the only sign of infection, although septic patients may have chills.
- Infected catheter sites may be erythematous and tender to the touch.

Laboratory Tests

- CBC with differential
- Two blood cultures from each access site (peripheral and central), urinalysis, urine culture, chest X-ray, sputum cultures

Other Diagnostic Tests

- Detailed physical examination of the oral mucosa, sinuses, skin, catheter access sites, perineal area (no rectal examination because of the risk of bacteremia)

quinolones; quinolones are more effective prophylaxis against gram-negative infections. The Infectious Diseases Society of America (IDSA), American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN) guidelines recommend fluoroquinolone prophylaxis in patients who are at intermediate and high risk for neutropenia lasting more than 7 days.[16,17] Routine antibiotic prophylaxis is not recommended for low-risk patients because of the lack of a clear benefit on mortality rates and concerns regarding increasing antibiotic resistance. One exception is that SMZ-TMP is recommended for prophylaxis of *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonitis (PJP) in all at-risk patients (i.e., hematopoietic cell transplant recipients, AIDS, receiving the predisone equivalent of 20 mg or more daily for 4 or more weeks), regardless of the presence of neutropenia.[16,17]

Two systematic reviews with over 110 trials and involving more than 13,000 patients demonstrated the benefits of prophylactic antibiotics compared to no prohylaxis.[21,22] Patients receiving either fluoroquinolone or SMZ-TMP had lower rates of bacteremia, fever, infection, and infection-related mortality and in one analysis all-cause mortality.[21,22] Of note, the use of prophylactic antibiotics did not increase the patients' risk for *Clostridioides difficile* infection.[21,22] However, most of these studies were conducted in patients with hematologic malignancies (an inherently high-risk group). Although two additional randomized trials in patients with both solid tumors and hematologic malignancies demonstrated lower rates of FN, infection, and hospitalization with oral prophylactic levofloxacin compared with placebo,[23,24] both were significantly criticized for methodological concerns and theoretical concerns about drug resistance and effectiveness of early treatment in low-risk patients. NCCN, ASCO, and IDSA only recommend prophylactic fluoroquinolone (preferred levofloxacin) for patients with expected duration of neutropenia (defined as an ANC < 1000/μL [1.00×10^9/L]) for more than 7 days because of the:

- Unknown long-term consequences on the development of resistant organisms
- Emergence of *Clostridioides difficile* and methicillin-resistant *Staphylococcus aureus* (MRSA) from fluoroquinolone overuse
- Ability to treat lower-risk patients on an outpatient basis, reducing the need for prophylactic antibiotics

In summary, the use of prophylactic quinolones in patients who are at intermediate and high risk for infection (ie, hematologic malignancies receiving high-dose chemotherapy for allogeneic stem-cell transplant) is reasonable; however, use should not be routine for low-risk patients. If prophylactic quinolone use is adopted, changes in local patterns of resistance should be closely monitored. If patients are intolerant to fluoroquinolone therapy, SMZ-TMP or a third-generation cephalosporin may be considered.

Colony-Stimulating Factors

The colony-stimulating fractors (CSFs) stimulate the maturation and differentiation of neutrophil precursors. Four agents are currently approved for use in the United States (Table 99–7). The prophylactic use of these agents decreases days of hospitalization and use of empiric antibiotics by shortening the duration of severe neutropenia (defined as ANC less than 500/μL [0.50×10^9/L]). There is little to no effect on the depth of neutrophil nadir. A meta-analysis found that the use of prophylactic granulocyte CSF (either filgrastim or pegfilgrastim) results in a 46% risk reduction of FN and a 48% risk reduction in infectious mortality, although

Table 99–7

Overview of CSF

Agent	Effector Cell(s)	Dosage	Common Adverse Effects	Comments[a]
Filgrastim (G-CSF, Neupogen; filgrastim-sndz, Zarzio; tbo-filgrastim, Granix; filgrastim-aafi, Nivestym)	Neutrophil	5 mcg/kg/day SC or IV or round to 300- *or* 480-mcg vial size	Bone pain (~25%)	Begin 1–3 days after chemotherapy
Pegfilgrastim (Neulasta; Neulasta On-body Injector; pegfilgrastim-apgf, Nyvepria; pegfilgrastim-bmez, Ziextenzo; pegfilgrastim-cbqv, Udenyca; pegfilgrastim-jmdb, Fulphila)	Neutrophil	6 mg SC once *or* Apply 1 device once	Bone pain (~25%)	Self-mediated clearance via neutrophils Once per cycle dosing Administer 1–3 days after chemotherapy
Sargramostim (Leukine GM-CSF)	Neutrophil, eosinophil, macrophage	250 mcg/m^2/day SC or IV or round to 250- *or* 500-mcg vial size	First dose effect (hypotension, flushing) Low-grade fever Bone pain Injection site skin reaction	Indicated for use after induction chemotherapy in older patients with AML Limited experience and lack of FDA approval for prevention of FN

[a] No renal or hepatic dose adjustments are required for any product listed in this table.

AML, acute myeloid leukemia; FDA, Food and Drug Administration; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; SC, subcutaneous.

absolute differences are small (3.3% vs 1.7%).[25] A more recent meta-analysis also found that a small (7%) but statistically significant reduction in the relative risk of all-cause mortality was found for patients treated with G-CSF prophylactically, with the benefit (11%) greater for patients receiving dose-dense regimens.[26] It is critical to note that patients who receive these agents may still experience FN despite the risk reduction. The primary limitation of the use of these agents is cost, and in fact, ASCO identified inappropriate G-CSF use as one of the "Top 5" interventions clinicians can make to reduce cancer care costs without compromising patient care.[27] Use of biosimilar filgrastim offers significant cost saving over standard filgrastim or pegfilgrastim and would be the most cost-efficient approach to prophylaxis.[28] CSFs are recommended beginning with the first cycle (primary prophylaxis) of chemotherapy when the risk of FN is greater than or equal to 20%, regardless of whether the goal of therapy is curative or palliative.[29] This is the point where the use of CSFs is cost effective when balanced against the cost of hospitalization and antimicrobials. Secondary prophylaxis refers to the subsequent prophylactic use of a CSF after a patient has had an episode of FN. This strategy should be used especially when the chemotherapy is being given in patients with the intention of cure (i.e., Hodgkin lymphoma, early breast cancer). In this circumstance, administration of full doses of chemotherapy on time without delays has been shown to improve patient outcomes.[25,26]

Although generally well tolerated, CSFs may cause bone pain in approximately 25% of patients. This may be managed with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), although attention to the platelet count is warranted with the use of NSAIDs. Sargramostim in particular may result in low-grade fever and myalgias, perhaps as a result of its wider pattern of effector cell stimulation.[29]

TREATMENT

Desired Outcomes

Because rapid death may occur with certain infections in neutropenic patients, prompt and emergent treatment is indicated. The primary goal is to prevent morbidity and mortality during the neutropenic period. This is accomplished by effectively treating subclinical or established infections.

General Approach to Treatment

KEY CONCEPT A risk assessment should be performed at presentation of FN to identify low-risk patients for potential outpatient treatment (see Table 99–6). Patients who do not meet low-risk criteria should be hospitalized for parenteral administration of broad-spectrum antibacterials. The IDSA has published evidence-based guidelines for the management of FN (Figure 99–1).[16] The choice of initial antimicrobial agent(s) depends on the following factors:

- Presence of a central venous catheter
- Drug allergies
- Concurrent renal dysfunction or use of nephrotoxic agents
- Use of prophylactic antibiotics
- Institutional and/or community susceptibility patterns
- Cost

KEY CONCEPT The administration of empiric therapy should begin immediately after cultures are taken. Therapy should not be withheld until after culture results are obtained.

As illustrated in Figure 99–1, specific criteria exist for the addition of vancomycin for coverage of resistant gram-positive organisms or agents for coverage of fungal infections. Additional agents are necessary in the setting of continued fever or declining clinical status in neutropenic patients. In general, all empiric therapy is continued until recovery of the ANC to levels above 500 cells/μL (0.500×10^9/L) in patients with negative culture results. If a specific etiology is identified, appropriate therapy should generally be continued until 7 days after neutropenia resolves. Specific regimens with recommended dosages are summarized in Table 99–8.

▶ *Nonpharmacologic Therapy*

Prevention of infection is key. Handwashing is critical in the prevention of disease transmission. It is also important to ensure

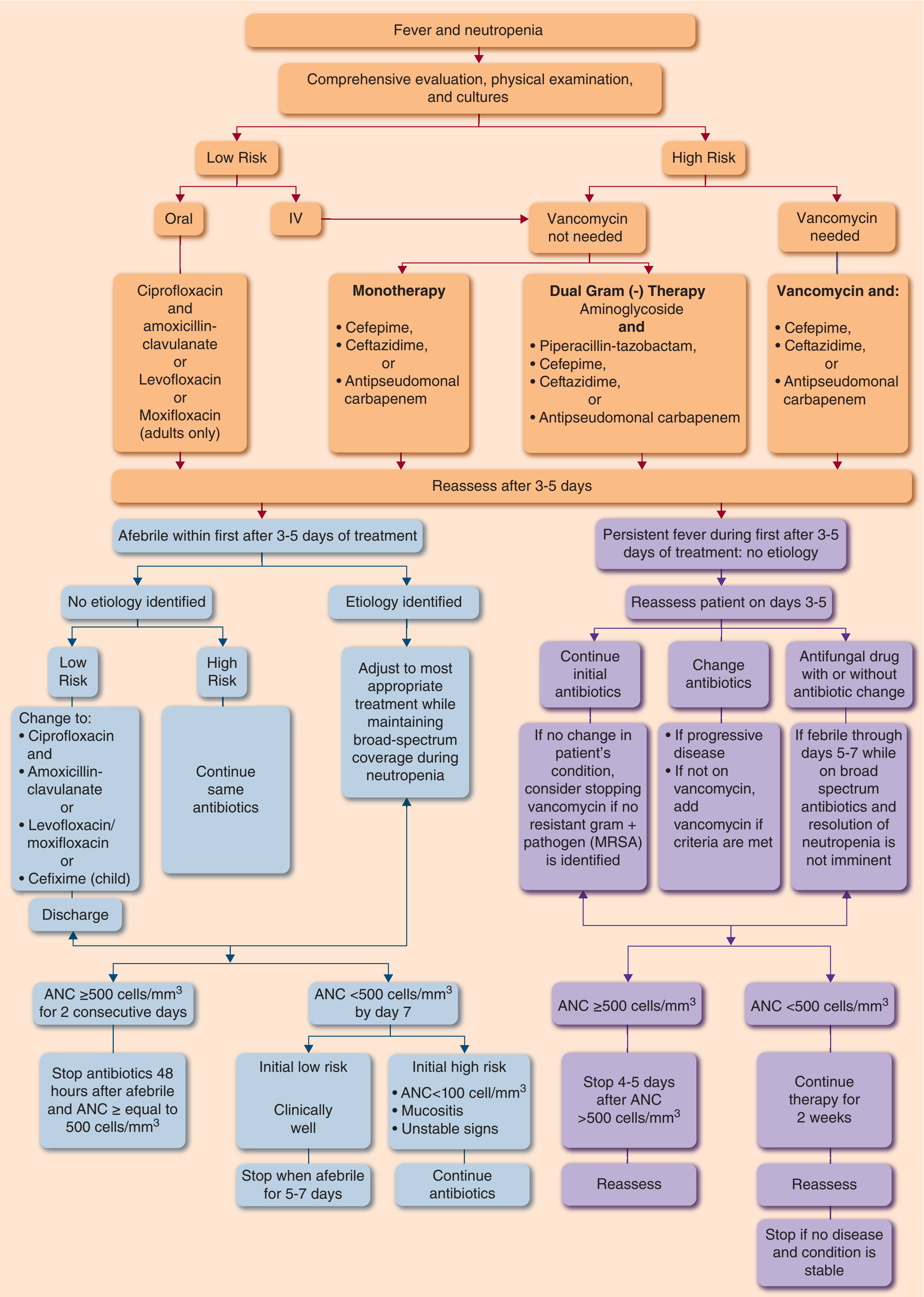
Fever and neutropenia
Comprehensive evaluation, physical examination, and cultures
Low Risk
High Risk
Oral
IV
Vancomycin not needed
Vancomycin needed
Ciprofloxacin and amoxicillin-clavulanate or Levofloxacin or Moxifloxacin (adults only)
Monotherapy
• Cefepime,
• Ceftazidime,
or
• Antipseudomonal carbapenem
Dual Gram (-) Therapy
Aminoglycoside
and
• Piperacillin-tazobactam,
• Cefepime,
• Ceftazidime,
or
• Antipseudomonal carbapenem
Vancomycin and:
• Cefepime,
• Ceftazidime,
or
• Antipseudomonal carbapenem
Reassess after 3-5 days
Afebrile within first after 3-5 days of treatment
Persistent fever during first after 3-5 days of treatment: no etiology
No etiology identified
Etiology identified
Reassess patient on days 3-5
Low Risk
High Risk
Adjust to most appropriate treatment while maintaining broad-spectrum coverage during neutropenia
Continue initial antibiotics
Change antibiotics
Antifungal drug with or without antibiotic change
Change to:
• Ciprofloxacin and
• Amoxicillin-clavulanate
or
• Levofloxacin/moxifloxacin
or
• Cefixime (child)
Continue same antibiotics
If no change in patient's condition, consider stopping vancomycin if no resistant gram + pathogen (MRSA) is identified
• If progressive disease
• If not on vancomycin, add vancomycin if criteria are met
If febrile through days 5-7 while on broad spectrum antibiotics and resolution of neutropenia is not imminent
Discharge
ANC ≥500 cells/mm³ for 2 consecutive days
ANC <500 cells/mm³ by day 7
ANC ≥500 cells/mm³
ANC <500 cells/mm³
Stop antibiotics 48 hours after afebrile and ANC ≥ equal to 500 cells/mm³
Initial low risk
Clinically well
Initial high risk
• ANC<100 cell/mm³
• Mucositis
• Unstable signs
Stop 4-5 days after ANC >500 cells/mm³
Continue therapy for 2 weeks
Stop when afebrile for 5-7 days
Continue antibiotics
Reassess
Reassess
Stop if no disease and condition is stable

FIGURE 99–1. Management of febrile episodes in neutropenic cancer patients. (ANC, absolute neutrophil count.)

Table 99–8

Dosing Guidelines for Empiric Antimicrobial Agents in FN

Regimen Type	Agents and Dosing[a]	Comments
Antibacterial		
β-Lactam monotherapy	Cefepime 2 g IV every 8 hours Ceftazidime 2 g IV every 8 hours Imipenem 500 mg IV every 6 hours Meropenem 1 g IV every 8 hours or 500 mg IV every 6 hours Piperacillin–tazobactam 4.5 g IV every 6 hours	Although piperacillin–tazobactam is not recommended in the IDSA guidelines, recent data demonstrate equivalence to other monotherapy and dual therapy regimens. All these agents require renal dose adjustment, and none requires adjustment in hepatic dysfunction.
Dual therapy with antipseudomonal β-lactam plus aminoglycoside	Cefepime, ceftazidime, imipenem, meropenem, piperacillin–tazobactam (above dosages), and either amikacin, gentamicin or tobramycin (consider extended interval dosing)	Extended interval dosing, gentamicin/tobramycin 7 mg/kg V daily or amikacin 15 mg/kg IV daily. Traditional dosing: gentamicin or tobramycin 2 mg/kg or amikacin 5 mg/kg loading dose followed by doses adjusted by serum concentrations; once-daily dosing of aminoglycosides may be used. Amikacin, gentamicin, and tobramycin require renal dose adjustment but are dosed based on serum levels. No dose adjustments are for hepatic dysfunction.
Empiric regimens containing vancomycin	Cefepime, ceftazidime, imipenem, meropenem (above dosages) and vancomycin 0.5–1 g every 6–12 hours with or without aminoglycoside	Vancomycin dosages may be adjusted based on serum levels and are adjusted for renal disease and dialysis. No dose adjustment is recommended for hepatic dysfunction.
Vancomycin intolerance or contraindications	Daptomycin 6–12 mg/kg IV every 24 hours, higher doses can be used for specific indications	Both agents are effective for the treatment of vancomycin-resistant enterococci (VRE). Daptomycin (8–12 mg/kg) is not FDA indicated for VRE but is used clinically. Daptomycin frequency adjustment instead of dose reduction needed for renal dysfunction and dialysis. Weekly creatine phosphokinase (CPK) to monitor for rhabdomyolysis. Daptomycin is inactivated by pulmonary surfactants.
	Linezolid 600 mg IV/PO every 12 hours	Linezolid requires no dose adjustment for renal or hepatic dysfunction. Hematologic toxicy may occur, thrombocytopenia most common, typically after 2 weeks of therapy. Caution use with selective serotonin reuptake inhibitors due to Serotonin syndrome.
Dual therapy containing fluoroquinolone	Ciprofloxacin 400 mg IV every 8 hours and piperacillin–tazobactam or ceftazidime (above dosages)	Cannot be used in patients who receive fluoroquinolone prophylaxis. Dose adjusted in renal disease and dialysis, but not for hepatic dysfunction.
Low-risk oral regimen	Ciprofloxacin 750 mg po every 12 hours and amoxicillin–clavulanate 875 mg po every 12 hours	For patients with MASCC scores ≥ 21 not receiving fluoroquinolone prophylaxis. Amoxicillin–clavulanate is adjusted in renal disease and dialysis but not hepatic dysfunction.
	Levofloxacin 500–750 mg po or IV daily Moxifloxacin 400 mg po or IV daily	Improved gram-positive activity compared to ciprofloxacin. Levofloxacin has limited to no activity against enteric anaerobes. Moxifloxacin has insufficient activity against Pseudomonas.
Pneumocystis jiroveci	Sulfamethoxazole-trimethoprim (SMZ-TMP) Prophylaxis: single strength tablet orally daily or double strength tablet 3 times per week Treatment: 15/mg/kg/day in divided doses every 6–8 hours based on the TMP component	Monitor for renal insufficiency, myelosuppression, hepatotoxicity, and hyperkalemia. Interactions with methotrexate. Dose adjusted in renal disease and dialysis but not for hepatic dysfunction.
Antifungal		
Amphotericin B deoxycholate	0.5–1 mg/kg IV daily	Premedication with acetaminophen and diphenhydramine; 500-mL normal saline boluses before and after. No dose adjustments are recommended for renal or hepatic dysfunction or during dialysis.
Liposomal amphotericin B	3–5 mg/kg IV daily	Lower incidence of nephrotoxicity and infusion reactions; more expensive. No dose adjustments are recommended for renal or hepatic dysfunction or during dialysis.
Anidulafungin	200 mg IV loading dose on day 1, then 100 mg IV daily	No dose adjustments required for renal or hepatic dysfunction or during dialysis.
Caspofungin	70 mg/kg IV loading dose on day 1 followed by 50 mg/kg IV daily	Dosage adjustment in hepatic dysfunction but not for renal disease or dialysis.
Micafungin	100–150 mg IV daily	No dose adjustments required for renal or hepatic dysfunction or during dialysis.
Fluconazole	400 mg IV or po daily	Dosage adjustment in renal disease or dialysis. No dose adjustment for hepatic dysfunction. *C. glabrata* is associated with variable resistance and requires higher doses.

(Continued)

Table 99–8

Dosing Guidelines for Empiric Antimicrobial Agents in FN (*Continued*)

Regimen Type	Agents and Dosing[a]	Comments
Itraconazole	200 mg po three times a day for the first three days, then 200 mg po two times a day	No dose adjustments required for renal or hepatic dysfunction or during dialysis. H_2-antagonists and proton pump inhibitors may inhibit absorption. Oral liquid formulation is preferred for absorption.
Isavuconazole	372 mg IV or po loading dose every 8 hours for 2 days followed by 372 mg IV or po daily	Can be considered in patients intolerant or refractory to first-line antimold therapy. No dose adjustments required for renal or hepatic dysfunction or during dialysis
Posaconazole	Prophylactic: 200 mg po three times a day with food 300 mg IV twice a day on day 1, then 300 mg IV daily Salvage: 200 mg po four times a day with food; then 400 mg po two times a day when stable	Not FDA-approved for primary or salvage therapy for invasive fungal infections but used clinically; no dose adjustments required for renal or hepatic dysfunction or during dialysis.
Voriconazole	6 mg/kg IV loading dose every 12 hours on day 1 followed by 4 mg/kg po or IV every 12 hours	Dosage adjustment in hepatic dysfunction; IV formulation contraindicated if creatinine clearance < 50 mL/min (0.83 mL/s); multiple drug interactions.

[a]Dosing for adult patients; adjust doses for renal dysfunction.

AML, acute myeloid leukemia; FDA, Food and Drug Administration; IDSA, Infectious Diseases Society of America; IV, intravenous; MDS; myelodysplastic syndrome; NCCN, National Comprehensive Cancer Network; po, oral; National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Prevention and treatment of cancer-related infections (version 2.2020). Last Accessed Date: August 11, 2020

that patients receive annual influenza vaccines and have had a pneumococcal and meningococcal vaccine, and neutropenic patients should avoid individuals with active respiratory infections. Indwelling catheters are often sources of infection; however, the IDSA acknowledges that catheters do not always need to be removed.[16] Catheters should be removed in the following circumstances: established tunnel infection (subcutaneous tunnel or periport infection, septic emboli, endocarditis, hypotension associated with catheter use, or a nonpatent catheter), sepsis with hemodynamic instability, recurrent infection, or no response to antibiotics within 2 or 3 days. Wound debridement should also be performed upon catheter removal. In the setting of peripheral blood stem-cell or bone marrow transplant, the Centers for Disease Control and Prevention recommends the use of high-efficiency particulate air (HEPA) filtration systems in patient rooms, and the NCCN suggests that HEPA filters are reasonable to be considered for other patients who experience prolonged neutropenia. HEPA filters are likely to be most useful in preventing mold infections. Although several small studies have attempted to evaluate the effectiveness of isolation of neutropenic patients as a mechanism for infection prevention, no clear data are available to support this practice, nor are neutropenic diets, footwear exchange, and other dietary interventions.[16,17]

▶ *Pharmacologic Therapy*

There are two primary choices for the initial management of high-risk FN: monotherapy and dual therapy (see Figure 99–1). Both regimens have been shown to be equivalent in randomized studies and meta-analyses. Monotherapy avoids the nephrotoxicity of the aminoglycosides and is potentially less expensive but lacks significant gram-positive coverage and may increase selection of resistant organisms. Dual therapy provides synergistic activity, decreased resistance, and dual coverage of *Pseudomonas aeruginosa* but also lacks gram-positive coverage and requires therapeutic monitoring for aminoglycosides. The choice between monotherapy and dual therapy is usually provider and institution preference, although dual therapy may be preferred in an acutely symptomatic patient (eg, hypotensive) or cases of bacterial resistance.

Vancomycin adds broad-spectrum gram-positive coverage; however, the increasing emergence of vancomycin-resistant organisms (i.e., *Enterococcus* spp.) prompts conservative use of this medication. Vancomycin should only be included as part of the initial therapy if patients are at high risk for a serious gram-positive infection such as the following clinical situations:

- Soft tissue infection (particularly in regions where MRSA infections is common)
- Blood cultures positive for gram-positive bacteria before final identification and susceptibility testing
- Clinically unstable (eg, hypotension or shock), pending the results of cultures
- Known colonization with penicillin/cephalosporin-resistant pneumococci or MRSA
- Clinically apparent, serious IV catheter-related infection

Vancomycin may be added to the empiric regimen after 3 to 5 days in persistently febrile patients or if cultures reveal gram-positive organisms. Vancomycin should be reassessed within 2 to 3 days of initiation and changed if the gram-positive organism is susceptible to other antibacterials or discontinued in patients with persistent fever after 3 days with negative culture results. Linezolid, quinupristin–dalfopristin, tigecycline, and daptomycin may be used in cases of vancomycin-resistant organisms or if vancomycin is not an option because of drug allergy or intolerance.

Empiric antifungal agents are typically added in persistently febrile patients after 5 to 7 days, especially if continued neutropenia is expected. Amphotericin B has historically been the drug of choice because of its broad-spectrum activity against both yeast (*Candida* spp.) and mold (*Aspergillus* spp.)

infections. Because frequent toxicity (nephrotoxicity, infusion reactions) limits the use of amphotericin B, less toxic alternatives have been studied. Lipid formulations of amphotericin provide decreased toxicity, and liposomal amphotericin B (AmBisome) has been shown to be equivalent to conventional amphotericin B as empiric therapy but is significantly more expensive. Echinocandins are active against *Candida* and *Aspergillus* species. Caspofungin is equivalent with less toxicity compared with liposomal amphotericin B in a randomized trial and is FDA-approved for this indication. Micafungin was compared to voriconazole in a randomized trial, and no significant difference in clinical efficacy was detected. Anidulafungin has not been studied specifically for empirical antifungal therapy in febrile neutropenia, but clinical experts consider it likely be effective based on data from the other echinocandins.[17] Voriconazole is equivalent to liposomal amphotericin in mortality, but response was improved in those receiving liposomal amphotericin. Voriconazole does not have an indication, but it is sometimes used. Itraconazole has also been used in some institutions, but its use is complicated by poor bioavailability of oral preparations and numerous drug interactions. Posaconazole is FDA-approved for the prevention of invasive *Aspergillus* and *Candida* infections in patients at high-risk due to being severely immunocompromised (i.e., prolonged neutropenia; hematopoietic stem-cell transplant patients with graft-versus-host-disease). The oral suspension of posaconazole is also approved for the treatment of local oropharyngeal Candidiasis. It is not FDA-approved as primary or salvage therapy for the treatment of invasive fungal infections, but it is approved by the European Union for invasive aspergillosis and other fungal infections that are refractory to standard antifungal agents. Isavuconazonium sulfate is FDA-approved for invasive aspergillosis and mucormycosis. In clinical trials, isavuconazonium sulfate was shown to be noninferior to voriconazole for invasive aspergillosis. Posaconazole and isavuconazonium sulftate should be considered for invasive, refractory fungal infections or those with intolerance to amphotericin B formulations.[17]

As stated earlier, low-risk patients fulfilling the MASCC criteria (see Table 99–6) may be treated empirically as an outpatient with a regimen combining amoxicillin–clavulanic acid and ciprofloxacin or ciprofloxacin and clindamycin in penicillin-allergic patients. Monotherapy with either levofloxacin or moxifloxacin is an alternative, but only in to low-risk patients who have not received a quinolone therapy previously as prophylaxis. The CSFs should not routinely be used for treatment of FN in conjunction with antimicrobial therapy.[16,17] However, the use of CSFs in certain high-risk patients with hypotension, documented fungal infection, pneumonia, or sepsis is reasonable. A meta-analysis demonstrated that hospitalization and neutrophil recovery are shortened and infection-related mortality is marginally improved with CSF prophylaxis in high-risk patients.[25] As with prophylactic use of these agents, cost considerations limit their use to high-risk patients.

OUTCOME EVALUATION

The success of the treatment of FN depends on the adequate recovery of the ANC and either optimal antimicrobial coverage of identified organisms or empiric coverage of unidentified organisms. Daily patient assessment should include an evaluation of response to empiric antimicrobial therapy, in terms of changes in sign and/or symptoms of infection and fever trends. Monitor the complete blood count (CBC) with differential and $T_{\max}$ (maximum temperature during previous 24 hours) daily. Assess renal and hepatic function at least twice weekly, especially in patients receiving nephrotoxic agents. Vital signs should be taken every 4 hours. Follow up on blood and urine culture results daily because many cultures do not become positive for several days. Assess the patient daily for pain that may indicate an infectious source. Conduct daily physical examination of common sites of infection. Repeat cultures and chest X-ray in persistently febrile patients and culture developing sources of infection (ie, stool cultures for diarrhea).

CARDIOVASCULAR COMPLICATIONS: SUPERIOR VENA CAVA SYNDROME (SVCS)

INTRODUCTION

Superior vena cava syndrome (SVCS) is a relatively rare complication that may occur in patients with cancer. SVCS is rarely immediately life threatening except in patients with airway compromise and/or laryngeal or cerebral edema. However, rapid recognition of typical presenting symptoms facilitates referral for tissue diagnosis (if unknown) and treatment.

EPIDEMIOLOGY AND ETIOLOGY

SVCS occurs in around 15,000 patients per year, 90% of which are caused by malignancy. Specific cancers most commonly associated with SVCS are listed in Table 99–9. Lung cancer is the most frequent cause, of which small cell lung cancer (SCLC) is the most frequent subtype associated with SVCS. In fact, SVCS is the presenting symptom for the diagnosis of lung cancer in approximately 60% of the cases.[31] This is thought to be because of its predilection for the central and perihilar areas of the lung. Interestingly, right-sided lung cancers are four times more likely than left-sided lesions to cause SVCS. Mediastinal masses from lymphomas are the second most common cause.

Clinical Presentation and Diagnosis of SVCS[30]

General

- Presentation depends on the degree of SVCS obstruction.
- Almost complete obstruction is necessary to demonstrate symptoms.

Signs and Symptoms

- Most common: swelling of face, neck, and upper extremity edema; dyspnea; cough; dilated upper extremity veins; orthopnea.
- Less common: hoarseness, dysphagia, dizziness, headache, lethargy, chest pain.
- Patients with elevated ICP may have mental status changes.
- Patients with airway obstruction may have shortness of breath.

Diagnostic Tests

- Tissue biopsy to determine underlying malignancy (if unknown), chest X-ray, CT scan, **bronchoscopy, mediastinoscopy**.

Table 99–9

Tumors Most Commonly Associated with SVCS

Cause	Frequency (%)
Non–small cell lung cancer	50
Small-cell lung cancer	22
Lymphoma	12
Metastatic cancer (especially breast)	9
Germ cell tumor	3
Thymoma	2
Mesothelioma	1

Data from Wilson LD, Detterbeck FC, Yahalom J. Superior vena cava syndrome with malignant causes. N Engl J Med. 2007;356(8):1862–1869.

The most common nonmalignant etiology of SVCS is catheter-related thrombosis, primarily caused by the increasing use of central access devices. Other causes include benign teratoma, tuberculosis, silicosis, and sarcoidosis.

PATHOPHYSIOLOGY

The SVC is the primary drainage vein for blood return from the head, neck, and upper extremities. It is a relatively thin-walled vein that is particularly vulnerable to obstruction from adjacent tumor invasion or thrombosis. The obstruction leads to elevated venous pressure, although collateral veins partially compensate. This is one reason for the relatively slow onset of the classic symptoms of SVCS. In fact, 75% of patients have signs and symptoms for more than one week before seeking medical attention.[30]

CLINICAL PRESENTATION AND DIAGNOSIS TREATMENT

Desired Outcomes

KEY CONCEPT The primary goal of treatment of SVCS is to relieve the obstruction of the SVC by treating the underlying malignancy. In the case of SVCS caused by thrombosis, the goal is to eliminate the thrombus and prevent further clot formation. Resolution of the obstruction will rapidly relieve symptoms and restore normal SVC function. The final goal of therapy is to avoid potentially fatal complications of SVCS such as cerebral edema from rapid increases in intracranial pressure (ICP) and intracranial thrombosis or bleeding.

General Approach to Treatment

Because the majority of SVCS is not immediately life threatening, a tissue diagnosis (if malignancy is unknown) to specifically identify the cancer origin is critical because treatment approaches vary considerably according to tumor histology. Thus, therapy can typically be withheld until a definitive tissue diagnosis is established. While biopsy results are pending, supportive measures such as head elevation, diuretics, corticosteroids, and supplemental oxygen may be used.

▶ *Nonpharmacologic Therapy*

Radiation therapy is the treatment of choice for chemotherapy-resistant tumors such as non–small cell lung cancer (NSCLC) or in chemotherapy-refractory patients with SVCS. Between 70% and 90% of the patients experience relief of symptoms. Radiation therapy may also be combined with chemotherapy for chemotherapy-sensitive tumors such as SCLC and lymphoma. In the rare emergency situations of airway obstruction or elevated ICP, empiric radiotherapy before tissue diagnosis should be used. In most patients, symptoms resolve within 1 to 3 weeks.

Surgical options for the management of SVCS include stent placement and surgical bypass. SVC stenting may provide longer-term relief of symptoms than radiotherapy, so it is often used in the palliative care setting when chemotherapy has failed.[30] One disadvantage of SVC stenting is the need for anticoagulation, especially in patients at high risk for thrombosis. The role of surgical bypass is limited to patients with complete SVC obstruction or patients who are refractory to chemotherapy and radiotherapy; thus, it is rarely indicated.

▶ *Pharmacologic Therapy*

Cytotoxic chemotherapy is the treatment of choice for chemotherapy-sensitive tumors such as SCLC and lymphoma. As indicated earlier, chemotherapy may also be combined with radiotherapy, especially in patients with lymphoma who have bulky mediastinal lymphadenopathy.

Corticosteroids can be used to manage of SVCS, particularly in cases of lymphoma, because these tumors are inherently responsive to corticosteroid therapy. They are also helpful in the setting of respiratory compromise. Corticosteroids benefit patients who are receiving radiation therapy by reduction of local radiation-induced inflammation and patients with increased ICP. Dexamethasone 4 mg IV or by mouth every 6 hours is a frequently used regimen. The dosage should be tapered upon completion of radiation therapy or resolution of symptoms. The use of corticosteroid may impact the ability to obtain histology in cases in which the first biopsy is found to be insufficient.[31]

The role of diuretics in the management of SVCS is controversial. Although patients may derive symptomatic relief from edema, complications such as dehydration and reduced venous blood flow may exacerbate the condition. If diuretics are used, furosemide is most frequently used with diligent monitoring of the patient's fluid status and blood pressure.

In the case of thrombosis-related SVCS, anticoagulation is controversial because there is a lack of survival benefit. However, thrombolytics (i.e., alteplase) and anticoagulation with heparin and warfarin may be beneficial in patients with thrombosis caused by indwelling catheters if used within 7 days of onset of symptoms, although catheter removal may be required.[30]

OUTCOME EVALUATION

The major measure of outcome of treatment of SVCS is the relief of symptoms, regardless of the therapy used.

NEUROLOGIC COMPLICATIONS: SPINAL CORD COMPRESSION

INTRODUCTION

Although not typically life threatening, spinal cord compression is a true oncologic emergency because delays in treatment by mere hours may lead to permanent neurologic dysfunction. Practitioners must quickly recognize the signs and symptoms of this condition to facilitate rapid management strategies.

Clinical Presentation and Diagnosis of Spinal Cord Compression

General

- Once neurologic deficits appear, progression to irreversible paralysis may occur within hours to days.
- Around 30% to 50% of patients present with multiple sites of spinal involvement.

Signs and Symptoms

- Back pain is present in more than 90% of patients.
- Initially localized and increases in intensity over several weeks.
- Aggravated by movement, supine positioning, coughing, sneezing, neck flexion, straight leg raise, **Valsalva maneuver**, palpation of spine
- Sensory deficit
- Cervical spine compression: quadriplegia
- Thoracic spine compression: paraplegia
- Upper lumbar spine compression: bowel and bladder dysfunction (constipation and urinary retention) and abnormal extensor plantar reflexes
- Weakness

Diagnostic Tests

- MRI with gadolinium enhancement is the gold standard.
- X-rays may be helpful to identify bone abnormalities.

EPIDEMIOLOGY AND ETIOLOGY

Around 20,000 patients with cancer experience spinal cord compression in the United States every year, most of which involves the thoracic spine (~70%). Cancers that inherently metastasize to the bone (ie, breast, prostate, and lung) are the most frequent underlying malignancies associated with this complication. Most spinal cord compression occurs in patients with a known malignancy; however, 20% to 25% of cases occur as the initial presentation of cancer, especially in patients with non-Hodgkin lymphoma, multiple myeloma, and lung cancer.[32]

PATHOPHYSIOLOGY

The spinal cord emerges from the brain stem at the base of the skull and terminates at the second lumbar vertebra. The thoracic spine is most vulnerable to cord compression because of natural kyphosis and because the width of the thoracic spinal canal is the smallest among the vertebrae. Most spinal cord compression is caused by adjacent vertebral metastases that compress the spinal cord or from pathologic compression fracture of the vertebra. This results in significant edema and inflammation in the affected area.

Patients with spinal cord compression are in acute, severe back and/or neck pain and may present to the emergency department for evaluation. Diagnosis is made based on symptoms and imaging studies that show fractured vertebrae.

TREATMENT

Desired Outcomes

KEY CONCEPT Because patients with cancer and spinal metastases are generally incurable, the primary goal of treatment of spinal cord compression is palliation. The most important prognostic factor for patients presenting with spinal cord compression is the degree of underlying neurologic dysfunction. Only around 10% of patients who present with paralysis are able to ambulate after treatment.[32] Therefore, the goals of treatment are recovery of normal neurologic function, local tumor control, pain control, and stabilization of the spine. Therapeutic options depend primarily on the following factors:

- Underlying malignancy
- Prior therapies
- Stability of the spine at presentation
- Overall patient prognosis

▸ *Nonpharmacologic Therapy*

Radiation therapy (RT) at 20 Gy in 5 daily fractions or 30 Gy in 10 daily fractions is generally considered to be the treatment of choice for most patients. Exceptions to this include patients with prior radiation to the treatment site and patients with inherently radio-resistant tumors (i.e., melanoma, renal cell carcinoma). The radiation field should include two vertebral bodies above and below the involved area.

Surgery for spinal cord compression typically involves either laminectomy for posterior lesions or decompression with fixation. Surgery should be considered in patients with metastatic spinal cord compression, spinal instability, or failed prior RT, with the main aim to preserve neurological function, reduce pain, and stabilizing the weakened vertebral column. Surgery followed by radiation therapy may be superior to radiotherapy alone in terms of increased ambulation time after treatment, maintenance of continence, and rates of nonambulatory patients becoming ambulatory.[32] Surgery is also useful for establishing a tissue diagnosis in cases of unknown malignancy. Overall, the risks and benefits of surgery must be weighed against the expected prognosis of the patient in light of the significant rehabilitation required after surgery.

▸ *Pharmacologic Therapy*

Corticosteroids play a vital role in the management of spinal cord compression. Dexamethasone is most frequently used to reduce edema, inhibit inflammation, and delay the onset of neurologic complications. Early use of corticosteroids is crucial, ideally within 12-hours of symptom onset, with definitive therapy with RT or surgery to follow.[32] Significant controversy exists regarding the optimal dosing of dexamethasone though both the UK and Canadian guidelines recommend 16 mg orally or IV immediately, followed by a short course of 8 mg by mouth or intravenously twice daily. Higher doses may be used in cases of rapidly progressing symptoms, but adverse effects, including GI bleeding and psychosis, are more severe and have not shown to be beneficial. Steroids should be continued during radiation therapy and then tapered appropriately.

Pain management is also of critical importance in patients with spinal cord compression. Although dexamethasone will provide some benefit, opioid analgesics should also be used and titrated rapidly to achieve adequate pain control.

OUTCOME EVALUATION

Patients who receive definitive treatment with radiation and/or surgery generally derive benefit within days.

Clinical Presentation and Diagnosis of Brain Metastasis

General

- Almost all patients with brain metastases are symptomatic.
- New cerebral neurologic symptoms in a cancer patient should initiate evaluation for brain metastases.
- Other causes of brain lesions, including hemorrhage, infection, and infarct, should be ruled out.

Signs and Symptoms

- Headache (most common): May be of gradual onset or sudden in the case of hemorrhage
- Altered mental status: Loss of consciousness, irritability, confusion, cognitive impairment
- **Hemiparesis**, **aphasia**, **papilledema**, weakness, seizure, nausea, and vomiting

Diagnostic Tests

- MRI with contrast enhancement is the gold standard.
- CT scans may be used in patients with pacemakers but may miss small metastases.

COMPLICATIONS OF BRAIN METASTASES

INTRODUCTION

Brain metastases are among the most feared complications of cancer and generally carry a poor prognosis. One serious consequence of brain metastases is elevated ICP, which can rapidly lead to fatal intracranial herniation and death. Rapid identification of the signs and symptoms of brain metastases is critical to improve long-term outcome and avoid mortality. The signs and symptoms of brain metastasis can be confused with common psychological distress or other neurologic problems (eg, headaches) that may go unrecognized. It is important that patients who are suspected to have brain metastasis are quickly referred for appropriate management.

EPIDEMIOLOGY AND ETIOLOGY

Brain metastasis is the most common neurologic complication seen in patients with cancer. Approximately 170,000 patients develop brain metastases in the United States each year.[33] Many malignancies are frequently associated with brain metastases (Table 99–10). Although melanoma is the tumor type most likely to metastasize to the brain, brain metastases caused by lung and breast cancer are seen more often because they are among the most common cancers. In addition, brain metastases may be diagnosed at the same time as the primary malignancy. Around 80% of brain metastases occur in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brain stem.

Table 99–10

Cancers Most Frequently Associated with Brain Metastases

Type of Cancer	Frequency (%)
Lung cancer	18–64
Breast cancer	2–21
Melanoma	4–16
Colorectal cancer	2–11
Hematologic malignancies (ie, leukemia)	~10 (primarily caused by leptomeningeal spread)

Data from Lin X, DeAngelis LM. Treatment of brain metastases. J Clin Oncol. 2015;33(30):3475–3484.

PATHOPHYSIOLOGY

A delicate balance of normal pressure is maintained in the brain and spinal cord by brain, blood, and cerebrospinal fluid. Because the brain is contained within a confined space (skull), any foreign mass contained within that space causes adverse sequelae. This results in either destruction or displacement of normal brain tissue with associated edema. Most brain metastases occur through hematogenous spread of the primary tumor and around 80% of patients have multiple sites of metastases within the brain.

TREATMENT

Desired Outcomes

Therapeutic modalities used for the management of brain metastases may be divided into symptomatic management and definitive management. **KEY CONCEPT** The goals of treatment of brain metastases are to manage symptoms by reducing cerebral edema, treat the underlying malignancy both locally and systemically, and improve survival.

General Approach to Treatment

Patients with brain metastases have a poor prognosis. Untreated patients generally have a median survival of 1 month. Recent advances in drug therapy and radiation/stereotactic radiosurgery now yield median survival times as long as 13.5 months in some patients with solitary brain lesions and good performance status. The choice of treatment depends primarily on the status of the patient's underlying malignancy and the number and sites of brain metastases. The primary definitive treatments for brain metastases are surgery and radiation therapy. Pharmacologic modalities such as corticosteroids and antiepileptics are primarily used to control symptoms, although cytotoxic chemotherapy plays a limited role in the management. Monoclonal antibodies have a large molecular size and, therefore, would not be expected to cross the blood–brain barrier (BBB); however, BBB permeability may be enhanced due to physical disruption from the brain metastasis itself, and some of the targeted oral therapies have better BBB penetration. Immunotherapies have shown to confer benefits in some settings; however, the efficacy could be reduced by the concurrent use of corticosteroids.[34]

▸ *Nonpharmacologic Therapy*

Radiation therapy is the treatment of choice for most patients with brain metastases. Most patients receive whole-brain radiation (WBRT) because the majority of brain metastases are multifocal. Another method known as stereotactic radiosurgery provides intense focal radiation, typically using a **linear accelerator** or **gamma knife**, in patients who cannot tolerate surgery or have lesions that are surgically inaccessible (i.e., brain stem). Stereotactic radiosurgery is also often used for selected patients with up to three lesions that are each less than 4 cm.[33] WBRT can cause long-term problems with memory and cognitive function but this risk is less than that seen with declines due to brain disease, and thus, the benefits of WBRT outweigh the risks in appropriate patients. Because brain metastases can occur in up to 50% of patients with small cell lung cancer, prophylactic cranial irradiation (PCI) is recommended in patients with limited stage disease with good performance status who at least partially respond to chemotherapy to both prevent the development of brain metastases and prolong survival; there is conflicting evidence on the role of PCI in extensive stage SCLC though generally many patients will be offered treatment.[35] Furthermore, a recent randomized controlled trial has shown that PCI did not improve overall survival compared with routine surveillance and treatment of asymptomatic brain metastases upon detection.[36] Although other cancers can metastasize to the brain, the benefits of routine prophylactic cranial irradiation have only been demonstrated in studies conducted in patients with small cell lung cancer. For patients who receive PCI, prophylactic use of memantine is shown to preserve cognitive function in patients.[37]

Surgery plays a key role in the management of patients with brain metastases, particularly in patients whose systemic disease is well controlled and in patients with solitary lesions. Surgery may also benefit patients with multiple metastatic sites who have a single dominant lesion with current or impending neurologic sequelae.

▶ *Pharmacologic Therapy*

Corticosteroids are a mainstay in the management of brain metastases. They reduce edema that typically surrounds sites of metastases, thereby reducing ICP. A loading dose of dexamethasone 10 to 24 mg IV followed by 4 mg by mouth or IV every 6 hours or 8 mg by mouth twice daily is typically used. Symptom relief may occur shortly after the loading dose, although the maximum benefit may not be seen for several days (after definitive therapy).[38] Slow tapering of dexamethasone, over 3 days to 2 weeks, is recommended.

Mannitol is an agent that may be used in patients with impending cerebral herniation. Mannitol is an osmotic diuretic that shifts brain osmolarity from the brain to the blood. Doses of 100 g (1–2 g/kg) as an IV bolus should be used. Repeated doses are typically not recommended because mannitol may diffuse into brain tissue, leading to rebound increased ICP.

Approximately 20% patients with brain metastases may present with seizures and require anticonvulsant therapy. There is no evidence that a specific antiepileptic drug is more effective than another. Hence, the choice of anticonsulvant should be based on patient-related factors including the type of epilepsy, age, comorbidity, and concomitant drugs. Levetiracetam, which has fewer side effects and drug interaction potential, is currently the therapy of choice for management of seizures in patients with brain metastases.[39] Prophylactic anticonvulsants have frequently been used; however, current guidelines do not support this practice. Thus, because adverse effects and drug interactions are common, the routine use of prophylactic anticonvulsants is not recommended.

OUTCOME EVALUATION

The success of therapy is based on the ability to decrease symptoms, treat the underlying sites of disease within the brain, and prolong survival.

UROLOGIC COMPLICATIONS: HEMORRHAGIC CYSTITIS

INTRODUCTION

Hemorrhagic cystitis is defined as acute or insidious bleeding from the lining of the bladder. Although therapy with certain medications is the most common cause, it is also the most preventable. Once it occurs, hemorrhagic cystitis causes significant morbidity and mortality rates between 2% and 4%. This section focuses on preventive strategies for chemotherapeutic causes of hemorrhagic cystitis.

Table 99–11

Primary Causes of Hemorrhagic Cystitis

Pharmacologic	Nonpharmacologic
Cyclophosphamide	Pelvic irradiation
Chronic low doses	Viral infection
High doses used in BMT	CMV
Ifosfamide	Papovavirus
Intravesicular thiotepa	Herpes simplex virus
Chronic oral busulfan	Adenovirus
Anabolic steroids	

BMT, bone marrow transplantation; CMV, cytomegalovirus.

Data from Payne H, Adamson A, Bahl A, et al. Chemical- and radiation-induced hemorrhagic cystitis: current treatments and challenges. BJU Int. 2013;112(7):885–897.

EPIDEMIOLOGY AND ETIOLOGY

Numerous etiologies have been linked to hemorrhagic cystitis (Table 99–11).[40] Of these, the oxazaphosphorine alkylating agents (cyclophosphamide and ifosfamide) are most frequently implicated. Hemorrhagic cystitis is the dose-limiting toxicity of ifosfamide and predisposes patients with bladder cancer. Incidence rates vary considerably but generally range between 20% and 25% with high-dose (300 mg/m^2 or more) cyclophosphamide in the absence of prophylactic measures and even more commonly with ifosfamide. Chronic, low-dose oral cyclophosphamide as typically used in autoimmune disorders and chronic lymphocytic leukemia is infrequently associated with hemorrhagic cystitis. Cystitis occurs in 80% of patients treated with intravesicle Bacillus Calmette-Guerin (BCG) for bladder cancer, with 20% also experiencing hematuria.

Around 20% patients receiving pelvic irradiation may experience hemorrhagic cystitis, especially with concurrent cyclophosphamide. Notably, this toxicity can present acutely or long after treatment with radiation has ended (up to 15 years). Viral infections commonly associated with this condition most frequently occur in bone marrow transplant recipients who may also receive cyclophosphamide.

PATHOPHYSIOLOGY

Cyclophosphamide- or ifosfamide-induced damage to the bladder wall is primarily caused by their shared metabolite known as acrolein. Acrolein causes sloughing and inflammation of the bladder lining, leading to bleeding and hemorrhage. This is most common when urine output is low because higher concentrations of acrolein come into contact with the bladder urothelium for longer periods of time. Radiation treatment directly damages the protective glycosaminoglycan layer of the bladder epithelium.

PREVENTION

KEY CONCEPT The use of effective prevention strategies can decrease the incidence of hemorrhagic cystitis to fewer than 5% in patients receiving cyclophosphamide or ifosfamide. Three methods are used to reduce the risk: administration of

Clinical Presentation and Diagnosis of Hemorrhagic Cystitis

General

- Presentation may be mild (microscopic hematuria) or severe (massive hemorrhage) and develops during or shortly after chemotherapy infusion.
- Presentation may be delayed when associated with pelvic radiation.

Signs and Symptoms

- Suprapubic pain and cramping, urinary urgency and frequency, dysuria and burning, and hematuria
- Urinary retention leading to hydronephrosis and renal failure may occur if large blood clots obstruct the ureters or bladder outlet

Laboratory Tests

- Urine dipsticks for blood
- Urinalysis reveals more than three RBCs per high-power field: microscopic hematuria
- CBC with differential, prothrombin time or international normalized ratio, activated partial thromboplastin time, blood urea nitrogen, creatinine

mesna (2-mercaptoethane sulfonate), hyperhydration, and bladder irrigation with catheterization. Mesna is the primary method used with ifosfamide; all three strategies are used with cyclophosphamide.

Mesna is a thiol compound that is rapidly oxidized in the bloodstream after administration to dimesna, which is inactive. However, after being filtered through the kidneys, dimesna is reduced back to mesna, which binds to acrolein, leading to its inactivation and excretion. ASCO has published evidence-based guidelines for the dosing and administration of mesna (Table 99–12).[41] The dose of oral mesna must be double the IV dose because of its oral bioavailability between 40% and 50%. Because the half-life of mesna (~1.2 hours) is much shorter than that of ifosfamide or cyclophosphamide, prolonged administration of mesna beyond the end of the chemotherapy infusion is critical (Figure 99–2). Patients should receive at least 2 L of IV fluids beginning 12 to 24 hours before and ending 24 to 48 hours after the last dose of chemotherapy.[41]

Hyperhydration with normal saline at 3 L/m^2/day with IV furosemide to maintain urine output greater than 100 mL/hour has also been used with cyclophosphamide. Continuous bladder irrigation by catheterization uses normal saline at 250 to 1000 mL/hour to flush acrolein from the bladder. Mesna is equivalent to both strategies in patients receiving high-dose cyclophosphamide and avoids the discomfort and infection risk with catheterization and the intensity of hyperhydration. Thus, mesna is the preventative method of choice.[41]

TREATMENT

Desired Outcomes

If hemorrhagic cystitis occurs, the goals of treatment are to decrease exposure to the offending etiology, establish and maintain urine outflow, avoid obstruction and renal compromise, and maintain blood and plasma volume. Restoration of normal bladder function is the ultimate goal following acute treatment.

General Approach to Treatment

The treatment of hemorrhagic cystitis first involves discontinuation of the offending agent. Agents such as anticoagulants and

Table 99–12

ASCO Guidelines for the Use of Mesna with Ifosfamide and High-Dose Cyclophosphamide

Chemotherapy Schedule	Dosing Schedule for Mesna	Comments
Low-dose ifosfamide < 2 g/m^2/day	Oral: 100% of total daily dose of ifosfamide given 20% IV: 15 minutes before and 40% po 2 and 6 hours after start of ifosfamide	Available in 400-mg tablets Peak urinary thiol concentrations with oral mesna is at 3 hours If patient vomits within 2 hours of administration, repeat dose po or IV
Standard-dose ifosfamide equal to 2.5 g/m^2/day	Bolus: 60% of total daily dose of ifosfamide given IV in 20% increments 15 minutes before and 4 and 8 hours after start of ifosfamide Infusion: 60% of total daily dose of ifosfamide given 20% IV 15 minutes before and 40% by continuous infusion during and for 12–24 hours after end of ifosfamide	Peak urinary thiol concentrations with IV mesna is at 1 hour Compatible with ifosfamide and cyclophosphamide by Y-site administration or when admixed in the same bag
High-dose ifosfamide > 2.5 g/m^2/day	Lack of evidence for dosing, but higher doses for longer duration recommended based on longer half-life of ifosfamide at high doses	
Standard-dose cyclophosphamide	Use of mesna is not routinely necessary	
High-dose cyclophosphamide (BMT)	Bolus: 40% of cyclophosphamide dose given IV at hours 0, 3, 6, and 9 after cyclophosphamide Infusion: 100% of cyclophosphamide dose given by continuous infusion until 24 hours after cyclophosphamide	Should be combined with saline diuresis (1.5 L/m^2/day of normal saline)

ASCO, American Society of Clinical Oncology; BMT, bone marrow transplantation; IV, intravenous; mesna, 2-mercaptoethane sulfonate; po, oral.

Data from Hensley ML, Hagerty KL, Kewalramani T, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol. 2009;27(1):127–145.

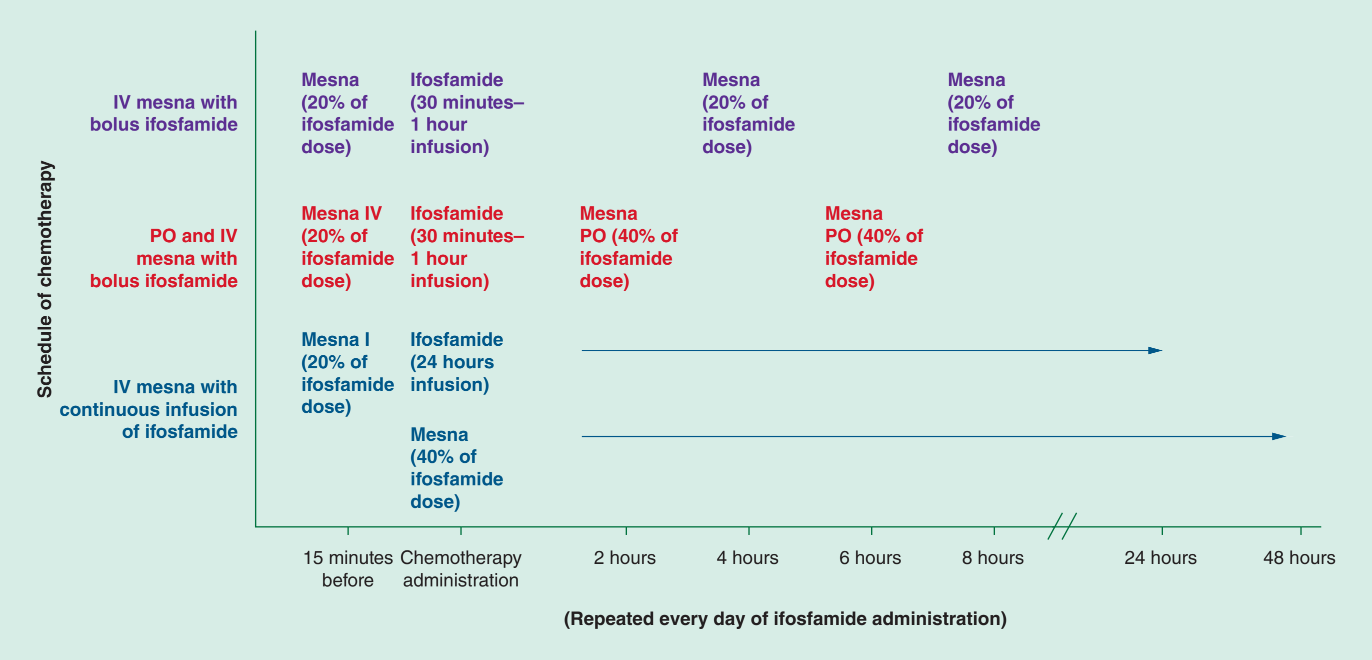
Schedule of chemotherapy
IV mesna with bolus ifosfamide
Mesna (20% of ifosfamide dose)
Ifosfamide (30 minutes–1 hour infusion)
Mesna (20% of ifosfamide dose)
Mesna (20% of ifosfamide dose)
PO and IV mesna with bolus ifosfamide
Mesna IV (20% of ifosfamide dose)
Ifosfamide (30 minutes–1 hour infusion)
Mesna PO (40% of ifosfamide dose)
Mesna PO (40% of ifosfamide dose)
IV mesna with continuous infusion of ifosfamide
Mesna I (20% of ifosfamide dose)
Ifosfamide (24 hours infusion)
Mesna (40% of ifosfamide dose)
15 minutes before
Chemotherapy administration
2 hours
4 hours
6 hours
8 hours
24 hours
48 hours
(Repeated every day of ifosfamide administration)

FIGURE 99–2. Examples of mesna (2-mercaptoethane sulfonate) administration with ifosfamide. (IV, intravenous; po, oral.)

inhibitors of platelet function should also be discontinued. Intravenous fluids should be aggressively administered to irrigate the bladder.[41,42] Blood and platelet transfusions may be necessary to maintain normal hematologic values. Pain should be managed with opioid analgesics. Local intravesicular therapies may be necessary if hematuria does not resolve (Figure 99–3).

▶ *Nonpharmacologic Therapy*

A large-diameter, multihole urethral catheter should be inserted to facilitate saline lavage and evacuation of blood clots. Surgical removal of blood clots under anesthesia may be required if saline lavage is ineffective. Active bleeding from isolated areas may be cauterized with an electrode or laser. In severe cases that are unresponsive to local or systemic pharmacologic intervention, urinary diversion with percutaneous nephrostomy or surgical removal of the bladder may be required.

▶ *Pharmacologic Therapy*

A number of local or systemic agents are used in the treatment of hemorrhagic cystitis.[42] Local (direct instillation into the bladder), one-time administration of hemostatic agents such as alum, prostaglandins, silver nitrate, and formalin may be used; however, general anesthesia is required, especially with formalin, because of pain. Aluminum toxicity has been noted with alum irrigation, particularly in children. Systemic agents, including estrogens, vasopressin, aminocaproic acid, and hyperbaric oxygen (HBO), may be used in patients who are refractory to local therapy, although they introduce the risk of systemic side effects. HBO is particularly useful for radiation- and cyclophosphamide-induced cystitis. These agents should be continued until bleeding stops.

Antispasmodic agents such as oxybutynin 5 mg by mouth two to three times daily may be used for bladder spasms. In patients with refractory pain, opioid analgesics should be titrated to adequate pain control. In very severe cases refractory to medical therapy, surgical procedures may be warranted.

OUTCOME EVALUATION

The goal of treatment is resolution of bladder symptoms and appropriate pain management.

Monitor the patient for resolution of hematuria after each successive therapeutic intervention. The frequency of monitoring is based on the severity of hemorrhaging. Monitor urinary output and serum chemistries (including sodium, potassium, chloride, blood urea nitrogen [BUN], and serum creatinine) daily for renal dysfunction. Check the CBC at least daily to monitor hemoglobin and platelet count.

METABOLIC COMPLICATIONS: HYPERCALCEMIA OF MALIGNANCY

INTRODUCTION

Hypercalcemia is the most common metabolic abnormality experienced by patients with cancer. A small percentage of undiagnosed patients present with hypercalcemia. Once hypercalcemia occurs, it is associated with a very poor prognosis because of the frequent association with advanced or metastatic disease.[43]

EPIDEMIOLOGY AND ETIOLOGY

Hypercalcemia occurs in 10% to 30% of patients with cancer during the course of their disease. The most common tumor types associated with hypercalcemia are breast cancer; squamous cell carcinomas of the head, neck, and lung; and renal cancer. Hematologic malignancies such as multiple myeloma and, rarely, lymphomas are other underlying malignancies associated with hypercalcemia.

PATHOPHYSIOLOGY

Around 99% of calcium is contained in the bones; the other 1% resides in the extracellular fluid. Of this extracellular calcium, approximately 40% is bound to albumin, and the remainder is in

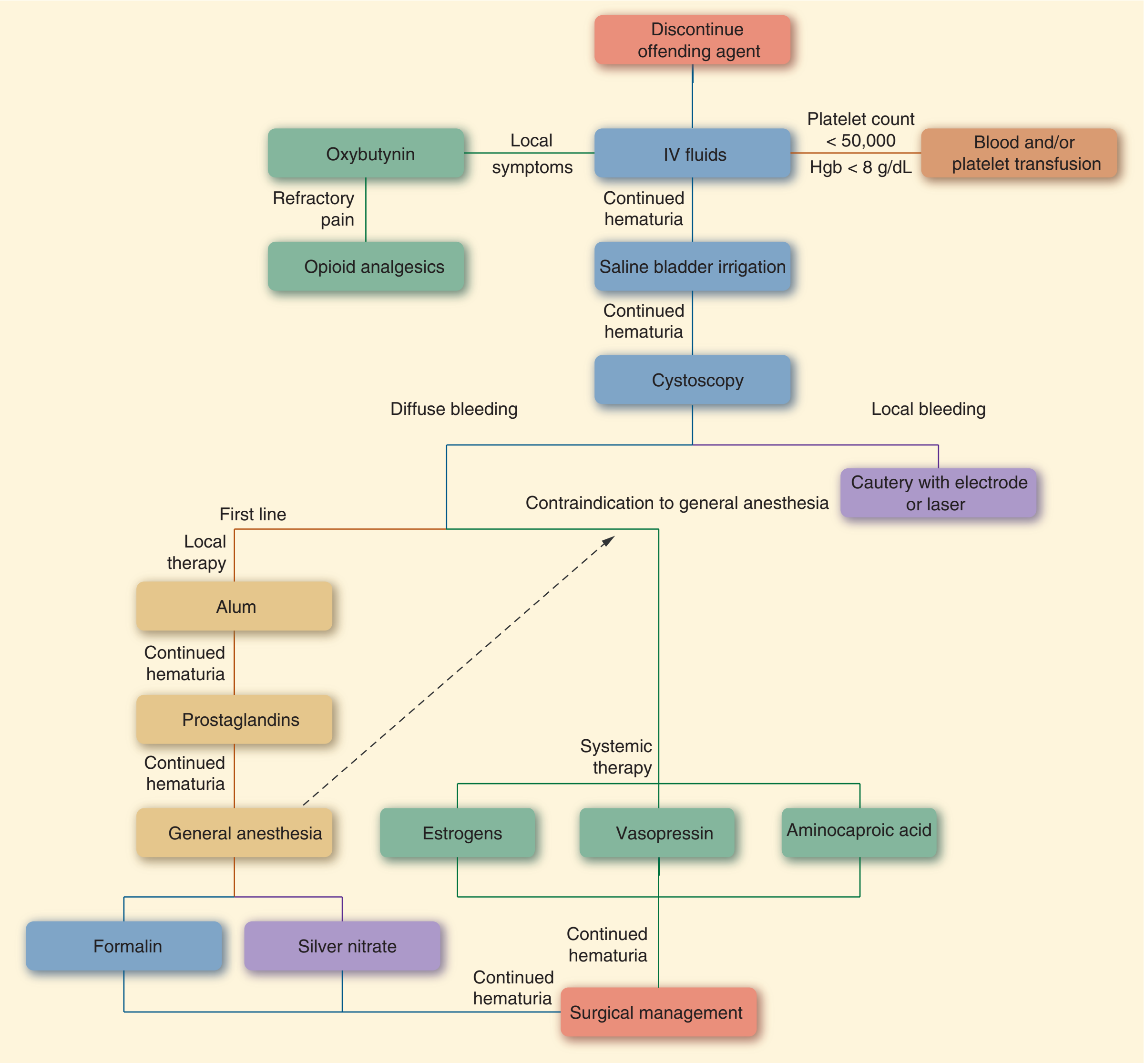
Discontinue offending agent
Oxybutynin
Local symptoms
IV fluids
Platelet count < 50,000
Hgb < 8 g/dL
Blood and/or platelet transfusion
Refractory pain
Opioid analgesics
Continued hematuria
Saline bladder irrigation
Continued hematuria
Cystoscopy
Diffuse bleeding
Local bleeding
Cautery with electrode or laser
Contraindication to general anesthesia
First line
Local therapy
Alum
Continued hematuria
Prostaglandins
Continued hematuria
General anesthesia
Systemic therapy
Estrogens
Vasopressin
Aminocaproic acid
Formalin
Silver nitrate
Continued hematuria
Continued hematuria
Surgical management

FIGURE 99–3. Treatment of hemorrhagic cystitis.

the ionized, physiologically active form. Normal calcium levels are maintained by three primary factors: parathyroid hormone (PTH), 1,25-dihydroxyvitamin D, and calcitonin. PTH increases renal tubular calcium resorption and promotes bone resorption. The active form of vitamin D, 1,25-dihydroxyvitamin D, regulates absorption of calcium from the GI tract. Calcitonin serves as an inhibitory factor by suppressing osteoclast activity and stimulating calcium deposition into the bones.[43]

The delicate balance maintained by these factors is altered in patients with cancer by two principal mechanisms: tumor production of humoral factors that alter calcium metabolism in the absence of bone metastasis (humoral hypercalcemia) and by local osteolytic activity from bone metastases. Humoral hypercalcemia causes around 80% of all hypercalcemia cases and is primarily mediated by systemic secretion of PTH-related protein (PTHrP). This protein mimics the action of endogenous PTH on bones. Local osteolytic activity causes 20% to 30% of hypercalcemia cases, although local osteolytic activity may also have a humoral component. Local production of various factors such as PTHrP, transforming growth factor-β, interleukin-1, and interleukin-6, and tumor necrosis factor-α promotes RANK ligand expression on osteoblasts. RANK ligand signaling to the RANK receptor on osteoclasts causes osteoclast maturation and activation, leading to bone resorption. Thus, these metastatic tumors perpetuate their own growth through this mechanism. Calcium is also released by the osteolytic activity, resulting in hypercalcemia. Of note, multiple myeloma, breast, and lung cancer patients tend to develop osteolytic lesions and are at increased risk for hypercalcemia, whereas prostate cancer patients tend to develop osteoblastic lesions and are more at risk for hypocalcemia. A third and less common mechanism is production of 1,25-dihydroxyvitamin D by tumor cells (usually lymphoma), which increases GI absorption of calcium and enhances osteoclastic bone resorption.

TREATMENT

Desired Outcomes

KEY CONCEPT The primary goal of treatment for hypercalcemia is to control the underlying malignancy. Therapies directed at lowering the calcium level are temporary measures that are useful until anticancer therapy begins to work. The goals of calcium-lowering therapy are to (a) lower the corrected calcium to normal levels,

Clinical Presentation and Diagnosis of Hypercalcemia[43,44]

General

- Presence of symptoms depends not only on the calcium level but the rapidity of onset.
- Normal calcium level is 8.5 to 10.5 mg/dL (2.13–2.63 mmol/L) (varies by laboratory).
- Serum calcium level *must* be corrected for albumin level using the following formula:

Corrected calcium (mg/dL) = Serum calcium + 0.8 (4 – Serum albumin) for serum calcium expressed in mg/dL and albumin in g/dL.

or

Corrected calcium (mmol/L) = Serum calcium + 0.02 (40 – serum albumin) for serum calcium expressed in mmol/L and albumin in g/L.

Signs and Symptoms

- Five primary organ systems may be affected:
  - GI: lack of appetite, nausea, vomiting, constipation
  - Musculoskeletal: weakness, bone pain, fatigue, ataxia
  - CNS: confusion, headache, lethargy, seizures, coma
  - Genitourinary: polydipsia, polyuria, renal failure
  - Cardiac: Bradycardia, ECG abnormalities, arrhythmias

Laboratory Tests

- Elevated corrected serum calcium level (≥ 10.5 mg/dL [2.63 mmol/L]), low serum albumin, low to normal serum phosphate.
- Patient may have elevated blood urea nitrogen and serum creatinine.
- Elevated alkaline phosphatase may indicate bone destruction.
- ECG may indicate prolonged PR interval, shortened QT interval, widened T wave.

Other Diagnostic Tests

- Rule out other causes of hypercalcemia, including primary hyperparathyroidism, hyperthyroidism, vitamin D intoxication, chronic renal failure.

(b) regain fluid and electrolyte balance, (c) relieve symptoms, and (d) prevent life-threatening complications.[43,44] Hypercalcemia is often indicative of a progressing cancer, with survival rates ranging from 2 months to 4.5 months.

General Approach to Treatment

Therapeutic options for the treatment of hypercalcemia should be directed toward the level of corrected serum calcium and the presence of symptoms (Figure 99–4). Hypercalcemia may

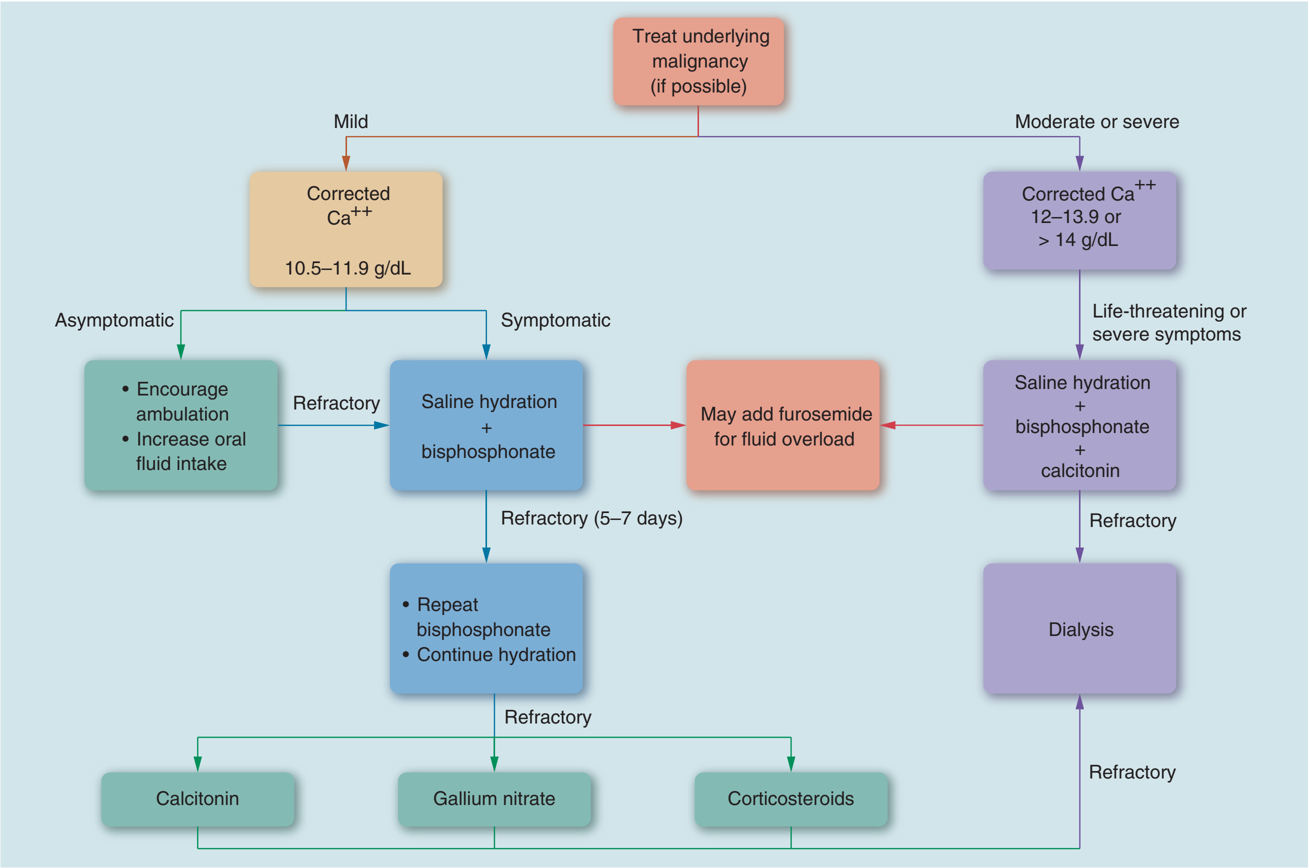
Treat underlying malignancy (if possible)
Mild
Moderate or severe
Corrected Ca^{++} 10.5–11.9 g/dL
Corrected Ca^{++} 12–13.9 or > 14 g/dL
Asymptomatic
Symptomatic
Life-threatening or severe symptoms
• Encourage ambulation • Increase oral fluid intake
Refractory
Saline hydration + bisphosphonate
May add furosemide for fluid overload
Saline hydration + bisphosphonate + calcitonin
Refractory (5–7 days)
Refractory
• Repeat bisphosphonate • Continue hydration
Dialysis
Refractory
Calcitonin
Gallium nitrate
Corticosteroids
Refractory

FIGURE 99–4. Treatment algorithm for the hypercalcemia of malignancy.

be classified as mild (corrected calcium equal to 10.5–11.9 mg/dL [2.63–2.98 mmol/L]), moderate (12–13.9 mg/dL [3.00–3.49 mmol/L]), and severe (more than 14 mg/dL [3.50 mmol/L] or more).[43,44] Adequate treatment of mild or asymptomatic hypercalcemia may be achieved on an outpatient basis with nonpharmacologic measures. Moderate to severe or symptomatic hypercalcemia almost always requires pharmacologic intervention. Ultimately, effective treatment of the patient's underlying malignancy is the most important factor for the long-term prevention and management of hypercalcemia.[44]

▶ *Nonpharmacologic Therapy*

Calciuric therapy in the form of hydration is a key component in the treatment of hypercalcemia, regardless of severity or presence of symptoms. The goal is to achieve a goal urine output at 100 to 150 ml/hour. Mild or asymptomatic patients may be encouraged to increase their oral fluid intake (3–4 L/day). Patients with moderate to severe or symptomatic hypercalcemia should receive normal saline at 200 to 500 mL/hour according to their dehydration and cardiovascular status. Patients should be encouraged to ambulate as much as possible because immobility enhances bone resorption. Although calcium should be discontinued from parenteral feeding solutions, oral calcium supplementation minimally contributes to hypercalcemia unless it is mediated by vitamin D. In these cases, oral calcium should be discontinued. Finally, agents that may contribute to hypercalcemia (thiazide diuretics, vitamin D, lithium) or decrease renal function (NSAIDs) should be discontinued. Dialysis may be used in refractory cases or patients who cannot tolerate aggressive saline hydration.

▶ *Pharmacologic Therapy*

Multiple pharmacologic interventions are available for the treatment of hypercalcemia (Table 99–13). Intravenous furosemide dosed at 20 to 40 mg/day may be added to hydration after rehydration has been achieved to avoid fluid overload and enhance renal excretion of calcium. Although effective in relieving symptoms, hydration and diuretics are temporary measures that are useful until the onset of antiresorptive therapy; thus, hydration and antiresorptive therapy should be initiated simultaneously.

Table 99–13

Treatment Options for Hypercalcemia of Malignancy

	Agent	Dosage	Onset	Duration of Action	Reduction in Serum Calcium Concentration	Comments
Calciuric therapy	IV normal saline	200–500 mL/ hour 2	24–48 hours	2–3 days	0.5–2 mg/dL (0.13–0.50 mmol/L)	Avoid fluid overload, monitor electrolytes
	Furosemide	0–40 mg IV	4 hours	2–3 days		Monitor for hypokalemia, dehydration
Antiresorptive therapy	Pamidronate	60–90 mg IV over 2–24 hours[a]	24–72 hours	3–4 weeks	> 1 mg/dL (0.25 mmol/L)	Nadir not seen until after 4–7 days; may cause fever, renal dysfunction
	Zoledronic acid	4 mg IV over 15 minutes	24–48 hours	4+ weeks	> 1 mg/dL (0.25 mmol/L)	Monitoring for acute tubular necrosis and severe acute renal toxicity (rare), osteonecrosis of the jaw if used long term.
	Corticosteroids	Prednisone (or equivalent) 50–100 mg/day	5–7 days	3–4 days	0.5–3 mg/dL (0.13–0.75 mmol/L)	Monitor for hyperglycemia, insomnia, immunosuppression
	Calcitonin	4–8 IU/kg SC or IM every 6–12 hours	2–4 hours	1–3 days	2–3 mg/dL (0.50–0.75 mmol/L)	Salmon-derived formulation preferred; 1-unit test dose recommended; can be given in renal failure; may cause flushing, nausea
	Gallium nitrate	100–200 mg/m^2 CIV daily for 5 days	24–48 hours 48–96 hours	Up to 104 days	> 1 mg/dL (0.25 mmol/L)	Do not administer if creatinine > 2.5 mg/dL (221 μmol/L); may cause renal failure
	Denosumab	120 mg SQ days 1, 8, and 15, then day 1 only every 4 weeks				Not renally cleared, may be used in patients with renal dysfunction, but reduce dose as increased risk of hypocalcemia in renally impaired, osteonecrosis of the jaw if used long term.

[a] 60 mg of pamidronate may be used in smaller patients or in patients with mild hypercalcemia or renal dysfunction. May use longer infusion time in patients with renal dysfunction.

CIV, continuous intravenous infusion; IM, intramuscular; IV, intravenous; SC, subcutaneous.

Data from Body JJ, Niepal D, Tonini G. Hypercalcemia and hypocalcemia: finding the balance. Support Care Cancer. 2017;25(95):1639–1649; Zagzag J, Hu MI, Fisher SA, Perrier ND. Hypercalcemia and cancer: Differential diagnosis and treatment. CA Cancer J Clin. 2018; 68(5):377–386.

The antiresorptive therapy of choice for hypercalcemia of malignancy is a bisphosphonate. Because of poor oral bioavailability, only IV agents should be used. Pamidronate and zoledronic acid are most commonly used and potent inhibitors of osteoclast activity.[41] The bisphosphonates should be administered at diagnosis of hypercalcemia because of their delayed onset of action.

Calcitonin is the drug of choice in cases of emergent hypercalcemia (patients with life-threatening electrocardiographic [ECG] changes, arrhythmias, or central nervous system [CNS] effects) because of its rapid onset of action. Calcitonin inhibits osteoclast activity and decreases renal tubular calcium resorption. However, calcitonin does not yield sustained effects and bisphosphonates are usually necessary as well. Corticosteroids are useful in patients with steroid-responsive malignancies, such as lymphomas or multiple myeloma, and may delay tachyphylaxis to calcitonin. Gallium nitrate is another treatment option, although the 5-day administration regimen and risk of nephrotoxicity limit its use. Denosumab, a RANKL inhibitor, is FDA-approved for hypercalcemia refractory to bisphosphonates at 120 mg subcutaneously days 1, 8, and 15, then monthly thereafter.[44]

OUTCOME EVALUATION

The long-term success of therapy for hypercalcemia is determined primarily by the success of treatment of the underlying malignancy. The goal of treatment is to reduce serum calcium levels to normal range and relieve patient symptoms and life-threatening complications if present.

METABOLIC COMPLICATIONS: TLS

INTRODUCTION

Although not as common as hypercalcemia, TLS may cause significant morbidity and mortality if adequate prophylaxis and treatment are not instituted. TLS is the result of rapid destruction of malignant cells with subsequent release of intracellular contents into the circulation.

EPIDEMIOLOGY AND ETIOLOGY

The overall incidence of TLS is unknown, but has been linked to a number of patient- and tumor-related risk factors (Table 99–14). TLS typically occurs in malignancies with high tumor burden or high proliferative rates, such as hematological malignancies including aggressive leukemias and lymphomas. TLS is typically induced by cancer treatment modalities, including chemotherapy, hormonal therapy, radiation, biologic therapy, or corticosteroids, although some patients may present spontaneously before treatment.[45]

Table 99–14

Risk Factors for Tumor Lysis Syndrome

Characteristic	Risk Factor
Cancer type	Burkitt lymphoma Lymphoblastic lymphoma Diffuse large-cell lymphoma ALL Solid tumors with high proliferative rates and rapid response to therapy
Tumor burden/extent of disease	Bulky disease (10 cm) Elevated LDH (2ULN) Elevated WBC (25,000/L)
Patient's organ function	Preexisting renal failure: oliguria
Baseline uric acid	Baseline serum/plasma uric acid: 450 mol/L (7.5 mg/dL)

ALL, acute lymphoblastic leukemia; LDH, lactate dehydrogenase

Adopted from: Coiffer B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008; 2767–2778.

PATHOPHYSIOLOGY

Patients with TLS experience a wide range of metabolic abnormalities. The massive cell lysis that occurs leads to the release of intracellular electrolytes, resulting in hyperuricemia, hyperkalemia, and hyperphosphatemia. High concentrations of phosphate can bind to calcium, leading to hypocalcemia and calcium phosphate precipitation in the renal tubule. Purine nucleic acids are also released, which are subsequently metabolized to uric acid through multiple enzyme-mediated steps (Figure 99–5). Uric acid is poorly soluble at urinary acidic pH, leading to crystallization in the renal tubule. The precipitation of uric acid and calcium

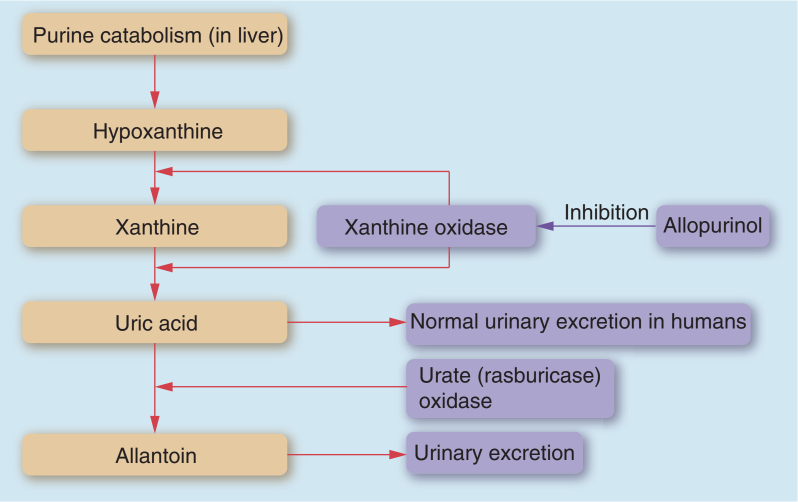

FIGURE 99–5. The role of allopurinol and rasburicase in the enzymatic degradation of purine nucleic acids.

Clinical Presentation and Diagnosis of TLS[45]

General

- Patients present primarily with laboratory abnormalities.
- Normal uric acid is equal to 2 to 8 mg/dL (119–476 μmol/L).
- Most often occurs within 12 to 72 hours of initiation of cytotoxic therapy.

Signs and Symptoms

- Most patients are asymptomatic; some patients may develop edema, fluid overload, and oliguria, which may progress to anuria with acute renal failure.
- Some patients with hyperuricemia may have nausea, vomiting, and lethargy.
- Hyperkalemia: lethargy, muscle weakness, **paresthesia**, ECG changes, bradycardia
- Hypocalcemia: muscle cramps, **tetany**, irritability, paresthesias, arrhythmias

Laboratory Tests (Adults)

- Serum uric acid level greater than 7.5 mg/dL (450 μmol/L)
- Serum potassium greater than 6 mEq/L (6 mmol/L)
- Serum phosphorus greater than 6.5 mg/dL (2.1 mmol/L)
- Serum calcium less than 7 mg/dL (1.75 mmol/L)
- Elevated blood urea nitrogen and creatinine once renal dysfunction develops

or

- A change of greater than 25% from baseline in the above laboratory values

phosphate leads to metabolic acidosis, facilitating further uric acid crystallization. Acute renal failure may be the end result.[45]

TREATMENT

Desired Outcomes

KEY CONCEPT The primary goals of management of TLS are (a) prevention of renal failure and (b) prevention of electrolyte imbalances. Thus, the best treatment for TLS is prophylaxis to enable delivery of cytotoxic therapy for the underlying malignancy. For patients who present with or develop TLS despite prophylaxis, treatment goals include (a) decreasing uric acid levels, (b) correcting electrolyte imbalances, and (c) preventing compromised renal function. These goals should be achieved in a cost-effective manner.

General Approach to Treatment

Prevention of TLS is generally achieved by increasing the urine output and preventing accumulation of uric acid. Prophylactic strategies should begin immediately upon presentation, preferably 48 hours prior to cytotoxic therapy. Treatment modalities for established TLS primarily increase uric acid solubility, maintain electrolyte balance, and support renal output.[45]

▶ *Nonpharmacologic Therapy*

Vigorous IV hydration with dextrose 5% in water with half normal saline at 3 L/m^2/day to maintain a urine output greater than or equal to 100 mL/m^2/hour is necessary unless the patient presents with acute renal dysfunction. Alkalinization of the urine to a pH greater than or equal to 7.0 with 50 to 100 mEq/L (50–100 mmol/L) of sodium bicarbonate has been used to promote uric acid solubility for excretion. This measure is controversial because xanthine and hypoxanthine are less soluble at alkaline pH, potentially leading to crystallization, especially during and after allopurinol therapy (see Figure 99–5).[45] Medications that increase serum potassium (angiotensin-converting enzyme inhibitors, spironolactone) or block tubular resorption of uric acid (probenecid, thiazides) should be discontinued. Nephrotoxic agents such as amphotericin B or aminoglycosides should also be avoided. Hemodialysis may be required in patients who develop anuria or uncontrolled hyperkalemia, hyperphosphatemia, hypocalcemia, acidosis, or volume overload.

▶ *Pharmacologic Therapy*

Allopurinol is a xanthine oxidase inhibitor that is used for prevention only because it has no effect on preexisting elevated uric acid. Studies have also evaluated the role of febuxostat, a potent xanthine oxidase inhibitor which does not require renal adjustment, for prevention of TLS. Rasburicase is a recombinant form of urate oxidase that is useful for both prevention and treatment but is expensive (Figure 99–6, Table 99–15). Although the approved dose is 0.2 mg/kg/day for 5 days, recent studies using abbreviated courses (1–3 days) and/or lower doses (0.05–0.1 mg/kg/day) may be equally efficacious with significantly reduced cost.[41] Because uric acid levels generally fall within 4 hours of the first dose, one dose may be administered with frequent, serial monitoring of the uric acid level for repeat dosing if necessary (see Figure 99–6). Of note, rasburicase continues to break down uric acid in blood samples drawn from patients. This can be avoided by immediately placing the sample in an ice bath for processing to avoid falsely lowered uric acid levels.[45]

Electrolyte disturbances that develop in patients with TLS should be aggressively managed to avoid renal failure and cardiac sequelae. One exception pertains to the use of IV calcium for hypocalcemia. Adding calcium may cause further calcium phosphate precipitation in the presence of hyperphosphatemia and should be used cautiously.

OUTCOME EVALUATION

The most successful outcome in TLS is prevention. If the condition is not able to be prevented, the goal of treating established TLS is to avoid renal failure and quickly return electrolytes to normal.

IMMUNOTHERAPY-RELATED TOXICITES

INTRODUCTION

Management of cancer has evolved over the past decade with the introduction of immunotherapy such as chimeric antigen receptor (CAR) T-cell therapies and immune checkpoint inhibitors (ICIs) into clinical practice. However, with the increased usage of immunotherapies for treatment of cancer, a myriad of toxicities associated with immunotherapy have also surfaced. Severe systemic inflammation is commonly observed with the use of CAR T-Cell therapies, known as cytokine release syndrome (CRS) in the literature, whereas toxicities associated with ICIs are commonly termed as immune-related adverse events (irAEs).[46]

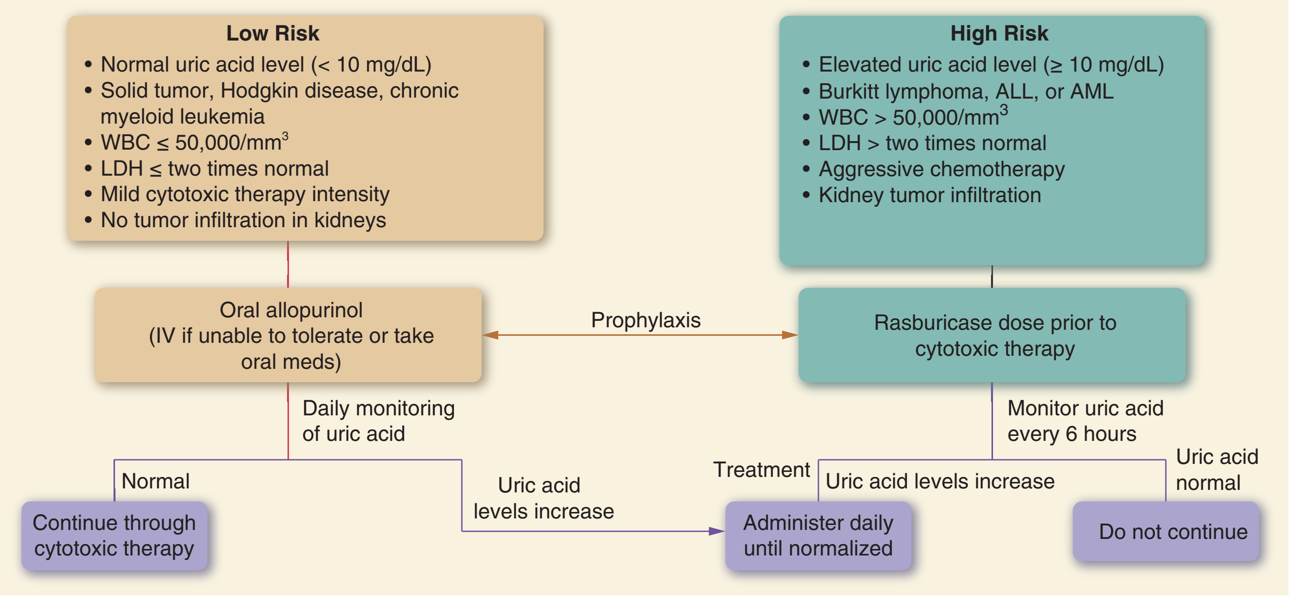
Low Risk
• Normal uric acid level (< 10 mg/dL)
• Solid tumor, Hodgkin disease, chronic myeloid leukemia
• WBC ≤ 50,000/mm³
• LDH ≤ two times normal
• Mild cytotoxic therapy intensity
• No tumor infiltration in kidneys
High Risk
• Elevated uric acid level (≥ 10 mg/dL)
• Burkitt lymphoma, ALL, or AML
• WBC > 50,000/mm³
• LDH > two times normal
• Aggressive chemotherapy
• Kidney tumor infiltration
Oral allopurinol (IV if unable to tolerate or take oral meds)
Prophylaxis
Rasburicase dose prior to cytotoxic therapy
Daily monitoring of uric acid
Monitor uric acid every 6 hours
Normal
Continue through cytotoxic therapy
Uric acid levels increase
Treatment
Uric acid levels increase
Uric acid normal
Administer daily until normalized
Do not continue

FIGURE 99–6. Prophylaxis and treatment of hyperuricemia associated with tumor lysis syndrome. (ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; IV, intravenous; LDH, lactate dehydrogenase; WBC, white blood cell.)

EPIDEMIOLOGY AND ETIOLOGY

The reported incidence of any grade irAEs associated with ICI monotherapy ranges widely across agents and trials, from approximately 15% to 90%. Severe irAEs requiring immunosuppression and hold or therapy discontinuation are estimated between 0.5% and 13%. On the other hand, rates of severe CRS between the two CD19-targeted CAR T-cell therapies (axicabtagene ciloleucel and tisagenlecleucel) are consistently high, with severe CRS ranging between 13% and 23%.[46]

PATHOPHYSIOLOGY

As immunotherapy works by activating the immune response, raised levels of cytokines as a downstream effect of T-cell activation can trigger systemic inflammation. The development of CRS occurs following an increase of inflammatory cytokines, such as IL-6, which are released after the activation and destruction of various blood cells including marcrophages, lymphocytes, and monocytes. Immune checkpoint antibodies can bind to targets that are expressed in normal organs, which could lead to complement-mediated inflammation. Furthermore, immunotherapy can also lead to an elevation of autoreactive antibiodies, triggering inflammatory responses.

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentations of toxicities associated with immunotherapy are phenotypically different from those observed with traditional anticancer therapies such as chemotherapy. Acute inflammation associated with CRS, within the first 2 to 3 days of infusion, are often observed with CAR T-cell therapies, which often manifest as high fevers, hypotension, hypoxia, and multiorgan damage. Neurologic toxicities can occur between in the median of 4 to 6 days after initiation of therapy.[47]

Table 99–15

Treatment Options for Tumor Lysis Syndrome

Drug	Dosing	Comments
Oral allopurinol (Zyloprim)	Adult: 600–800 mg/day in two to three divided doses Pediatric: 10 mg/kg/day or 200–300 mg/m^2/day	Adjust dose for renal impairment Avoid drug interactions (mercaptopurine) Monitor for skin rash Start 1–2 days prior to chemotherapy
IV allopurinol (Aloprim)	Adult: 200–400 mg/m^2/day Pediatric: 200 mg/m^2/day	As above Reserve for patients who cannot tolerate or take oral medications Maximum dose = 600 mg/day
Rasburicase (Elitek)	0.2 mg/kg/day for up to 5 days	Lower doses and abbreviated schedules may be used to decrease cost (0.05–0.1 mg/kg/day) May rarely cause nausea and vomiting Contraindicated in patients with G6PD deficiency → hemolytic anemia Rare cases of hypersensitivity and antibody formation

[a]Normalized for 70-kg patient or body surface area = 1.73 m^2; all costs are estimated and may vary.

AWP, average wholesale price; G6PD, glucose-6-phosphate dehydrogenase; po, oral.

From Wilson FP, Berns JS. Tumor lysis syndrome: new challenges and recent advances. Adv Chronic Kidney Dis. 2014;21(1):18–26.

Table 99–16

General Management of ICI-induced irAEs

Grade	Management Strategy
1 (mild)	ICI therapy should be continued with close monitoring, with the exception of some neurologic, hematologic, and cardiac toxicities. Corticosteroids are not usually required.
2 (moderate)	Hold ICI and consider resuming when symptoms and/or laboratory values revert to grade 1 or less. Low dose corticosteroids (0.5–1 mg/kg/day) should be considered.
3 (severe)	Hold ICI and initiate high-dose corticosteroids (prednisone 1–2 mg/kg/day or equivalent). Gradually taper corticosteroid dose over at least 4 to 6 weeks once symptoms improve to ≤grade 1.
4 (life-threatening)	Permanent discontinuation of ICI with the exception of endocrinopathies that have been controlled by hormone replacement. initiate high-dose corticosteroids (prednisone 1 to 2 mg/kg/day).

ICI = immune checkpoint inhibitor; irAEs = immune-related adverse events

From: Medina P, Jeffers KD, Trinh VA, Harvey RD. The Role of Pharmacists in Managing Adverse Events Related to Immune Checkpoint Inhibitor Therapy. J Pharm Pract 2020;33(3):338–349.

In contrast to CAR T-cell therapies and cytotoxic chemotherapy that often result in acute-onset adverse events, the onset of irAEs associated with ICI are generally slower in nature. Among all ICIs, cytotoxic T-lymphocyte-associated protein (CTLA)-4 inhibitors generally have higher rates and higher severity of irAEs than anti-programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitors, particularly in patients with baseline autoimmune conditions. Observed toxicities associated with ICI-based combination regimens are also more severe than that for ICI monotherapy. irAEs can essentially attack any organ systems causing toxicities. The most commonly observed toxicities include dermatological toxicity, gastrointestinal toxicity, endocrine toxicity, and pulmonary toxicity. There is also growing literature reporting toxicities related to the nervous and cardiovascular systems. Development of irAEs is unpredictable and does not appear to correlate with cumulative dose toxicity or anticancer efficacy.[46]

TREATMENT

Desired Outcomes

The goal is to reduce the prevent the onset and severity of immunotherapy-related toxicities, as these toxicities may affect patients' quality of life. In addition, it is important to ensure that the management of immunotherapy-related toxicities does not impact the efficacy of anticancer treatment.

General Approach to Treatment

Currently, a number of guidelines are available for the management of immunotherapy-related toxicities.[46,48,49] The general approach to management of ICI-induced iRAEs focuses on early recognition of symptoms and prompt intervention. Mild reactions of iRAEs often lead to temporarily withholding of immunotherapy, and severe iRAEs may require permanent discontinuation of the class of agent associated with the toxicity (Table 99–16).

On the other hand, the general approach to management of mild CRS is supportive in nature and consists of managing flu-like symptoms, headaches, fatigue, and myalgias. Severe CRS would require intensive care, incorporating rapid management of hypotension, hypoxia, and organ dysfunction with fluids, vasopressors, oxygen, and other supportive interventions.

▸ *Nonpharmacologic Therapy*

Due to the aggressive nature of CRS, CAR T-cell therapies are only available commercially at facilities certified through a Risk Evaluation and Mitigation Strategy (REMS) program. In patients receiving CAR T-cell therapies, aggressive preventive care and close monitoring must be undertaken before, during, and post CAR T-cell infusion. Precautions such as TLS precautions and baseline brain MRI should also be considered. Close monitoring of metabolic panel, coagulation profile, complete blood count, CRP, and ferritin should be routinely performed. Assessment of CRS and neurological function should be done at least twice daily when patients are at risk. Lastly, aggressive cardiac monitoring under telemetric conditions should be performed in patients presenting with grade 2 CRS. Similar to CAR T-cell therapies, recipient of ICI should receive comprehensive assessment prior to therapy include neurological examination, laboratory tests, and thyroid function testing.

▸ *Pharmacologic Therapy*

KEY CONCEPT Corticosteroids are the mainstay of treatment for more severe irAEs and CRS. Early administration of steroids (within 5 days from the onset of symptoms) has been associated with more rapid resolution of diarrhea and colitis compared with delayed steroid initiation. Depending on the type and severity of the irAEs, prednisone doses ranging from 0.5 to 2 mg/kg/day have been used. Generally, a minimum tapering duration of 4 to 6 weeks is recommended, since irAE recurrence and/or worsening

Patient Encounter 3: Immune-related adverse events

Your patient is a 48-year-old woman with metastatic melanoma began combination ipilimumab and nivolumab with normal labs and no significant adverse events after her first three doses of treatment. he is receiving her fourth dose today. She stated that she feels unwell with fevers, and her liver function tests (LFTs) revealed transaminitis (AST = 201, ALT = 237), fever, and an elevated alkaline phosphatase. Bilirubin was within normal limits. The oncologist suspects that she is manifesting immune-related hepatitis.

What is the severity of this patient's immune-related hepatitis?

How would you manage this patient at this time?

Patient Care Process

Collect Information:

- Review patient history of chemotherapy regimens and concurrent medications.
- Determine patient allergies, especially to antibiotics, antifungals, and antivirals.
- Evaluate risk of chemotherapy complications using appropriate NCCN practice guideline if available.
- Evaluate patient-specific risk factors.
- Review laboratory values, including WBC, electrolytes, hepatic and renal function, performance status, and vital signs.

Assess the Information:

- Determine complications (nausea, vomiting, febrile neutropenia, etc) to previous cycles of chemotherapy and risk with current cycle.
- Assess individual and treatment-related risk factors for chemotherapy complications.
- Determine insurance coverage for supportive care interventions, availability of appropriate storage conditions.

Develop a Care Plan:

- Communicate treatment goals of symptomatic management to the patient.
- Provide patient with education regarding appropriate use of supportive therapies and potential adverse effects.
- Educate patient about nonpharmacologic interventions to manage chemotherapy complications.
- Counsel patients regarding risk factors, symptoms to call their healthcare providers, and symptoms requiring a visit to the emergency room.

Implement the Care Plan:

- Initiate patient-specific supportive care therapy for managing chemotherapy complications.
- Coordinate follow-up with interprofessional team.

Follow-up: Monitor and Evaluate:

- Review laboratory values, including WBC, electrolytes, hepatic and renal function, performance status, and vital signs.
- Determine efficacy and adverse effects of supportive cancer intervention and determine if modifications in the treatment plan are required.
- Assess the patient for any new signs or symptoms of chemotherapy complications. Evaluate the patient for adverse drug reactions, drug allergies, and interactions. Have all medications been dose adjusted for renal or hepatic dysfunction?

may occur with rapid steroid taper.[48] For patients with severe irAEs that are not responsive to steroids within 48 to 72 hours, additional immunosuppression with another immunomodulator may be warranted.

In the management of CRS associated with CAR T-cell therapies, dexamethasone at 10 mg every 6 hours should be considered in patients who do not respond to anti-IL-6 therapy.[46] Antifungal prophylaxis should be considered in patients receiving corticosteroids for management of CRS. With the approval of tisagenlecleucel, tocilizumab was also FDA approved for the management of CRS. Tocilizumab is a humanized monoclonal antibody that is an IL-6 receptor antagonist. Traditionally, it has been used in the management of rheumatologic disorders but has also demonstrated efficacy in decreasing CRS-related symptoms after administration of CAR T cells.

In settings where immunotherapy-related toxicities are corticosteroid-refractory, a number of immunomodulators such as infliximab, vedolizumab, mycophenolate mofetil, cyclosporine, and intravenous immunoglobulin have been used in clinical practice. The use of immunosuppressants should be tailored carefully to prevent their potential on reducing antitumor efficacy. A number of retrospective studies have shown that immunosuppressive regimens administered in the setting of irAEs did not appear to compromise the outcomes of ICI therapies; however, it is still prudent to minimize the potential of systemic immunosuppression.

OUTCOME EVALUATION

The long-term success of therapy for management of immunotherapy related toxicities is determined primarily by the success of continuing immunotherapy without compromising efficacy.

Abbreviations Introduced in This Chapter

ANC	Absolute neutrophil count
AWP	Average wholesale price
BMT	Bone marrow transplantation
BUN	Blood urea nitrogen
CIV	Continuous intravenous infusion
CSF	Colony-stimulating factor
G6PD	Glucose-6-phosphate dehydrogenase
ICP	Intracranial pressure
IV	Intravenous
LDH	Lactate dehydrogenase
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non–small cell lung cancer
PCP	*Pneumocystis jiroveci* pneumonitis (formerly *Pneumocystis carinii*)
PTHrP	Parathyroid hormone–related protein
SCLC	Small cell lung cancer
SVCS	Superior vena cava syndrome

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Parenteral Nutrition

Melissa R. Pleva and Michael D. Kraft

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. List appropriate indications for parenteral nutrition (PN) in adult patients.
2. Describe the components of PN and their role in nutrition support therapy.
3. List key elements of nutrition assessment and factors considered in assessing an adult patient's nutritional status and nutritional requirements.
4. List important recommendations to improve PN safety.
5. Explain important pharmaceutical and compounding concerns with PN admixtures.
6. Develop a plan to design, initiate, and adjust a PN formulation for an adult patient based on patient-specific factors.
7. Describe the etiology and risk factors for PN macronutrient-associated complications in adult patients receiving PN.
8. Describe the etiology and risk factors for refeeding syndrome, as well as measures to prevent refeeding syndrome.
9. Design a plan to assess the efficacy and monitor for safety, as well as fluid, electrolyte, vitamin, and trace element abnormalities in adult patients receiving PN.

INTRODUCTION

Malnutrition in hospitalized patients is associated with significant complications (eg, increased infection risk, poor wound healing, prolonged hospital stays, increased mortality), especially in surgical and critically ill patients.[1] Maintaining adequate nutritional status, especially during periods of illness and metabolic stress, is an essential part of patient care. *Nutrition support therapy* refers to the administration of nutrients via the oral, enteral, or parenteral route for therapeutic purposes.[1] **KEY CONCEPT** Parenteral nutrition (PN), also called total parenteral nutrition (TPN), is the intravenous (IV) administration of fluids, macronutrients, electrolytes, vitamins, and trace elements for the purpose of weight maintenance or gain, to preserve or replete lean body mass and visceral proteins, and to support anabolism and nitrogen balance when the oral or enteral route is not feasible or adequate. PN is a potentially lifesaving therapy in patients with intestinal failure but can be associated with significant or life-threatening complications.

Desired Outcomes and Goals

The goals of nutrition support therapy include:

- Correction or avoidance of nutritional deficiencies
- Weight maintenance (or weight gain in malnourished patients and growing children)
- Preservation or repletion of lean body mass and visceral proteins
- Support of anabolism and nitrogen balance and improvement of healing
- Correction or avoidance of fluid, electrolyte, vitamin, and trace element abnormalities
- Improved clinical outcomes

Indications for PN Therapy

PN can be a lifesaving therapy when indicated, but the oral or enteral route is preferred when providing nutrition support therapy. Compared with PN, enteral nutrition is associated with a lower risk of hyperglycemia and fewer infectious complications (eg, pneumonia, intra-abdominal abscess, catheter-related infections).[1-3] However, if used appropriately, PN can be safe and effective and can improve nutrient delivery. Indications for PN are listed in Table 100–1.[4] PN should be reserved for patients with altered intestinal function or absorption or when the gastrointestinal (GI) tract cannot be used. The anticipated duration of adequate PN therapy should be at least 5 to 7 days because shorter durations are unlikely to have a beneficial effect on a patient's clinical and nutritional outcomes.[1,2]

PN COMPONENTS

PN should provide a *balanced* nutrition formula, including macronutrients, micronutrients, fluids, and electrolytes. Macronutrients, including amino acids, dextrose, and injectable lipid emulsions (ILE; also known as IV lipid emulsion or IV fat emulsion), are important sources of structural and energy-yielding substrates. In a balanced PN formulation for adult patients, total daily calories are typically provided as 10% to 20% from amino acids, 50% to 60% from dextrose, and 15% to 30% from ILE. Amino acids may provide more than 20% of the total daily calories in

Table 100–1

Indications for Parenteral Nutrition in Adults[4]

- Bowel obstruction
  - Physical or mechanical (eg, tumor compressing intestinal lumen)
  - Functional (eg, ileus, colonic pseudo-obstruction)
- Major small bowel resection (eg, short bowel syndrome)
  - Adult patients with < 120 cm of small bowel distal to the ligament of Treitz without a colon
  - Adult patients with < 60 cm of small bowel if the colon is intact
- Ischemic bowel
- Impaired absorption (eg, complication of bariatric surgery, severe intractable vomiting, or diarrhea)
- High output intestinal fistulas if EN cannot be provided above or below the fistula
- Severe pancreatitis—if patients have failed EN beyond the ligament of Treitz or cannot receive EN (eg, because of intestinal obstruction)
- Inability to achieve or maintain enteral access
- Preoperative nutrition support in patients with moderate-to-severe malnutrition who cannot tolerate EN and in whom surgery can be delayed safely for at least 7 days

patients with conditions that increase protein requirements. See additional dosing details in each macronutrient section. Electrolytes and micronutrients, including vitamins and trace elements, are required to support essential biochemical reactions and maintain cellular homeostasis. Patients require individual adjustments of PN components based on their nutritional status, nutritional requirements, underlying disease state(s), degree of metabolic stress, clinical status, and organ functions.

Macronutrients

▶ *Amino Acids*

Amino acids, the building blocks of proteins, are an essential component of PN admixtures. **KEY CONCEPT** Amino acids are provided to preserve or replete lean body mass and visceral proteins, to promote protein anabolism and wound healing. Amino acids provide 4 kcal/g (17 kJ/g) of energy.

Parenteral crystalline amino acid solutions are supplied by various manufacturers in various concentrations, with a 10% or 15% solution used commonly in PN compounding. Different formulations are tailored for specific age groups and disease states. Formulations for patients with hepatic encephalopathy contain

Patient Encounter, Part 1

DB is a 47-year-old man with a history of depression and Crohn disease, status post small bowel resection. He was admitted approximately 2 weeks ago with signs and symptoms consistent with a bowel obstruction. He was taken to the OR for an exploratory laparotomy and found with multiple adhesions causing small bowel obstructions in two locations. He underwent an additional small bowel resection (jejunum) and extensive lysis of adhesions and was discharged 8 days ago. DB is readmitted with foul-smelling drainage from his surgical incision × 2 days along with nausea, decreased appetite, and decreased oral intake (~30% of estimated energy requirements) for the past 2 to 3 days. Since his diagnosis of Crohn disease, he has had intermittent weight loss, poor oral intake, and malnutrition. Most recently, he reports an unintentional weight loss of about 16 lb (7.3 kg) over the past 4 to 5 weeks.

Past Medical History

Depression × 10 years

Crohn disease diagnosed 20 years ago, status post small bowel resections 2 years ago and 8 days ago

Intermittent malnutrition since diagnosis of Crohn disease

Past Surgical History

Small bowel resection 2 years ago

Exploratory laparotomy with small bowel resection and lysis of adhesions due to small bowel obstruction (> 100 cm of small intestine remaining, ileocecal valve intact, all the colon remaining)

Family History

Mother and father: Hypertension, hyperlipidemia

Grandmother: Chronic constipation, depression

Social History

20 pack-year smoking history, quit 2 years ago; patient reports only occasional alcohol; no recreational drugs

Medications Prior to Admission

Sertraline 50 mg PO daily

Docusate 100 mg PO twice daily

Allergies

NKDA

Physical Examination

Height, 178 cm (~5 ft, 10 in); actual body weight, 72 kg (158 lb); ideal body weight, 75 kg (165 lb); temperature 37.2°C (99.0°F); heart rate, 75 beats/min; blood pressure, 116/69 mm Hg; respiratory rate, 14 breaths/min; alert and oriented × 3; mucous membranes and skin appear cool and dry; lungs clear

Abdomen: Soft, tender around incision, faint bowel sounds, drainage of apparent enteric contents from surgical incision

Physical examination otherwise unremarkable.

Diagnoses

Likely enterocutaneous fistula, probably from small bowel/jejunum (most recent surgery/small bowel resection), mild dehydration, and malnutrition

Plan

The patient was admitted to the hospital (non-ICU) for evaluation of a possible enterocutaneous fistula. The team performed a fistulogram and confirmed presence of an enterocutaneous fistula apparently originating in the proximal- to mid-jejunum. Given the patient's recent surgery, surgical intervention was deemed to not be an appropriate option at this time. A drain was placed into the fistula to control drainage and quantify output; the fistula drained ~ 600 mL in the first 24 hours. Against medical orders, the patient drank approximately 1 L of water, and the following day his fistula drained approximately 1500 mL of fluid. It is now hospital day #2.

Is PN therapy indicated in this patient? Why or why not?

higher amounts of branched-chain and lower amounts of aromatic amino acids. These specialized formulations have not been clearly shown to improve patient outcomes and are not routinely used in clinical practice. Crystalline amino acid solutions have an acidic pH (pH ≈ 5–7) and may contain inherent electrolytes (eg, sodium, potassium, acetate, phosphate).

▶ *Dextrose*

KEY CONCEPT Dextrose (D-glucose) is the major energy source in PN, and it is vital for cellular metabolism, body protein preservation, and cellular growth. The central nervous system, red blood cells, and the renal medulla depend primarily on dextrose as a source of energy.

Typically, a 70% (70 g/100 mL) parenteral dextrose (hydrous dextrose) stock solution is used in PN compounding. Hydrous dextrose provides 3.4 kcal/g (14.2 kJ/g). A dextrose infusion rate of 2 mg/kg/min in adult patients is typically sufficient to suppress gluconeogenesis and spare proteins from being used for energy.[5] Dextrose infusion rate in hospitalized adult patients should not exceed 4 to 5 mg/kg/min when PN is infused over 24 hours.[6] Use adjusted body weight (AdjBW; see Assessment section for calculation), rather than actual weight, in obese patients when calculating the dextrose infusion rate.

▶ *Lipid Injectable Emulsions*

KEY CONCEPT Injectable lipid emulsions (ILE) are provided to prevent or treat essential fatty acid deficiency (EFAD) and as an energy source. ILE particles consist of a triglyceride core surrounded by a layer of egg phospholipids (emulsifiers). These particles carry a negative charge on their surface that creates repulsive electrostatic forces between droplets and maintains the stability of the emulsion. Glycerol is added to adjust the tonicity, and water is the solvent. The negative charges on the surface of lipid particles can be disrupted by cations, especially divalent cations (eg, calcium, magnesium) and trivalent cations (eg, iron), and extreme pH changes, particularly acidic pH.[7] Creaming, coalescence, and oiling out are signs of a destabilized ILE. If there is any apparent disruption to ILE, it should *not* be infused into a patient.

ILEs differ in their concentration (10%, 20%, and 30%), caloric density by volume, natural source of fats/triglycerides, and ratio of phospholipids to triglycerides (PL:TG ratio). Table 100–2 shows a comparison of commercially available ILEs in the United States. Most standard ILEs in the United States contain long-chain triglycerides derived from soybean oil. Because of the addition of phospholipid emulsifiers and glycerol, the caloric density of ILEs by weight is 10 to 11 kcal/g (42–44 kJ/g; see Table 100–2; dietary fat is ~ 9 kcal/g [38 kJ/g]). Compared with the 10% ILE, 20% and 30% ILEs have a lower PL:TG ratio and lower phospholipid content, and this translates to better plasma clearance and lower rates of hypertriglyceridemia compared to the 10% ILE.[7] The 30% ILE is only approved by the Food and Drug Administration (FDA) for infusion in a total nutrient admixture (TNA) and should not be infused directly into patients nor via Y-site injection.

More recently the FDA approved three additional ILE products for use in the United States; two products for use in adult patients: SMOFLipid and Clinolipid and one product in pediatric patients: Omegaven (see Table 100–2). SMOFLipid is a combination of soybean oil, medium-chain triglycerides (MCTs), olive oil, and fish oil. Clinolipid is a mixture of refined olive and soybean oil. Omegaven is the first non–soybean oil–containing ILE available in the United States and contains only fish oil. All three alternative formulations result in a reduced amount of omega-6 fatty acids, and SMOFLipid and Omegaven have a higher concentration of omega-3 fatty acids. This may have a positive impact on inflammation and immune function, but significant data demonstrating improved clinical outcomes are lacking.[8] The optimal role of each of these ILE products in patient care is not yet known, but increasing evidence suggests a potential role for these alternative oil products in treatment of PN-associated liver disease (PNALD) (refer to "Complications of PN").[8]

The essential fatty acids that cannot be produced endogenously in humans are linoleic acid (C18:2 n-6) and α-linolenic acid (C18:3 n-3) (long-chain fatty acids). Arachidonic acid (C20:4 n-6) is also essential but can be synthesized in vivo from linoleic acid. Adult patients should receive a minimum of 2% to 4% of total daily calories as linoleic acid and 0.25% to 0.5% of total daily calories as α-linolenic acid to prevent EFAD.[7] This can be achieved by providing a minimum of ~ 100 g of soybean oil–based ILE per week (in a single dose or divided doses) for most adult patients. Higher total doses of new alternative ILE formulations may be required to prevent EFAD. The typical daily dose of ILE in adults is about 0.5 to 1 g/kg/day (or ~ 15%–30% of total daily calories). The maximum dose is 2.5 g/kg/day[7] or 60% of total daily calories, although soybean oil ILE doses this high are rarely used in practice and should be avoided to prevent complications.

Biochemical evidence of EFAD (eg, decreased serum linoleic acid, α-linolenic acid, and arachidonic acid concentrations; elevated mead acid concentrations; elevated triene-to-tetraene ratio) can develop in well-nourished adult patients within 2 to 4 weeks of receiving PN without ILE. Clinical manifestations (eg, dry skin, skin desquamation, hair loss, hepatomegaly, anemia, thrombocytopenia, poor wound healing) may begin to appear after an additional 1 to 2 weeks.[9]

Complications and safety concerns related to the administration of ILE include severe hypertriglyceridemia, infection, anaphylactic reactions, and infusion-related reactions. Patients with a history of hypertriglyceridemia, acute kidney injury, chronic kidney disease, hepatic dysfunction, severe metabolic stress, or pancreatitis (particularly if caused by hypertriglyceridemia) may have reduced lipid clearance and be at risk of developing hypertriglyceridemia.

ILEs support the growth of bacterial and fungal pathogens; bacterial growth is slower in total nutrient admixtures (TNAs) than in ILE alone due to the acidic pH of amino acid solutions and higher osmolarity of PN formulations.[10,11] Because of this, the Centers for Disease Control and Prevention (CDC) recommends that TNA infusions be completed within 24 hours of initiation. Recent guidelines suggest that ILE infusion should be completed ideally within 12 hours if administered from the original manufacturer container (within 24 hours if 12 hours not feasible for medical reasons), but completed within 12 hours if repackaged/transferred to another container and infused separately from a 2-in-1 PN admixture (although repackaging/transfer to another container was not recommended).[12]

Patients with an allergy to eggs (egg phospholipids), soybean (soybean oil), legumes (soybean oil), fish (fish oil), olives (olive oil), or other ingredients may develop cross-allergic reactions to ILE products.[13] Rarely, infusion-related adverse effects may occur with rapid infusion, including fever, chills, headache, palpitations, dyspnea, chest tightness, and nausea. Extending the ILE infusion time can minimize infusion-related adverse events and improves ILE clearance. The maximum recommended infusion rate of ILE is 0.11 g/kg/hour.[7]

Table 100–2

Comparison of Lipid Injectable Emulsion Products Approved in the United States

Brand Names	Intralipid			Nutrilipid	Liposyn III			SMOFLipid	Clinolipid	Omegaven[a]
Oil source(s)	Soybean oil			Soybean oil	Soybean oil			Soybean oil (30%) MCT (30%) Olive oil (25%) Fish oil (15%)	Olive oil (80%) Soybean oil (20%)	Fish oil
Concentration	10%	20%	30%[b]	20%	10%	20%	30%[b]	20%	20%	10%
Linoleic acid[c] (%)	44–62			48–58	54.5			14–25	13.8–22	1.5
α-Linolenic acid[d] (%)	4–11			4–11	8.3			1.5–3.5	0.5–4.2	1.1
Phospholipids (egg yolk) (%)	1.2			1.2	1.2	1.2	1.8	1.2	1.2	1.2
PL:TG ratio	0.12	0.06	0.04	0.06	0.12	0.06	0.06	0.06	0.06	0.12
Caloric density[e] (kcal/mL)	1.1	2	3	2	1.1	2	3	2	2	1.12
Approximate osmolality[f] (mOsm/kg water) or osmolarity (mOsm/L)	300 mOsm/kg	350 mOsm/kg	310 mOsm/kg	390 mOsm/kg	284 mOsm/L	292 mOsm/L	293 mOsm/L	380 mOsm/kg	340 mOsm/kg	342 mOsm/kg
Approximate mean pH (range)	8 (6–8.9)			6.8 (6–8.9)	8.3 (6–9)		8.4 (6–9)	6–9	6–9	6–9

[a] Only FDA approved for use in pediatric patients.

[b] Only approved for compounding in a 3-in-1 admixture, not for direct patient administration.

[c] Omega-6 (ω-6) fatty acid.

[d] Omega-3 (ω-3) fatty acid.

[e] One kcal/mL is equivalent to 4.184 kJ/mL.

[f] One mOsm/kg is equivalent to mmol/kg, and one mOsm/L is equivalent to mmol/L.

PL, phospholipid; TG, triglyceride.

Table 100–3

Approximate Daily Maintenance Electrolyte Requirements for Adults[1,12]

Electrolyte	Approximate Daily Maintenance Requirements[a]	Electrolyte Salts Used in PN	Maximum Suggested Concentration in PN
Sodium	1–2 mEq/kg (mmol/kg)	Chloride, acetate, phosphate	154 mEq/L (mmol/L, equivalent to normal saline)
Potassium	1–2 mEq/kg (mmol/kg)	Chloride, acetate, phosphate	120 mEq/L (mmol/L) (central PN)
Phosphorus	20–40 mmol (~10–15 mmol per 1000 kcal [2.4–3.6 mmol per 1000 kJ])	Sodium phosphate, potassium phosphate	See text section on calcium–phosphate solubility Maximum calcium + magnesium = 20 mEq/L in 3-in-1 admixture
Calcium	10–15 mEq (5–7.5 mmol)	Gluconate	
Magnesium	8–20 mEq (4–10 mmol)	Sulfate	20 mEq/L (10 mmol/L)[b]
Chloride	[c]	Sodium, potassium	Linked to limitations of sodium and potassium. Usual ratio of chloride to acetate ~ 1:1 to 1.5:1
Acetate	[c]	Sodium, potassium	
Conversions	1 mmol potassium phosphate = 1.47 mEq potassium 1 mmol sodium phosphate = 1.33 mEq sodium 1 gram of calcium gluconate = 4.65 mEq (2.32 mmol) calcium 1 g of magnesium sulfate = 8.1 mEq (4 mmol) magnesium		

[a] Electrolyte requirements are adjusted based on serum electrolyte concentrations and vary depending on kidney function, gastrointestinal losses, nutritional status, specific metabolic and endocrine functions, and medication therapy that affect electrolyte losses or retention.

[b] For 3-in-1 formulations only.

[c] As needed to maintain acid–base balance; linked to amounts of sodium and potassium provided (as chloride and acetate salts).

▶ *Fluid*

KEY CONCEPT Parenteral nutrition should not be used to treat acute fluid abnormalities. PN should be adjusted to provide maintenance fluid requirements and to minimize worsening of underlying fluid disturbances, considering other fluids the patient is receiving. Daily maintenance fluid requirements for adults can be estimated with the following equation:

$$\text{Total daily maintenance fluid requirements} \\ = 1500\ \text{mL} + (20\ \text{mL/kg} \times [\text{Wt (kg)} - 20])^{*}$$

For patients with significant fluid deficits, it is safer and more cost effective to correct fluid abnormalities using standard IV fluids. Minimizing PN fluid volume may be indicated in patients with fluid overload, patients with oliguric or anuric acute kidney injury, or those with congestive heart failure or symptomatic pleural effusion. It is reasonable to provide total daily fluid requirements (maintenance requirements and replacement for GI or other abnormal losses) in the PN admixture in patients who require long-term PN if stability and compatibility limits are maintained with dilution of the PN admixture.

Micronutrients

KEY CONCEPT Electrolytes, vitamins, and trace elements are essential for numerous biochemical and metabolic functions and should be added to PN daily unless otherwise not indicated.

▶ *Electrolytes*

KEY CONCEPT Electrolytes are essential for many metabolic and homeostatic functions, including enzymatic and biochemical reactions, maintenance of cell membrane structure and function, neurotransmission, hormone function, muscle contraction, cardiovascular function, bone composition, and fluid homeostasis. The causes of electrolyte abnormalities in patients receiving PN may be multifactorial, including altered absorption and distribution; excessive or inadequate intake; altered hormonal, neurologic, and homeostatic mechanisms; altered excretion and losses via the GI tract (eg, gastric, diarrhea, ostomy, enterocutaneous fistula) and kidneys; changes in fluid status and fluid shifts; and medication therapies. PN should not be used to treat acute electrolyte abnormalities but should be adjusted to meet maintenance requirements and to minimize worsening of underlying electrolyte disturbances.

Electrolytes that are included routinely in PN admixtures include sodium, potassium, phosphorus (as phosphate), calcium, magnesium, chloride, and acetate. Always assess the patient's kidney function when determining electrolyte doses in PN admixtures. Typical daily electrolyte maintenance requirements for adults with normal kidney function are listed in Table 100–3.[1,14] For additional details regarding management of fluid, electrolyte, and acid–base disorders refer to Chapters 28 and 29.

Calcium–Phosphate Solubility The FDA published a safety alert in response to two deaths from microvascular pulmonary emboli associated with calcium–phosphate precipitation in PN.[15] Because calcium and phosphate can bind and precipitate in solution, caution must be exercised when mixing these two electrolytes in PN admixtures. Several factors can affect calcium–phosphate solubility, including:

- *pH:* Largely affected by the amino acid brand and concentration, to a lesser extent by the dextrose concentration; the lower the solution pH, the less chance for calcium–phosphate precipitation. Monobasic phosphates predominate at low pH, leaving fewer free dibasic phosphates for precipitation with divalent calcium; monobasic calcium phosphate is more soluble than dibasic calcium phosphate.

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[*] For patients greater than 60 years old, use 15 mL/kg for every kilogram above 20 kg.

- *Amino acid brand and concentration:* Primary factor that affects pH of the PN admixture. The pH of amino acid stock solutions may vary between commercial products. In general, the higher the final amino acid concentration, the lower the pH of the final admixture. Phosphates can also bind with amino acids, leaving fewer phosphates available to bind with calcium.
- *Calcium salt:* Calcium gluconate is the preferred calcium salt in PN because it has a lower dissociation constant in solution with less free calcium available at a given time to bind phosphate.
- *Time.* The longer calcium and phosphate are in solution, the more calcium and phosphate will dissociate over time and increase the risk for calcium–phosphate precipitation.
- *Temperature:* As temperature increases, more calcium and phosphate dissociate and increase the risk of calcium–phosphate precipitation.
- *Order of mixing:* Calcium and phosphate should not be added simultaneously or consecutively when compounding PN admixtures (eg, add phosphate first, then add other PN components, and then add calcium near the end of compounding). The volume in the PN admixture at the time calcium is added (not necessarily the final volume) must be used to determine the maximum calcium that can be added.

When compounding PN admixtures, use calcium–phosphate solubility curves (based on the specific brand and final concentration of amino acids and dextrose) to determine safe and appropriate calcium and phosphate concentration limits.

Acetate Acetate is converted to bicarbonate at a 1:1 molar ratio. Bicarbonate should *never* be added to or coinfused with PN admixtures. This can lead to the release of carbon dioxide and result in the formation of insoluble calcium or magnesium carbonate salts.

▶ *Vitamins*

Water-soluble and fat-soluble vitamins in the parenteral multivitamin products are essential cofactors for numerous biochemical reactions and metabolic processes. Parenteral multivitamins are added daily to the PN admixture. Water-soluble vitamins, with the exception of vitamin B_{12}, are generally readily excreted and not stored in the body in significant amounts. Deficiencies of water-soluble vitamins can occur rapidly in the absence of adequate vitamin supplementation in PN. Severe refractory lactic acidosis and deaths were reported in patients who received PN without added thiamin. Thiamin is an essential cofactor in carbohydrate metabolism (via the tricarboxylic acid cycle). Deficiency of thiamin pyrophosphate prevents the formation of acetyl-CoA from pyruvate, which is instead converted to lactate via anaerobic metabolism, resulting in lactic acidosis. Parenteral multivitamin products contain 150 mcg of vitamin K in accordance with FDA recommendations. A parenteral adult multivitamin formulation is available without vitamin K, but standard compounding of PN formulations should include a product that contains vitamin K unless otherwise indicated.

▶ *Trace Elements*

Trace elements are essential cofactors for numerous biochemical processes. Trace elements added routinely to PN in the U.S. include zinc, selenium, copper, manganese, and possibly chromium. ASPEN developed recommendations for daily trace element doses for adult patients receiving PN (Table 100–4). Various individual and multi-ingredient parenteral trace element formulations can be added to PN admixtures. Previously, multi-ingredient formulations in the U.S. did not align with recommended daily parenteral trace element doses, specifically containing higher-than-recommended doses of manganese, chromium, and copper.[16] As part of an initiative to evaluate products that have been on the market since prior to current approval requirements, the FDA has been assessing trace element formulations on the market and approving newer formulations. The first new multi-trace element product, aligning with updated ASPEN recommendations, was approved for adult patients and pediatric patients weighing over 10 kg in July 2020.[17] The new patent exclusivity granted to reformulated single- and multi-trace element products has resulted in a significant increase in the cost of trace elements added to PN.

Trace element dosing and supplementation in PN may require individualization based on the patient's underlying diagnoses, clinical condition, organ function, and unique needs or losses, rather than using a fixed dose multi-trace element product.[18] Some patient populations may require dose reduction of specific trace elements (eg, reduction of manganese and/or chromium doses in long-term PN-dependent patients, reduction of manganese and/or copper doses in patients with cholestasis—serum direct bilirubin concentrations that exceed 2 mg/dL [34.2 µmol/L], etc), and others may require increased/supplemental doses of specific trace elements (eg, increased selenium and/or zinc doses in patients with malabsorption or intestinal losses, especially small bowel losses [high-output enterocutaneous fistulas, short bowel syndrome, diarrhea, etc]). However, it is essential to monitor the patient closely and use patient data to guide therapy decisions (eg, serum trace element levels, signs/symptoms of deficiency or toxicity, clinical and nutritional status) in order to avoid inducing deficiency or toxicity. A complete discussion of all trace element needs and dosing for various patient conditions is beyond the scope of this chapter.

Trace element status should initially be monitored approximately every 3 months in patients at risk for trace element deficiency or accumulation. When stable, serum trace element

Table 100–4

Recommended Daily Parenteral Trace Element Doses for Adults[16,a]

Zinc (Zn)	Selenium (Se)	Copper (Cu)	Manganese (Mn)	Chromium (Cr)
2.5–5 mg	60–100 mcg	0.3–0.5 mg	55 mcg	None or maximum of 1 mcg

[a] Requirements may vary based on patients' kidney function, liver function, gastrointestinal losses, nutritional status, specific metabolic and endocrine functions, serum levels, and medication therapy. Contamination of some PN ingredients with trace elements (eg, chromium, manganese) can contribute significantly to the total amount the patient receives. Monitor serum trace element levels in patients receiving long-term PN therapy.

From American Society for Parenteral and Enteral Nutrition Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN J Parenter Enteral Nutr. 2002;26:1SA–138SA.

concentrations can be monitored every 6 to 12 months. These levels should always be interpreted by a knowledgeable nutrition support professional, in context of the clinical stability of the patient (eg, unreliable in context of significant inflammation) and combined with a clinical assessment of signs and symptoms of deficiency or toxicity.

PN Additives

In general, avoid or minimize the use of medication additives in PN admixtures to limit the risk of incompatibilities and improve safety. Some medications are compatible with PN admixtures and appropriate for administration over a prolonged infusion time (eg, 12–24 hours), and it may be reasonable to add these to PN admixtures when indicated.

▶ *Regular Insulin*

Regular insulin may be added to PN admixtures for glycemic control; if that is part of the institution's or individual's practice, it should be done with caution. The dose depends on the patient's clinical condition, severity of hyperglycemia, predisposing factors for hyperglycemia, renal function, and daily insulin requirements. Generally, after the patient is receiving his or her goal dextrose dose in PN and is clinically stable, about 50% to 70% of the total insulin units administered over the previous 24 hours as sliding scale or continuous infusion can be added to the next PN admixture. In patients with type 2 diabetes, typical IV insulin doses in the PN admixture to maintain euglycemia range from 0.05 to 0.2 unit of insulin per gram of dextrose. Use caution when insulin is added to PN to avoid hypoglycemia, especially when reversible causes of hyperglycemia have resolved (eg, stress, acute pancreatitis, corticosteroid therapy) or more than one form of insulin therapy is used concurrently. Adding insulin to PN does not provide the flexibility of frequent titration (vs a continuous IV infusion). Only regular insulin should be added to PN; other forms of insulin should not be added to PN admixtures because they are not a true solution (eg, NPH insulin), and/or their pharmacokinetics/duration of action may not be appropriate for infusion over a prolonged time.

▶ *Histamine-2 Receptor Antagonists*

Intravenous histamine-2 receptor antagonists (eg, famotidine) at typical therapeutic doses are compatible with PN admixtures and can be added when indicated.

▶ *Parenteral Iron*

Chronic PN-dependent patients are at risk for iron deficiency due to underlying clinical conditions and the lack of regular iron supplementation in PN. Although iron dextran may be compatible with lipid-free PN admixtures, iron is not compatible with ILE at therapeutic doses and is not commonly added to PN admixtures due to the incompatibility and the potential for infusion-related reaction. Other parenteral iron formulations (eg, iron sucrose, ferric gluconate) should *not* be added to PN admixtures due to incompatibility or a lack of compatibility data.

▶ *Other Additives*

Other nonnutrient additives should only be included in PN admixtures if there are data supporting physicochemical compatibility and stability and if there are clinical data demonstrating the efficacy and safety of use when administered in the manner of PN administration (ie, continuous infusion over ~12–24 hours).[12]

NUTRITION ASSESSMENT AND NUTRIENT REQUIREMENTS

A nutrition assessment is used to determine a patient's nutritional status, identify patients with malnutrition, identify risk factors for nutrition-related problems, identify or rule out specific nutrient deficiencies, and determine nutrient requirements.[1] A complete description of nutrition assessment is beyond the scope of this chapter, and a nutrition assessment should be completed by a healthcare professional with appropriate training and expertise (eg, dietitian, nutrition-certified pharmacist or nurse, physician). Briefly, key components of a nutrition assessment include[1,19]:

- Patient history.
- Anthropometric measurements including height, weight, ideal body weight (IBW), body mass index (BMI = weight [kg]/height [m^2]), and recent weight changes (intentional or unintentional) (refer to Chapter 102 for additional information).
- Physical examination of the musculoskeletal system (eg, biceps, triceps, quadriceps, temporalis, deltoid, and interosseous muscles) for loss of muscle mass or decreased grip strength, and examination of the skin and mucous membranes for abnormalities (eg, dry or flaky skin, bruising, edema, ascites, poorly healing wounds) and loss of subcutaneous fat.
- Changes in eating habits, GI function, and associated GI symptoms.
- Presence and severity of underlying and concurrent disease(s).
- Serum visceral protein concentrations (eg, albumin, prealbumin). Hypoalbuminemia at baseline or before hospitalization may indicate malnutrition, and severe hypoalbuminemia may be associated with poor outcomes. Serum albumin (half-life ~ 20 days) and prealbumin (half-life ~ 2 days) are negative acute-phase proteins and therefore are neither sensitive nor specific indicators of nutritional status and protein stores in patients under metabolic stress or with evidence of inflammatory response. Measuring C-reactive protein (CRP), white blood cell count, and blood glucose levels may help assess inflammatory response. Synthesis and distribution of albumin and prealbumin may be altered, and serum concentrations are affected by nonnutritional factors, including hydration status, kidney function, and liver function.
- Biochemical evidence of vitamins, trace elements, and iron studies if clinical suspicion and minimal to no inflammation.
- Functional assessment including handgrip strength.

Table 100–5 outlines the two most commonly used sets of criteria for diagnosing malnutrition. Each set of criteria also contains objective parameters to describe severity of malnutrition as either moderate or severe.[19,20]

After performing a nutrition assessment, estimate the patient's daily energy and protein requirements (Table 100–6).[1,2,21,22] Indirect calorimetry involves measuring the volumes of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) to determine the resting metabolic rate (RMR) or resting energy expenditure (REE) and respiratory quotient ($RQ = VCO_2/VO_2$). The REE or RMR is the amount of calories required during 24 hours by the body in a nonactive state and is approximately 10% higher than the basal energy expenditure (BEE, metabolic

Table 100–5

Criteria for Diagnosis of Malnutrition[19,20]

	ASPEN/AND[a] Criteria	GLIM[b] Criteria
Diagnostic Criteria	Requires 2 or more of: • Insufficient energy intake • Weight loss • Loss of muscle mass • Loss of subcutaneous fat • Localized or generalized fluid accumulation that may sometimes mask weight loss • Diminished functional status as measured by hand-grip strength	Requires 1 from each category: Phenotypic • Nonvolitional weight loss • Low body mass index • Reduced muscle mass Etiologic • Reduced food intake or assimilation • Disease burden/inflammatory condition
Diagnosis Categorization	Based on presence and severity of inflammation: • No inflammation: Starvation-related malnutrition (pure chronic starvation, anorexia nervosa) • Mild-to-moderate inflammation: Chronic disease-related malnutrition (organ failure, pancreatic cancer, rheumatoid arthritis, sarcopenic obesity) • Marked inflammatory response: Acute disease or injury-related malnutrition (major infection, burns, trauma, closed head injury)	According to underlying etiology Malnutrition related to: • Chronic disease with inflammation • Chronic disease with minimal or no perceived inflammation • Acute disease or injury with severe inflammation • Starvation including hunger/ food shortage associated with socioeconomic or environmental factors

[a] ASPEN/AND American Society for Parenteral and Enteral Nutrition and The Academy of Nutrition and Dietetics.

[b] GLIM Global Leadership Initiative on Malnutrition.

Table 100–6

Estimating Daily Nutritional Requirements in Adults[1,2,19,21,22]

Determining Energy Expenditure:	
Penn State equations (for critically ill, mechanically ventilated, nonobese adult patients)	$\text{RMR} = (0.85 \times \text{BEE}^a) + (33 \times V_E) + (175 \times T_{max}) - 6433$ $\text{RMR} = (0.96 \times \text{BMR}^b) + (31 \times V_E) + (167 \times T_{max}) - 6212$
Mifflin-St. Jeor equations (for nonobese and obese, non-critically ill adult patients)	Men: $\text{BMR} = (10 \times \text{Wt}) + (6.25 \times \text{Ht}) - (5 \times \text{Age}) + 5$ Women: $\text{BMR} = (10 \times \text{Wt}) + (6.25 \times \text{Ht}) - (5 \times \text{Age}) - 161$
Harris-Benedict equations (historical, not currently recommended for use in acute setting)	Men: $\text{BEE} = 66.42 + (13.75 \times \text{Wt}) + (5 \times \text{Ht}) - (6.78 \times \text{Age})$ Women: $\text{BEE} = 655.1 + (9.65 \times \text{Wt}) + (1.85 \times \text{Ht}) - (4.68 \times \text{Age})$ Energy expenditure then multiplied by a stress factor. To estimate the TEE: Bed rest ≈ 1.2 × BEE Ambulatory ≈ 1.3 × BEE Anabolic ≈ 1.5 × BEE Energy requirements should also be increased ~12% with each degree of fever above 37°C (98.6°F).
Energy expenditure per body weight (ie, kcal/kg)[c]	Range of ~20–30 kcal/kg/day, possibly up to 35 kcal/kg/day Maintenance ~20–25 kcal/kg/day Repletion, postoperative wound healing, critical illness, sepsis, severe trauma, severe burns ~25–30 kcal/kg/day, possibly up to 35 kcal/kg/day

Determining Amino Acid Requirements

Patient Clinical Condition	Daily Amino Acid Requirements[d] (g/kg)
Maintenance or nonstressed	0.8–1
Repletion	1.3–2
Trauma, burns, sepsis, critical illness, wound healing	1.5–2
Hepatic failure with encephalopathy	0.8–1
Acute kidney injury, predialysis	0.8–1
Acute kidney injury receiving IHD	1.2–1.5
Chronic kidney disease receiving CAPD	1.2–1.5
Acute kidney disease receiving CRRT	1.5–2.5

BEE, basal energy expenditure; BMR, basal metabolic rate; CAPD, continuous ambulatory peritoneal dialysis; CRRT, continuous renal replacement therapy; Ht, height (cm); IHD, intermittent hemodialysis; RMR, resting metabolic rate; TEE, total energy expenditure; T_{max}, maximum body temperature in degrees Celsius; V_E, minute ventilation in liters per minute; Wt, weight (kg).

[a] BEE calculated using the Harris-Benedict equation.

[b] BMR calculated using Mifflin-St. Jeor equation.

[c] One kcal/kg is equivalent to 4.184 kJ/kg.

[d] Amino acid requirements are based on actual body weight for normal body sized or malnourished adult patients and on ideal body weight (IBW) for obese patients.

activity required to have variable energy expenditure (EE), and indirect calorimetry is a valuable tool in assessing EE in these patients. Indirect calorimetry requires specific equipment and trained personnel and therefore is not feasible in all settings.

More than 200 equations and derivations have been developed to predict EE for adults, although none of the equations have been demonstrated to be completely accurate, and accuracy varies based on the patient population. The Penn State, Mifflin-St. Jeor, and Harris-Benedict equations are some of the most widely used, and they take into account several variables including a patient's sex, weight, height, age, and mechanical ventilation data to determine the REE (see Table 100–6). A "stress" or "injury" factor is sometimes applied to estimate the daily total EE (TEE), although there is debate about the appropriateness and validity of this approach. Alternatively, EE can be estimated based on body weight. However, dry weight or hospital admission weight should be used, and this estimation may not be appropriate in obese or elderly patients. There is debate over the best method to estimate energy requirements for obese patients. Indirect calorimetry is the preferred method but may not always be available. Several equations have been developed to estimate EE in obese patients. Although there is no consensus on the weight used to estimate EE in obese patients, it is reasonable to use an adjusted body weight (AdjBW) in obese patients to avoid overfeeding. AdjBW can be calculated with 25% to 50% of the difference between the actual weight and IBW added to the IBW. Using a 25% difference in calculating the AdjBW further avoids overfeeding when estimating energy requirements:

$$\text{AdjBW} = \text{IBW} + (0.25 \times [\text{Actual weight} - \text{IBW}])$$

Hypocaloric feeding is another approach for nutrient dosing in obese critically ill patients (discussed below).

Amino acid requirements are based on the patient's nutritional status, clinical condition(s), kidney function, and liver function. Amino acids are needed in adequate amounts to facilitate anabolism, restore lean body mass, and promote wound healing while avoiding adverse effects from excessive amino acid loading (eg, azotemia). No evidence-based data are available confirming the optimal body weight (actual, ideal, or adjusted) to use for dosing amino acids in adult patients. It is suggested to dose amino acids based on actual body weight for normal body sized or malnourished adult patients (ie, when actual weight is at or below IBW) and based on IBW or AdjBW for obese patients.

Hypocaloric nutrition support is an approach to dosing nutrition therapy for obese patients (BMI $\geq$ 30 kg/m^2). Hypocaloric feeding involves providing high doses of protein ($\geq$ 2–2.5 g/kg IBW/day) to support anabolism with lower amounts of total calories (~11–14 kcal/kg [~46–59 kJ/kg] actual weight/day or ~22–25 kcal/kg [~92–105 kJ/kg] IBW/day) with primary goals to promote net protein anabolism and avoid hyperglycemia or exacerbation of metabolic stress in critically ill patients.[2,21] Other benefits could include avoiding fat weight gain or promoting fat weight loss. Most data with hypocaloric feeding are in critically ill adult patients, but this approach has been used in other patients. Hypocaloric feeding should not be used in patients with kidney or liver failure. The optimal safe duration of hypocaloric feeding is unknown.

PARENTERAL NUTRITION SAFETY

Serious and sometimes fatal adverse events have occurred with inappropriate use of PN, and PN is classified as a high-risk medication.[23] Shortages of key PN components have also presented challenges to meet nutritional needs of patients requiring PN therapy. The American Society for Parenteral and Enteral Nutrition (ASPEN) has published several key PN safety documents, including PN safety recommendations[23] and revised guidelines that address PN ordering, order review, compounding, labeling, and dispensing.[12] ASPEN also provides guidance for managing shortages of PN components. These are essential resources for the safe and efficacious use of PN therapy, and they represent the standards of practice for PN prescribing, compounding, stability, compatibility, labeling, administration, and quality assurance. There are several key points and recommendations in these documents to improve the safety of the PN use process, including:

- Adopt published guidelines and literature.
- Develop standardized processes for PN prescribing, order verification, compounding, labeling, dispensing, administering, and monitoring.
- Develop PN-specific policies and procedures.
- Develop education and competency assessments at least annually for all healthcare professionals involved in the PN use process.
- Optimize electronic health records (EHR) and clinical decision support for PN orders.
- Build, test, and heed clinical decision support warnings in EHR systems and in automated compounding devices.
- Avoid use of handwritten PN orders and eliminate manual transcription.
- Match templates between ordering/EHR, compounding software/automated compounding devices, and PN labels.
- PN use process and development of policies, procedures, education, and competencies should include healthcare professionals with expertise in nutrition support, preferably from multiple disciplines.

Although application of these guidelines is voluntary, healthcare professionals who are involved in prescribing, compounding, dispensing, administering, and monitoring PN therapy should review and apply them to their practice.

PREPARING THE PN PRESCRIPTION: ADMINISTRATION, COMPOUNDING, AND PHARMACEUTICAL ISSUES

After performing a nutrition assessment and estimating nutritional requirements, determine the optimal route to provide nutrition support therapy (eg, oral, enteral, or parenteral). If PN is indicated, venous access for PN infusion must be obtained. Finally, formulate a PN prescription and administer PN according to safety guidelines.

Route of PN Administration: Peripheral Versus Central Vein Infusion

KEY CONCEPT PN can be administered via a smaller peripheral vein or via a larger central vein (Figure 100–1). Peripheral PN (PPN) is generally reserved for short-term administration (eg, up to 7 days) when central venous access is not available. PN formulations are hyperosmolar, and thrombophlebitis and extravasation are significant complications that can limit tolerance of PPN therapy.[12] Factors that increase the risk of phlebitis include high solution osmolarity, extreme pH, rapid infusion rate, vein properties, catheter properties (eg, diameter, material), and infusion time via the same vein.[23] The osmolarity of PPN admixtures should be limited to $\leq$ 900 mOsm/L (mmol/L) to minimize the risk of phlebitis.[12]

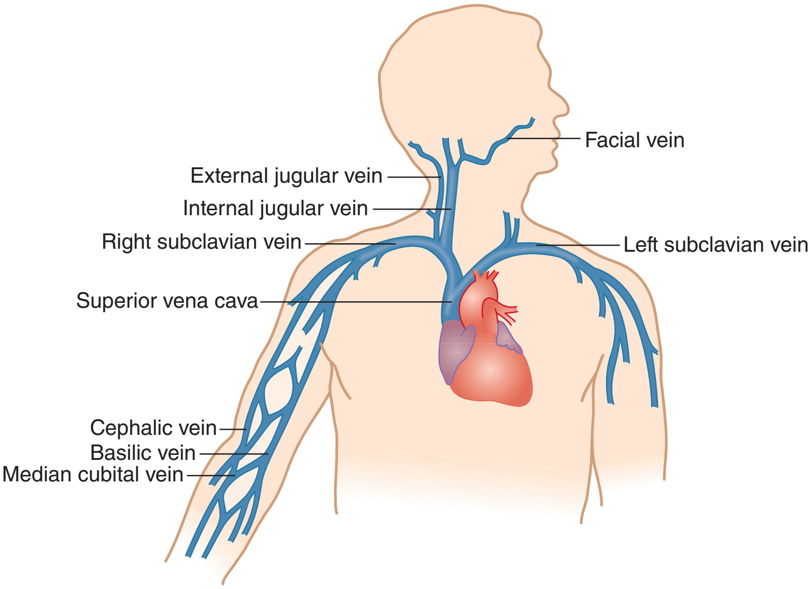

FIGURE 100–1. Selected vascular anatomy. (Reprinted from Neal AM, Drogan K. Parenteral access devices. In: Mueller CM, ed. The ASPEN Adult Nutrition Support Core Curriculum, 3rd ed. Silver Spring, MD: ASPEN; 2017.)

The approximate osmolarity of a PN admixture can be calculated from the osmolarity of the individual components:

- Amino acids ~10 mOsm/g (mmol/g; or 100 mOsm/L% final concentration in PN)
- Dextrose ~5 mOsm/g (mmol/g; or 50 mOsm/L% final concentration in PN)
- Sodium (chloride, acetate, and phosphate) = 2 mOsm/mEq (or 2 mOsm/mmol)
- Potassium (chloride, acetate, and phosphate) = 2 mOsm/mEq (or 2 mOsm/mmol)
- Calcium gluconate = 1.4 mOsm/mEq (2.8 mOsm/mmol)
- Magnesium sulfate = 1 mOsm/mEq (2 mOsm/mmol)

PPN admixtures should be coinfused with ILE when using 2-in-1 PN administration (see "Types of PN Formulations" below) because the iso-osmolarity and near-neutral pH of ILE may decrease the risk of phlebitis (see Table 100–2). Infectious and mechanical complications may be lower with PPN compared with central venous PN administration. Because of the risk of phlebitis, severe soft tissue damage if extravasation occurs, and osmolarity limit, PPN admixtures have low macronutrient concentrations and therefore usually require large fluid volumes to meet a patient's nutritional requirements.[24] These factors limit the utility of PPN therapy, and every effort should be made to obtain central venous access and initiate central PN in patients who have an appropriate indication (see Table 100–1).

Central PN refers to the administration of PN via a large central vein, and the catheter tip must be positioned in the superior vena cava (see Figure 100–1). Central PN allows the infusion of a highly concentrated, hyperosmolar nutrient admixture. The typical osmolarity of a central PN admixture is about 1500 to 2000 mOsm/L (mmol/L). Central veins have much higher blood flow, and the PN admixture is diluted rapidly on infusion, so phlebitis is usually not a concern. Patients who require PN therapy for longer periods of time (> 7 days) should receive central PN. Central PN requires placement of a central venous catheter and an x-ray to confirm placement of the catheter tip. A commonly used central catheter for PN infusion is a peripherally inserted central venous catheter (PICC), which is inserted into a peripheral vein, but the catheter tip is placed in the superior vena cava (Figure 100–2). Patients receiving long-term PN therapy often have a tunneled central venous catheter (Figure 100–3). Central venous catheter placement may be associated with complications, including pneumothorax, arterial injury, air embolus, venous thrombosis, infection, chylothorax, and brachial plexus injury.[1,24]

Types of PN Formulations: 3-in-1 Versus 2-in-1

KEY CONCEPT PN admixtures can be prepared by mixing all components into one container, or ILE may be infused separately

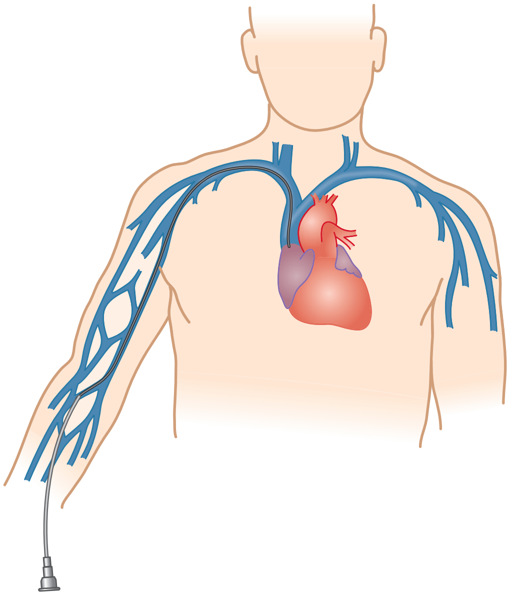

FIGURE 100–2. Peripherally inserted central venous catheter. (Reprinted from Krzywda EA, Andris DA, Edmiston CE, Wallace JR. Parenteral access devices. In: Gottschlich MM, ed. The A.S.P.E.N. Nutrition Support Core Curriculum: A Case-Based Approach—The Adult Patient. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2007:300–322.)

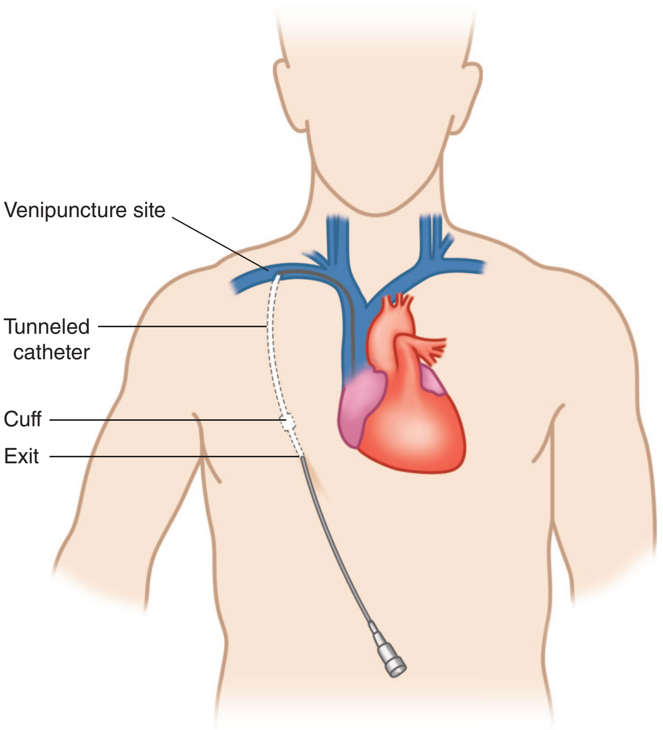

FIGURE 100–3. Tunneled central venous catheter. (Reprinted from Krzywda EA, Andris DA, Edmiston CE, Wallace JR. Parenteral access devices. In: Gottschlich MM, ed. The A.S.P.E.N. Nutrition Support Core Curriculum: A Case-Based Approach—The Adult Patient. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2007:300–322.)

(via a Y-site infusion or through a separate IV catheter or lumen). When all components are mixed together, it is referred to as a 3-in-1 admixture or TNA. When dextrose, amino acids, and all other PN components are mixed together without ILE (which is infused separately), this is referred to as a 2-in-1 PN admixture. There are various advantages and disadvantages to using either TNA or 2-in-1 PN admixtures (Table 100–7). With a 2-in-1 PN admixture, ILE can be infused separately on a daily or intermittent basis. When ILE is mixed in the PN, the TNA becomes an emulsion with respect to physical and chemical characteristics. The final concentration of ILE in a 3-in-1 admixture should be greater than or equal to 2% (20 g/L) to prevent compromising the stability of the emulsion.[12] Electrolyte, dextrose, and amino acid concentrations may also be more limited in a 3-in-1 admixture.

The FDA has provided recommendations for safe infusion of PN admixtures containing calcium and phosphate:

- A 0.22-μm air-eliminating in-line filter should be used for infusion of non–ILE-containing PN. (A 0.22-μm filter cannot be used on a TNA or ILE infusion line because the average size of ILE particles is approximately 0.3–0.5 μm.)
- A 1.2-μm in-line filter should be used for the infusion of a TNA because it can remove particulates and microparticulates (such as large/unstable fat droplets).[8,23]

Medications should not be admixed or coinfused with PN unless necessary, and it should only be done if reasonable and safe (based on toxicity profile, pharmacokinetic and pharmacodynamic considerations).[23] *Always* consult compatibility data before adding a medication to or coinfusing with a PN admixture. Many IV medications have limited compatibility with 3-in-1 formulations but may be coinfused with a 2-in-1 formulation.[25,26] Some medications can be coinfused at the Y-site; few medications can be mixed directly into the PN admixture or coinfused with ILE; and some cannot be mixed or coinfused with the PN admixture.[25,26]

Standardized, Commercially Available (Premixed or Multichamber) PN Formulations

Standardized, commercially available PN formulations, also called premixed PN formulations or multichamber PN bags (MCBs), are products available from a manufacturer that require fewer compounding steps before administration.[27] These products are available for adult patients in the United States in a two-chamber bag containing amino acids and dextrose with or without electrolytes, or in a three-chamber bag containing amino acids, dextrose, ILE, and electrolytes. However, these products are not “ready to

Table 100–7

Potential Advantages and Disadvantages of Using 3-in-1 (TNA) or 2-in-1 PN Admixtures

	3-in-1 (TNA)	2-in-1
Advantages	Simplified regimen for patient Increased patient compliance at home Decreased labor (less nursing time) Decreased supply and equipment costs Decreased risk of contamination (less manipulation; all components aseptically compounded) Inhibited bacterial growth vs separate ILE Minimize infusion-related reactions from ILE and possibly improved lipid clearance (if infused over > 12 hours) Decreased vein irritation (with PPN)	Improved stability compared with TNA Increased number of compatible medications Decreased bacterial growth (in dextrose–amino acid component) compared with TNA Easier visual inspection Can use 0.22-μm bacterial retention filter
Disadvantages	Decreased stability compared to 2-in-1 PN Cannot use 0.22-μm bacterial retention filter; must use 1.2-μm filter Increased bacterial growth compared with 2-in-1 PN Visual inspection is difficult Limited compatibility with medications	Increased labor and costs (if ILE infused separately) Increased vein irritation with PPN, especially if not coinfused with ILE

ILE, IV lipid emulsion; PN, parenteral nutrition; PPN, peripheral parenteral nutrition; TNA, total nutrient admixture.

administer" as provided; before safely administering to a patient, several essential steps must be completed[23]:

- Manually add vitamins and trace elements.
- ILE can be added to the two-chamber product if desired to create a TNA (or can be infused separately).
- Activate products (ie, break seals between chambers) correctly and then appropriately agitate/mix.
- Manipulations and/or additions to these products should be performed by trained pharmacy personnel.
- Correctly label the product and assign a proper beyond use date and expiration date.
- All of these steps must be completed based on manufacturer instructions, published compatibility and stability data, proper sterile compounding technique, and USP Chapter 797 requirements.

Potential advantages of MCB products include improvements in safety (decreased compounding errors, reduced risk of microbiologic contamination and infections), improvements in ergonomics (reduced time for preparation and administration), and a cost–benefit with comparable nutrition efficacy.[27] The safety advantages are logically related to fewer manual manipulations of the system, but clinical trial data are lacking. In addition, some data suggest an increase in bloodstream infections and hospital costs if additions are made to MCBs under non-aseptic conditions.[27] Cost advantages have been demonstrated in some trials, with others finding no difference or increased costs.[27] Limitations with the use of these products in the United States include relatively low amino acid concentrations, limited available volumes, limited variability in electrolyte content, and no formulations available for neonates and infants. Manufacturers of these products are planning to address some of these limitations with new formulations, including more concentrated amino acid formulation availability in the United States anticipated in early 2021. These limitations may make standardized commercial PN admixtures less appropriate for some patients (eg, critically ill, obese, those with organ dysfunction or who require fluid restriction). Failure to correctly activate or add ingredients to these products will introduce significant safety risks and can lead to patient harm. Finally, conclusions about MCB products should be interpreted with caution because much of the available data are from retrospective studies.

Patient Encounter, Part 2

It is now hospital day #3. Given that DB has malnutrition, an enterocutaneous fistula originating from the jejunum with high output (> 500 mL/day, increased when the patient drank water) and had recent abdominal surgery; the surgery team decided to manage DB conservatively: control fistula drainage, NPO status, and begin parenteral nutrition (PN) support today. A peripherally inserted central catheter (PICC) was placed for PN therapy.

Laboratory Data

Na = 134 mEq/L (mmol/L), K = 3.2 mEq/L (mmol/L), Cl = 91 mEq/L (mmol/L), HCO_3 = 24 mEq/L (mmol/L), BUN = 6 mg/dL (2.1 mmol/L), serum creatinine = 0.4 mg/dL (35 μmol/L), blood glucose = 91 mg/dL (5.1 mmol/L), total Ca = 8.4 mg/dL (2.10 mmol/L)], ionized Ca = 2.38 mEq/L (1.19 mmol/L), Mg = 1.5 mg/dL (0.62 mmol/L), phosphorus = 2.5 mg/dL (0.81 mmol/L), TG = 129 mg/dL (1.46 mmol/L), albumin = 2.9 g/dL (29 g/L), WBC count = 8300/mm^3 (8.3 × 10^9/L), hemoglobin = 11.4 mg/dL (114 g/L; 7.08 mmol/L), hematocrit = 35.1% (0.35), and platelets = 204,000/mm^3 (204 × 10^9/L)

Determine appropriate nutritional goals for DB (calorie and protein requirements).

What other patient data should be collected to help formulate a PN prescription?

Formulating a PN Admixture and Regimen

After completing a full nutrition assessment; estimating the patient's daily fluid, energy, and protein requirements (see Table 100–6); and determining if PN is indicated (see Table 100–1), develop an appropriate PN prescription.

Initiating PN

Exercise caution when initiating PN to avoid hyperglycemia and fluid and electrolyte abnormalities. After determining the goal daily PN volume, initiate PN at a lower infusion rate (eg, ~50% of goal for anywhere from ~6 to 24 hours) on day 1 with no more than 150 to 200 g of dextrose per day (or a maximum initial dextrose infusion rate of ~2 mg/kg/min). Increase PN to goal over the following ~24 hours, provided that glycemic control is maintained and the patient does not experience significant fluid or electrolyte abnormalities. Monitor electrolytes daily and correct as needed. Advance PN more slowly and cautiously in patients with severe malnutrition and monitor for refeeding syndrome (see Complications of PN).

Cycling PN

PN should be administered over 24 hours in most hospitalized patients to minimize glucose, fluid, and electrolyte abnormalities. However, administering PN via an infusion over less than 24 hours, or *cycling PN*, may be advantageous in certain patients and situations. Cycling PN involves administering the same PN formulation over a goal infusion time, usually over 12 to 18 hours, rather than over 24 hours. Begin with the PN infusion over 24 hours, then adjust the PN infusion to the goal cycle over 2 to 4 days (eg, 24 hours, then 18–20 hours the next day, then 14–16 hours the next day, and then 12 hours the next day). Titrate the PN infusion rate up over 1 to 2 hours to peak rate to avoid hyperglycemia and taper down over 1 to 2 hours at the end of the

Patient Encounter, Part 3

The surgical team asks for your recommendations for PN therapy for DB.

Develop a plan for a complete and balanced PN prescription for amino acids (including fluid, total calories, dextrose, amino acids, ILE, electrolytes, vitamins, trace elements, and any additives) and explain the rationale supporting your PN formulation and plan.

How should this PN admixture be initiated and titrated to goal?

Would you recommend any other treatments before initiating PN? (Hint: Is this patient at risk for refeeding syndrome?)

cycle to avoid reactive hypoglycemia. Most home infusion pumps can be programmed to cycle a given PN volume automatically over a given time; however, the clinician may have to develop an appropriate PN cycle if this functionality is not available.

Cyclic PN has the following potential advantages:

- It may improve the quality of life of patients receiving home PN by allowing the patient time off PN to engage in normal activities of daily living.
- While data are limited, it may help prevent and alleviate PN-associated liver disease by avoiding continuous compulsive nutrient overload on the liver.[28]

Concerns with cycling PN include hyperglycemia with high infusion rates, reactive hypoglycemia when PN infusion is stopped, and fluid and electrolyte abnormalities. Longer cycle times may limit these adverse effects. Random capillary blood glucose concentrations should be checked ~1 to 2 hours after reaching goal rate, 15 to 60 minutes after PN stops, and intermittently during the PN cycle as needed for glycemic control. Consider checking blood glucose after the PN cycle has ended only if the patient has signs/symptoms of hypoglycemia. This approach may prevent inadvertent treatment of borderline elevated glucose concentrations once PN has stopped and subsequently inducing hypoglycemia. During cyclic PN infusion, the potassium infusion rate should not exceed 10 mEq/hour (mmol/hour) if the patient is not on a cardiac monitor. If nocturnal cyclic PN infusion interferes with patient's sleep pattern by causing overdiuresis, the PN cycle can be extended over a longer infusion time, or PN can be infused during other times of the day that are most convenient to the patient.

Transition to Oral or Enteral Nutrition

The goal is to transition the patient to enteral or oral nutrition and taper off PN as soon as indicated. After initiation of enteral or oral nutrition, monitor the patient for glucose, fluid, and electrolyte abnormalities. When oral nutrition intake is inconsistent, perform calorie counts to determine the adequacy of nutrition via the oral route. When the patient is tolerating more than 50% of total estimated daily calorie and protein requirements via the oral or enteral route, decrease PN by about 50%. PN can be stopped when the patient is tolerating at least 75% of total daily calorie and protein requirements via the oral or enteral route, assuming that intestinal absorption is maintained.

COMPLICATIONS OF PN

KEY CONCEPT PN therapy is associated with significant complications, both with short- and long-term therapy (Table 100–8). Many complications are related to overfeeding (Table 100–9).

Table 100–8

Complications Associated With Parenteral Nutrition

Short Term	Long Term
Hyperglycemia	Infectious complications
Hypoglycemia	Liver toxicity
Electrolyte abnormalities	Vitamin abnormalities
Refeeding syndrome	Trace element abnormalities
Acid–base disturbances	Metabolic bone disease
Hyperlipidemia	Catheter/mechanical complications
Hypercapnia	
Infectious complications	
Catheter/mechanical complications	

Hyperglycemia

Hyperglycemia is one of the most common complications associated with PN therapy in adult patients.[24] Patients with stress and hypermetabolism (eg, trauma, burns, sepsis, severe acute pancreatitis) often have hyperglycemia due to increased endogenous glucose synthesis, decreased cellular glucose uptake, and increased insulin resistance.[29,30] Patients with diabetes and patients receiving certain medications (eg, corticosteroids, vasopressors, octreotide, tacrolimus) can also experience hyperglycemia. Uncontrolled hyperglycemia can lead to fluid and electrolyte disturbances, hyperglycemic hyperosmolar nonketotic syndrome, hypertriglyceridemia, organ dysfunction, increased infections, and increased mortality.[24,29,31] Critical illness is associated with increased endogenous glucose production (caused by increased glycogenolysis and gluconeogenesis) and insulin resistance.[29-31] Therefore, critically ill patients have lower tolerance for dextrose infusion compared with nonstressed patients. A portion of daily calories (~20%–30%) can be administered via ILE to help decrease hyperglycemia, provided that the patient does not have hypertriglyceridemia. Always avoid overfeeding (with dextrose and with total calories). Most recent data suggest that moderate glucose control is indicated in adult hospitalized patients receiving nutrition support (eg, capillary glucose concentrations between ~140 and 180 mg/dL [7.8 and 10.0 mmol/L]).[32] Refer to "PN Additives: Regular Insulin" regarding management of hyperglycemia with insulin in PN.

Hypoglycemia

Hypoglycemia can occur in patients when PN is interrupted suddenly (reactive hypoglycemia), especially when patients are treated with insulin or as a result of insulin overdosing.[1] It is essential to prevent hypoglycemia and, if it occurs, identify and treat it promptly. Reactive hypoglycemia typically is rare and usually can be avoided by tapering PN over 1 to 2 hours before discontinuation rather than abruptly stopping the infusion (especially if the patient is receiving insulin or if the patient is not receiving oral or enteral nutrition). Reactive hypoglycemia generally occurs within 15 to 60 minutes after stopping PN, although it can occur later than this after discontinuing PN.[1] Capillary blood glucose concentrations should be monitored about 15 to 60 minutes after stopping PN infusion to detect any potential hypoglycemia. If PN is interrupted abruptly (eg, because of lost IV access), infusing an

Table 100–9

Consequences of Overfeeding

Source of Overfeeding	Consequences
Dextrose	Hyperglycemia, hypertriglyceridemia, hepatic steatosis, hypercapnia; hyperglycemia may cause fluid and electrolyte disturbances and increased infection risk
IV lipid emulsions	Hypertriglyceridemia, hyperlipidemia, hepatic steatosis
Amino acids	Azotemia
Total calories	Hepatic steatosis, cholestasis, hypercapnia

IV solution containing dextrose 10% in water at the same rate as PN should prevent hypoglycemia. In patients with poor venous access, reduce the PN infusion rate by 50% for 1 hour before discontinuing. Another alternative to prevent reactive hypoglycemia is to provide a glucose source via the oral or sublingual route when feasible.

Hyperlipidemia/Hypertriglyceridemia

Patients receiving ILE may be at risk for hyperlipidemia and hypertriglyceridemia. Hyperlipidemia in patients receiving PN may lead to a reduction in pulmonary gas diffusion and pulmonary vascular resistance.[24,31] Severe hypertriglyceridemia (especially serum triglyceride concentrations exceeding 1000 mg/dL or 11.30 mmol/L) can precipitate acute pancreatitis.[7,31] Hypertriglyceridemia may develop as a result of increased fatty acid synthesis caused by hyperglycemia, impaired ILE clearance, in patients with history of hyperlipidemia, obesity, diabetes, alcoholism, kidney failure, liver failure, multiorgan failure, sepsis, or pancreatitis, or as a result of medications (eg, propofol, corticosteroids, cyclosporine, sirolimus).[31] Hyperglycemia is probably one of the most common causes of hypertriglyceridemia in patients receiving PN.[31]

Monitor serum triglyceride concentrations regularly during PN therapy (see Table 100–9). If a patient develops hypertriglyceridemia, identify and correct the underlying cause(s) if possible. Prolonging the infusion of ILE may improve lipid clearance. If a patient is receiving propofol, ILE should be withheld and the triglyceride load and calories from the 10% ILE in propofol should be considered (see Table 100–2). ILE should be held when the serum is lipemic or when serum triglyceride concentrations are greater than 400 mg/dL (4.52 mmol/L). When this occurs, restart ILE when the serum triglyceride concentration is approximately 200 to 400 mg/dL (2.26–4.52 mmol/L) (or less) and administer only the equivalent of 100 g soybean oil ILE per week, either as divided doses of soybean oil ILE or as one of the alternative ILE products, to prevent EFAD. Avoid completely holding ILE for more than 3 to 4 weeks due to risk of EFAD.

Hypercapnia

Hypercapnia can develop because of overfeeding with dextrose and/or total calories.[1,31,33] Excess carbon dioxide production and retention can lead to acute respiratory acidosis. Excess carbon dioxide will also stimulate an increase in respiratory rate, and this increase in respiratory workload could cause respiratory insufficiency that may require mechanical ventilation. Reducing total calorie and dextrose intake would result in resolution of hypercapnia if due to overfeeding.

Liver Complications

The incidence of liver complications associated with PN ranges from approximately 7% to 84%, and end-stage liver disease historically developed in as many as 15% to 40% of adult patients on long-term PN (likely lower in current practice with avoidance of overfeeding).[31] Patients may develop a mild increase in liver transaminases within 1 to 2 weeks of initiating PN, but this generally resolves as PN continues, provided overfeeding is avoided. Severe liver complications include hepatic steatosis, steatohepatitis, cholestasis, PNALD, and cholelithiasis.[24,31,34]

Hepatic steatosis is usually a result of excessive administration of carbohydrates or fats, but deficiencies of carnitine, choline, and essential fatty acids also may contribute. Hepatic steatosis can be minimized or reversed by avoiding overfeeding, especially from dextrose and ILE.[31]

PNALD is described as decreased bile flow not caused by mechanical obstruction or other causes of liver disease in patients receiving long-term PN therapy.[34] Factors that predispose PN patients to cholestasis and PNALD include lack of enteral nutrition, use of soybean oil–based ILE (which contains high amounts of omega-6 fatty acids and potentially toxic phytosterols), exposure to aluminum, overfeeding, bowel rest, long duration of PN, short bowel syndrome, bacterial overgrowth and translocation, and sepsis.[24,31,34] Patients may exhibit increased serum liver transaminase (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), alkaline phosphatase and γ-glutamyl transferase (GGT) concentrations, and mainly increased bilirubin concentrations with jaundice. The most sensitive marker of cholestasis is increased serum conjugated (direct) bilirubin concentration of greater than 2 mg/dL (34.2 μmol/L).[31] Cholestasis generally is reversible if PN is discontinued before permanent liver damage occurs. Serum liver function tests may take up to 3 months to return to normal after discontinuing PN. Steps to prevent cholestasis associated with PN include early enteral or oral feedings, using a balanced PN formulation, avoiding overfeeding, using cyclic PN infusion, and treating and avoiding sepsis.[31] Reducing the dose of soybean oil–based ILE (ie, "lipid restriction") or using one of the alternative ILE products (lower in omega-6 fatty acids, lower in potentially toxic phytosterols) may be effective in the treatment of cholestasis and PNALD.[8,34] Monitor for EFAD in patients receiving reduced doses of ILE or alternative ILE products. Pharmacologic treatments include ursodeoxycholic acid (ursodiol), which may improve bile flow and reduce the signs and symptoms of cholestasis. Ursodiol is only available in an oral dosage form, and absorption may be limited in patients with extensive intestinal resections.

Cholelithiasis can develop because of decreased gallbladder contractility, especially in the absence of enteral or oral intake. Lack of intestinal stimulation reduces secretion of cholecystokinin, a peptide hormone secreted in the duodenum that induces gallbladder contractility and emptying. The best prevention of cholelithiasis is early initiation of enteral or oral feeding.

Monitor liver function tests, including serum AST, ALT, alkaline phosphatase, total bilirubin, conjugated bilirubin, unconjugated bilirubin, and GGT at the initiation of PN therapy and regularly thereafter during PN therapy. The frequency of monitoring liver function tests depends on the presence or absence of liver disease, ranging from once weekly in the acute setting to monthly or less frequently in stable home PN patients.

Manganese Toxicity

Manganese accumulation can occur in patients with cholestasis or in patients receiving long-term PN therapy. Neurotoxicity is the most common manifestation (headache, somnolence, weakness, confusion, tremor, muscle rigidity, altered gait, and mask-like face [a Parkinson-like syndrome]), but liver toxicity may also occur.[31] Periodically monitor blood manganese concentrations in patients on long-term PN. Patients with cholestasis receiving PN may require restriction of manganese in PN to prevent accumulation and possible toxicity.

Metabolic Bone Disease

Metabolic bone disease (MBD) is a condition of bone demineralization leading to osteomalacia, osteopenia, or osteoporosis in patients receiving long-term PN. MBD may occur in as many as 40% to 100% of patients receiving long-term PN.[31] Often patients are asymptomatic, although symptoms can include bone pain, back pain, and fractures. Patients often have increased serum alkaline phosphatase concentrations, low to normal parathyroid hormone (PTH) concentrations, normal 25-hydroxyvitamin D and low 1,25-dihydroxyvitamin D concentrations, hypercalcemia or hypocalcemia, and hypercalciuria.[35] Because patients may be asymptomatic, diagnosis can be incidental. Radiographic techniques commonly used in diagnosing bone disease include quantitative computed tomography (CT) and bone mineral density.[35]

Factors that can predispose patients to developing MBD include deficiencies of phosphorus, calcium, and vitamin D; aluminum toxicity; amino acids and hyperosmolar dextrose infusions; chronic metabolic acidosis; corticosteroid therapy; and lack of mobility.[31,35] Calcium deficiency (caused by decreased intake or increased urinary excretion) is one of the major causes of MBD in patients receiving PN. Provide adequate amount and balance of calcium and phosphate with PN to improve bone mineralization and help to prevent MBD.

Aluminum toxicity appears to play a role in the development of MBD in patients on long-term PN, possibly by impairing calcium bone fixation, inhibiting the conversion of 25-hydroxyvitamin D to the active 1,25-dihydroxyvitamin D, and/or reducing PTH secretion.[31,35] The FDA issued a rule specifying acceptable aluminum concentrations in parenteral products used in compounding PN admixtures,[36] indicating that products contain no more than 25 mcg/L (0.93 μmol/L) of aluminum and defined a safe upper limit for parenteral aluminum intake at less than 4 to 5 mcg/kg/day. Pharmacies should use products with the lowest labeled aluminum content for the making of PN.

Encourage patients on long-term PN to engage in regular low-intensity exercise. Yearly bone density measurements also should be performed on patients on long-term PN and when MBD is suspected.

Refeeding Syndrome

Refeeding syndrome describes the metabolic derangements that occur during reintroduction of nutrition in patients who are starved, underweight, or severely malnourished.[37] Hypophosphatemia and hypokalemia (along with associated complications) are the classic signs and symptoms, but refeeding syndrome encompasses a constellation of electrolyte abnormalities and possibly thiamin deficiency affecting neurologic, cardiac, hematologic, neuromuscular, and pulmonary systems. Symptoms can range from mild to severe, and the most severe cases of refeeding syndrome have resulted in cardiac failure, seizures, coma, and death. Most of the literature on refeeding syndrome is based on retrospective observations and case reports, and high-quality clinical data are lacking.[37]

The reintroduction of energy substrates, especially carbohydrates, increases metabolism and utilization of glucose as the predominant fuel source. This increases insulin secretion and demand for phosphorylated intermediates of glycolysis (eg, ATP and 2,3-diphosphoglycerate [2,3-DPG]), inhibits fat metabolism, and causes an intracellular shift of phosphorus, potassium, and magnesium. These changes, potentially in combination with preexisting low total body stores of phosphorus, potassium, and magnesium in starved or malnourished individuals, and enhanced cellular uptake of phosphorus during anabolic refeeding, can result in hypophosphatemia, hypokalemia, and hypomagnesemia. Vitamin deficiencies (eg, thiamin) also may exist or be precipitated during refeeding. High carbohydrate intake increases the demand for thiamin, which can precipitate thiamin deficiency and cause lactic acidosis and neurologic abnormalities,[2] and possibly myocardial dysfunction.[37] Other metabolic alterations that may occur include expansion of the extracellular water compartment and edema, although it is not clear if this is a direct consequence of refeeding syndrome.[37]

Recent consensus recommendations suggest diagnosing refeeding syndrome based on the following occurring within 5 days of reintroducing or substantially increasing energy provision: a decrease in any one or more of serum phosphorus, potassium, and/or magnesium by 10% to 20% (mild), 20% to 30% (moderate), or greater than 30% (severe) and/or organ dysfunction that results from these electrolyte abnormalities and/or due to thiamin deficiency (severe).[37]

The primary goal is preventing refeeding syndrome when initiating PN in patients at risk[37]:

- Lack of adequate nutritional intake for more than 5 to 7 days or intake of less than 50% to 75% of estimated needs for more than 1 month or more than 5 to 7 days if acutely ill
- Approximately 5% to 10% weight loss
- Moderate-to-severe malnutrition
- Presence of electrolyte abnormalities prior to initiating feeding
- Loss of muscle and/or subcutaneous fat
- Anorexia nervosa
- Mental health disorders
- Alcohol and substance use disorders
- Cancer
- Bariatric surgery
- Extensive intestinal resection
- Malabsorption
- Critical illness

When initiating nutrition support, the rule of thumb to mitigate refeeding syndrome is generally to “start low and go slow.” Although carbohydrates are the primary macronutrient precipitating refeeding syndrome, most guidelines include dosing recommendations based on total calories. Initiate PN cautiously (eg, ~100–150 g of dextrose or ~10–20 kcal/kg (~42–84 kJ/kg) for the first 24 hours and gradually increase by ~33% of goal calories every 1 to 2 days.[37,38] When using standardized, commercially available PN admixtures, consider selecting a formulation with a lower dextrose concentration for the first several days of therapy. Correct electrolyte abnormalities before initiating PN and provide supplemental phosphate, potassium, and magnesium in and/or outside of PN. Doses of IV phosphate up to 0.64 to 1 mmol/kg may be used to treat severe hypophosphatemia (in patients with normal kidney function), and doses can be repeated as needed until serum phosphorus concentration has normalized.[39] Provide supplemental oral or IV thiamin 100 mg/day for 5 to 7 days in patients at high risk for deficiency or with known or suspected deficiency, in addition to the standard multivitamin in PN.[37] Assess patients for fluid balance, signs of edema, fluid overload, and weight gain; it is reasonable to be cautious with fluid and sodium intake during the first few days of PN.[2] Monitor patients closely for signs and symptoms of refeeding syndrome until they are tolerating PN at goal for a few days[37]:

- Vital signs, mental status, and neurologic and neuromuscular function every 4 hours
- Pulse oximetry and any electrocardiographic changes when indicated

Table 100–10

Suggested Frequency of Monitoring Parameters in Hospitalized Patients Receiving PN

Parameters	Initial	Daily (Unstable)	2–3 × Weekly (Stable)	Weekly	As Indicated
BUN, creatinine	X	X	X		
Sodium, potassium, chloride, bicarbonate	X	X	X		
Glucose	X	X	X		
Calcium, phosphorus, magnesium albumin, AST, ALT, LDH, alkaline phosphatase, total bilirubin	X	X	X		
Conjugated bilirubin	X			X	X
Prealbumin[a]	X				X
Triglycerides	X			X	X
RBC count, hemoglobin, hematocrit, WBC count ± differential, platelets, PTT	X				X
PT or INR				X	X
Nitrogen balance					X
Zinc, selenium, chromium, copper, manganese, iron					X
TIBC, ferritin					X
Vitamin concentrations					X
Blood cultures					X
Body weight	X	X	X		

[a] Only recommended/indicated in the absence of inflammatory response.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; TIBC, total iron-binding capacity; WBC, white blood cell.

- Serum laboratory values (including phosphorus, potassium, magnesium, and sodium) every 12 hours for the first 3 days, possibly more frequently depending on the patient's clinical status

Consider developing a specific electrolyte replacement protocol or plan for patients with evidence of refeeding syndrome. If a patient develops hypophosphatemia, hypokalemia, and/or hypomagnesemia during initiation of nutritional intake or when increasing nutrition delivery, other signs or symptoms of refeeding syndrome, decreasing dextrose intake by ~50% (or consider decreasing to the amount provided on day 1, or decreasing to ~ 20 kcal/hour [84 kJ/hour]) and gradually increase by ~33% of goal every 1 to 2 days back to goal.[37,38] Given the lack of robust literature and clinical trials on refeeding syndrome, it is important to monitor the patient carefully and adjust PN and other treatments based on clinical judgment and the patient's response and clinical condition.

Infectious Complications

Patients receiving central PN are at increased risk of developing infectious complications caused by bacterial and fungal pathogens.[1,24,40] Earlier studies found that patients without malnutrition who receive early PN (eg, within 48 hours of ICU admission) may have a higher incidence of infectious complications than patients who do not receive PN or receive late PN initiation (eg, > 7 days after ICU admission).[2,3,41] However, more recent studies have not demonstrated this same risk (potentially due to avoiding overfeeding, improvements in catheter care, glycemic control, and other aspects of ICU care).[42,43] Strict aseptic techniques must be used when placing the catheter along with continuous care of the catheter and infusion site. Catheter-related bloodstream infections are a common complication in long-term PN patients, often requiring hospital admission for parenteral antimicrobial therapy and/or removal of the catheter. Contamination of the PN admixture is possible but rare if protocols are followed for aseptic preparation of PN admixtures.

Mechanical Complications

Mechanical complications of PN are related to venous catheter placement and the equipment used to administer PN. A central venous catheter must be placed by a trained professional, and risks associated with placement include pneumothorax, arterial puncture, bleeding, hematoma formation, venous thrombosis, and air embolism.[1,24] Over time, the venous catheter may require replacement. Problems with the equipment include malfunctions of the infusion pump, IV tubing sets, and filters.

MONITORING PN THERAPY

KEY CONCEPT When initiating PN, patients should have important baseline laboratory values checked to assess electrolyte status, organ function, and nutritional status. Thereafter, these and other nutritional parameters should be monitored routinely or as indicated. Random capillary blood glucose concentrations also should be monitored every 6 to 8 hours when initiating PN, and regular insulin should be administered to control blood glucose concentrations as needed (Table 100–10).

Patient Encounter, Part 4

The surgical team plans to initiate PN for DB per your recommendations. Laboratory data were listed previously.

What monitoring parameters related to PN therapy should you follow in DB after initiating PN? List monitoring parameters and frequency.

What potential complications of PN should you monitor for in DB?

What special considerations must be made when developing a plan for nutrition support therapy and a PN formulation for patients with severe malnutrition?

Patient Care Process: Parenteral Nutrition

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. Identify allergies to medications and other substances.
- Review the medical history and physical assessment findings.
- Review diet/nutritional intake history (or perform this history if not available).
- Identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication and food access and other aspects of care.

Assess the Information:

- Determine whether the patient is taking any substance that could adversely affect nutritional status, nutrient intake, or interact with prescribed medications or specialized nutrition support.
- Review relevant laboratory tests pertinent to nutrition status and fluid/electrolyte balance (eg, electrolytes, lipids, liver panel, renal function, A_{1C}, basic metabolic profile, complete blood count).
- Determine whether the patient is at risk of refeeding syndrome or short- or long-term complications of parenteral nutrition.
- Determine or assess appropriateness of the patient's macronutrient goals.
- Assess the efficacy, safety, and patient adherence of current pharmacotherapy and specialized nutrition support.
- Identify any significant adverse drug effects or drug–drug or drug–nutrient interactions.

Develop a Care Plan:

- If patient is at risk for refeeding, develop plan for preventing refeeding while initiating and advancing parenteral nutrition.
- Develop an initial, and subsequently a goal, parenteral nutrition formulation that is appropriate, safe, and pharmaceutically stable/compatible.
- Once stabilized on goal nutrition regimen, determine monitoring plan appropriate for the patient's current clinical status.
- Develop cycle regimen for parenteral nutrition if patient has an indication for cycling PN.
- If patient unable to take oral medications, determine which medications can be given via alternate routes or identify other medication changes needed to address comorbid conditions.

Implement the Care Plan:

- Educate the patient about changes in drug and nutrition therapy, medication administration, potential adverse effects, and how to manage and report adverse effects that occur.
- Review the patient's practices and technique for self-administration of parenteral nutrition (including sterile technique) if patient will self-manage at home.
- Address any patient concerns about parenteral nutrition and its management.
- Determine whether the patient has insurance coverage for home parenteral nutrition if indicated.

Follow-up: Monitor and Evaluate:

- Follow up at regular intervals (frequency as appropriate for clinical status and stability of parenteral nutrition regimen) with laboratory monitoring.
- Review parenteral nutrition adherence, administration technique, any changes in oral or enteral nutrition intake, and gastrointestinal function (indication for parenteral nutrition).
- Review physical examination, laboratory tests, and results of other diagnostic tests to assess for short- and long-term complications of parenteral nutrition.

SUMMARY AND CONCLUSION

PN is an effective and potentially lifesaving therapy for patients who cannot receive adequate oral or enteral nutrition. The PN use process and PN orders are complex, and there are a number of significant safety concerns with PN ordering and order review, compounding, and administration. PN therapy can be associated with significant adverse effects and metabolic, infectious, and mechanical complications. Healthcare professionals must take appropriate steps to optimize the safety of PN therapy and the PN use process to minimize the risk of adverse effects and complications, and patients must be monitored closely while receiving PN to optimize outcomes.

Abbreviations Introduced in This Chapter

AdjBW	Adjusted body weight
ALT	Alanine aminotransferase
ASPEN	American Society for Parenteral and Enteral Nutrition
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
CT	Computed tomography
2,3-DPG	2,3-Diphosphoglycerate
FDA	Food and Drug Administration
GI	Gastrointestinal
IBW	Ideal body weight
ILE	Lipid injectable emulsion
kcal	Kilocalorie(s)
kJ	Kilojoule(s)
LDH	Lactate dehydrogenase
MBD	Metabolic bone disease
mEq	Milliequivalents
mmol	Millimoles
mOsm	Milliosmoles
PL	Phospholipid(s)
PN	Parenteral nutrition
PPN	Peripheral parenteral nutrition
PTH	Parathyroid hormone
TG	Triglyceride
TNA	Total nutrient admixture
TPN	Total parenteral nutrition

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101 Enteral Nutrition

Sarah J. Miller

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Discuss how gut structure and function impact choice of feeding route and outcome of feeding.
2. Estimate kilocalorie and protein requirements of an enteral feeding candidate and design an enteral nutrition (EN) regimen to meet these.
3. Evaluate patient-specific parameters to determine whether EN is appropriate.
4. Compare clinical efficacy, complications, and costs of EN versus parenteral nutrition (PN).
5. Formulate a monitoring plan for an EN patient.
6. Select appropriate medication administration techniques for an EN patient.

INTRODUCTION

Enteral nutrition (EN) is broadly defined as delivery of nutrients via the gastrointestinal (GI) tract. The terms *enteral nutrition* and *tube feedings* are often used synonymously. Formulas for EN usually are delivered in the form of commercially prepared liquid preparations, although some products are produced as powders for reconstitution, and some patients may appropriately receive specific blenderized foods via feeding tubes.[1] Nonvolitional feedings, in patients who cannot meet nutritional requirements by oral intake, include EN and parenteral nutrition (PN), which are collectively known as *specialized nutrition support* (SNS).

Several organizations have issued EN clinical guidelines. These include the American Society for Parenteral and Enteral Nutrition (ASPEN), European Society for Clinical Nutrition and Metabolism (ESPEN), and a Canadian team known as Critical Care Nutrition.[2-4] ASPEN and the Society for Critical Care Medicine (SCCM) have jointly issued guidelines for SNS in critically ill patients and COVID-19 patients.[5,6]

GI TRACT STRUCTURE AND FUNCTION

Anatomy and Absorptive Function

With normal volitional feeding, food is ingested via mouth. There, the process of breaking down complex foodstuffs into simpler forms begins. Solid food is chewed in the mouth, and enzymes begin digestion. Presence of food in specific GI tract regions triggers release for many enzymes and GI hormones. Food is swallowed and passes through the esophagus and the esophageal sphincter to the stomach, where additional digestive enzymes and acids further break it down. The stomach also mixes and grinds.

Food, now in liquid form known as *chyme*, passes through the pyloric sphincter into the duodenum, where stomach acid is neutralized. Food then passes into the jejunum, where most absorption of digested carbohydrate and protein occurs. Most fat absorption occurs within the jejunum and ileum, the final segment of the small bowel. The absorptive units on the intestinal mucosal membrane are infoldings known as *villi*, which are made up of epithelial cells called *enterocytes.* Projections from these enterocytes, called *microvilli*, increase surface area of the small bowel and make up the *brush-border membrane.*

Digestive substances secreted by the pancreas play a role in food breakdown. Large amounts of sodium bicarbonate neutralize stomach acid. Digestive substances flow from the pancreas through the pancreatic duct. The pancreatic duct typically joins the hepatic duct to become the common bile duct that empties through the sphincter of Oddi into the duodenum. Bile salts secreted by the liver help emulsify fat and facilitate fat absorption. Bile flows through bile ducts into the hepatic duct and common bile duct. Bile is stored in the gallbladder until needed to aid fat digestion, at which time it empties through the cystic duct to the common bile duct to the duodenum. Figure 101–1 illustrates digestion and absorption of nutrients.

Remaining undigested food passes from the ileum through the ileocecal valve to the colon. A major role of the colon is fluid absorption. Some water and sodium absorption is facilitated by short-chain fatty acids (SCFAs) formed from digestion of certain dietary fibers by colonic bacterial enzymes.

Gut Immune Function

The gut plays significant immune roles. The distal small bowel and colon host many bacteria and their endotoxins, and it is important that these organisms not gain access to internal body systems. This function is known as the *gut barrier function*.[7] Normal gut flora comprise one component. Normal flora, particularly some anaerobes, help prevent overgrowth of potential pathogens. A second component involves mechanical factors, including a mucus layer that prevents bacterial adherence. Small bowel peristalsis prevents bacterial stasis. Gut-associated lymphoid tissue (GALT), prominent in the small bowel, serves as a local immune system. Secretory immunoglobulin A produced at the mucosal surface in response to food prevents bacteria from invading the surface.

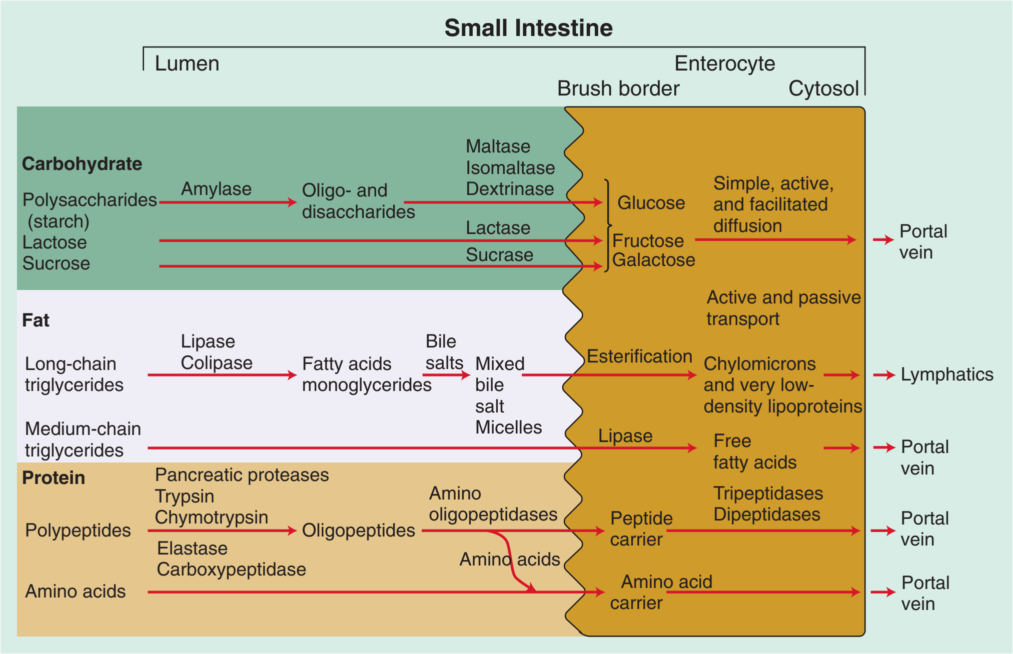
Small Intestine
Lumen
Enterocyte
Brush border
Cytosol
Carbohydrate
Polysaccharides (starch)
Lactose
Sucrose
Amylase
Oligo- and disaccharides
Maltase
Isomaltase
Dextrinase
Lactase
Sucrase
Glucose
Fructose
Galactose
Simple, active, and facilitated diffusion
Portal vein
Fat
Long-chain triglycerides
Lipase
Colipase
Fatty acids monoglycerides
Bile salts
Mixed bile salt Micelles
Active and passive transport
Esterification
Chylomicrons and very low-density lipoproteins
Lymphatics
Medium-chain triglycerides
Lipase
Free fatty acids
Portal vein
Protein
Polypeptides
Pancreatic proteases
Trypsin
Chymotrypsin
Elastase
Carboxypeptidase
Oligopeptides
Amino oligopeptidases
Amino acids
Peptide carrier
Tripeptidases
Dipeptidases
Portal vein
Amino acids
Amino acid carrier
Portal vein

FIGURE 101–1. Schematic of carbohydrate, fat, and protein digestion. (From Kumpf VJ, Mulherin DW. Enteral nutrition. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020; Figure 160–1.)

PATIENT SELECTION

In general, KEY CONCEPT EN is the preferred route if the gut can be used safely in patients who cannot meet nutritional requirements by oral intake, rather than PN. The timing of SNS (either EN or PN) is controversial.[3,6] Previously well-nourished patients can better afford not being fed for longer periods than previously poorly nourished patients. Most patients in the intensive care unit (ICU) benefit from early EN started within 24 to 48 hours of ICU admission.[3,6] Methods for assessing nutritional status and designing SNS regimens are covered in Chapter 100. Generally, nonobese hospitalized patients require 20 to 35 total kcal/kg of body weight/day (84–147 kJ/kg body weight/day) and 1.2 to 2 g protein/kg of body weight/day. Obese patients are often fed hypocaloric, high-protein diets; guidelines state to start feedings at 1.2 g protein/kg of actual body weight (or 2–2.5 g/kg of ideal body weight) and less than 14 kcal/kg actual body weight (59 kJ/kg actual body weight).[8]

Indications

Many potential indications for EN exist (Table 101–1). PN was used extensively in the past, but advances in EN technology now allow many patients to receive EN in both institutional and home settings.

Contraindications and Precautions

EN should be avoided or used with caution in certain conditions (Table 101–2). It is possible to use EN in some of these patients depending on severity of illness, location of abnormality, and experience of practitioners delivering care. Feeding in hemodynamic instability is controversial; the 2016 ASPEN/SCCM critical care guidelines recommend withholding feedings in hypotension or when vasopressors are being initiated or escalated.[6,9,10]

Table 101–1

Potential Indications for EN

Neoplastic Disease	**GI Disease**
Chemotherapy	Inflammatory bowel disease
Radiation therapy	Short bowel syndrome
Upper GI tumors	Esophageal motility disorder
Cancer cachexia	Pancreatitis
Organ Dysfunction	Fistulas
Liver disease/failure	Gastroesophageal reflux disease (severe)
Kidney insufficiency/failure	Esophageal or intestinal atresia
Cardiac cachexia	**Neurologic Impairment**
ARDS/ALI	Comatose state
Bronchopulmonary dysplasia	Cerebrovascular accident
Congenital heart disease	Demyelinating disease
Organ transplantation	Severe depression
Hypermetabolic States	Cerebral palsy
Closed head injury	**Other Indications**
Burns	AIDS
Trauma	Anorexia nervosa
Postoperative major surgery	Complications during pregnancy
Sepsis	Failure-to-thrive
	Geriatric patients with multiple chronic diseases
	Extreme prematurity
	Inborn errors of metabolism
	Cystic fibrosis

AIDS, acquired immune deficiency syndrome; ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

From Kumpf VJ, Mulherin DW. Enteral nutrition. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020.

Table 101–2

Contraindications and Precautions for EN
Severe hemorrhagic pancreatitis
Severe necrotizing pancreatitis
Necrotizing enterocolitis
Diffuse peritonitis
Small bowel obstruction
Paralytic ileus
Severe hemodynamic instability
Enterocutaneous fistulae
Severe diarrhea
Severe malabsorption
Severe GI hemorrhage
Intractable vomiting
Uncorrectable coagulopathy
Bowel ischemia

Enteral Versus Parenteral Feeding

PN by large central vein became popular in the 1960s. In the late 1980s and early 1990s clinical studies started demonstrating better clinical outcomes with EN compared to PN. Potential advantages of EN over PN are included here. First, EN is expected to preserve the gut barrier function better than PN. This could prevent translocation of bacteria and endotoxin from the gut lumen into the lymphatic system and systemic circulation, thus preventing infections. Some studies indicate **KEY CONCEPT** EN is associated with fewer infectious complications than PN. EN is cited frequently as having a better overall safety profile than PN, which is associated with more severe complications, such as pneumothorax and catheter sepsis. EN is associated with more nuisance complications, such as GI side effects. EN formulas typically are cheaper and less labor intensive to prepare than PN, although some specialty EN formulas approach the cost of PN formulas. Depending on the method of feeding tube placement, EN costs can mount if the tube must be placed by a radiologist or gastroenterologist.

Arguments in support of EN over PN have been questioned related to whether EN is beneficial compared with PN or whether PN as previously administered might have been detrimental. Overfeeding and hyperglycemia occur easily with PN, and the potential harm of hyperglycemia, especially in critical care populations, has been demonstrated, although the exact range optimal for glycemic control in ICU patients may differ for various critically ill subpopulations. PN historically led to increased infection risk and perhaps caused more harm than good in many instances unless patients were severely malnourished.[11] Whether EN truly prevents infections and improves clinical outcomes or PN is detrimental continues to be debated. Presently, most experts prefer EN over PN when the gut is functional. Use of PN to supplement EN during the first week of intensive care therapy when EN is not yet being tolerated at full rates is supported by European guidelines.[2] This is currently discouraged by American and Canadian ICU guidelines, although support is growing.[3,6] Randomized controlled trials relating to EN versus PN and deliberate (permissive) underfeeding (setting caloric goals below that necessary to achieve energy balance) have yielded disparate results.[12-20]

ROUTES OF ACCESS

There are several access sites for EN (Figure 101–2).[21,22] The feeding tube tip can end up in the stomach, duodenum, or jejunum. Advantages and disadvantages exist for each EN route (Table 101–3).

Gastric Feeding

Gastric feedings are commonly used. They require an intact gag reflex and normal gastric emptying for safety and success. Certain patients, such as those with head trauma, may not empty their stomachs efficiently and may not be good candidates for gastric feedings. Pooling of formula in the stomach could increase risk of aspirating feeding formula into the lungs.

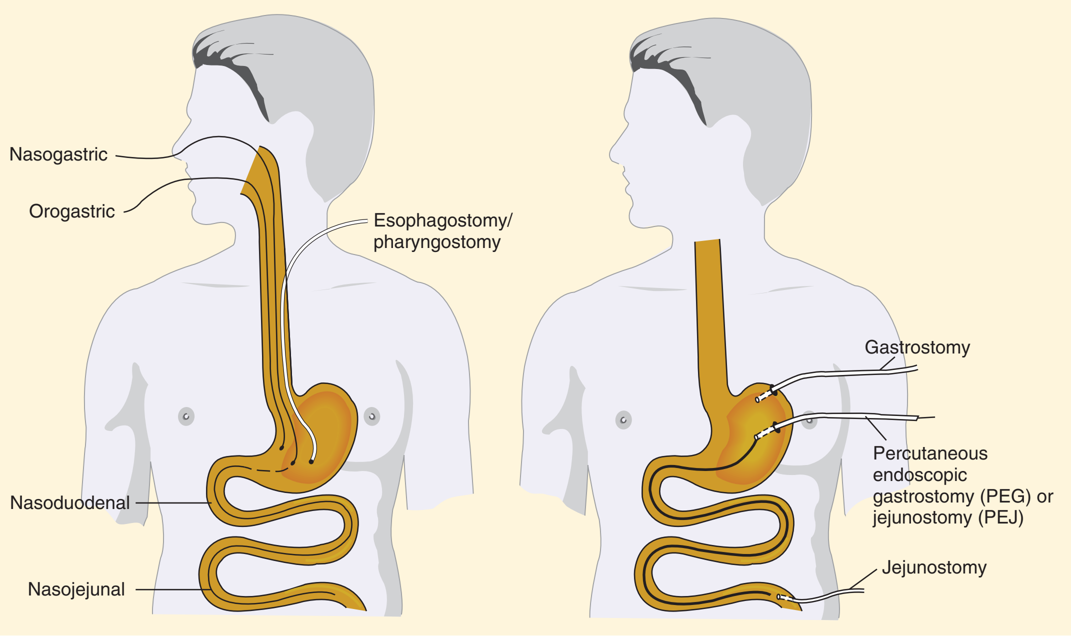

FIGURE 101–2. Access sites for tube feeding. (From Kumpf VJ, Mulherin DW. Enteral nutrition. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed, New York, NY: McGraw-Hill; 2020; Figure 160–2.)

Table 101–3

Options and Considerations in the Selection of Enteral Access

Access	EN Duration/Patient Characteristics	Tube Placement Options	Advantages	Disadvantages
Nasogastric or orogastric	Short term Intact gag reflex Normal gastric emptying	Manually at bedside	Ease of placement Allows for all methods of administration Inexpensive Multiple commercially available tubes and sizes	Potential tube displacement Potential increased aspiration risk
Nasojejunal	Short term Impaired gastric motility or emptying High risk of GER or aspiration	Manually at bedside Fluoroscopically Endoscopically	Potential reduced aspiration risk Allows for early postinjury or postoperative feeding Multiple commercially available tubes and sizes	Manual transpyloric passage requires greater skill Potential tube displacement or clogging Bolus or intermittent feeding not tolerated
Gastrostomy	Long term Normal gastric emptying	Surgically Endoscopically Radiologically Laparoscopically	Allows for all methods of administration Low-profile buttons available Large-bore tubes less likely to clog Multiple commercially available tubes and sizes	Attendant risks associated with each type of procedure Potential increased aspiration risk Risk of stoma site complications
Jejunostomy	Long term Impaired gastric motility or gastric emptying High risk of GER or aspiration	Surgically Endoscopically Radiologically Laparoscopically	Allows for early postinjury or postoperative feeding Potential reduced aspiration risk Multiple commercially available tubes and sizes Low-profile buttons available	Attendant risks associated with each type of procedure Bolus or intermittent feeding not tolerated Risk of stoma site complications

EN, enteral nutrition; GER, gastroesophageal reflux.

From Kumpf VJ, Mulherin DW. Enteral nutrition. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020.

The nasogastric (NG) route is used most commonly for short-term enteral access. The major advantage is that the tube can be placed quickly and inexpensively by the bedside nurse.

Gastrostomy tubes, in which an incision is made directly through the abdominal wall, are indicated for patients who can tolerate gastric feedings but in whom a minimum of 4 weeks of feedings is anticipated. Most commonly, gastrostomy tubes are either placed percutaneously by interventional radiology or are percutaneous endoscopic gastrostomy (PEG) tubes placed endoscopically. Gastrostomy tubes also can be placed laparoscopically or during an open surgical procedure. Placement of a gastrostomy tube radioscopically, endoscopically, or surgically is more expensive than bedside orogastric (OG) or NG placement but can result in a larger-bore tube.

Postpyloric Feedings

KEY CONCEPT For patients intolerant of gastric feedings or in whom the risk of aspiration is high, feedings delivered with the tip of the tube in the jejunum are preferred. This bypasses the problem of poor gastric emptying and adds another barrier (pyloric sphincter) through which tube feedings must traverse before lung aspiration. However, postpyloric feedings do not preclude possible aspiration. Many patients aspirate their own oropharyngeal secretions.

Nasoduodenal and nasojejunal (NJ) feeding tubes can be placed by trained, experienced bedside nurses. Bedside electromagnetic transmitter devices (eg, CORTRAK, Corpak Medsystems) may be helpful in achieving postpyloric tube placement. In some institutions, ND or NJ placements are done in radiology by a radiologist using fluoroscopy to visualize tube advancement, increasing the cost of EN therapy. NJ tubes generally are preferred over ND tubes; placement of the tube tip distal to the ligament of Treitz may reduce risk of aspiration. Alternatively, during a laparotomy, the surgeon can place an ND or NJ tube.

Surgically placed jejunostomy tubes are placed through the abdominal wall. These tubes are sometimes placed during laparotomy following abdominal trauma. Alternatively, jejunal access can be obtained by placing a jejunal extension through a PEG tube; the resulting tube is sometimes referred to as a *PEGJ tube* or *G-J tube*. Another option is to place a percutaneous endoscopic jejunostomy (/PEJ) tube directly; this is more technically difficult and is not available in some institutions.

METHODS OF DELIVERY

Enteral feedings are delivered by several methods. Continuous infusion must be used when duodenal or jejunal feedings are administered; intermittent feedings directly into the small bowel generally result in GI intolerance. For gastric feedings, bolus or intermittent feedings could be administered instead of continuous feedings. Each method has advantages and disadvantages.

In hospitals, EN is usually delivered by continuous infusion at a constant rate regulated by an infusion pump. A variation of continuous infusion is cyclic feeding, in which a constant rate is maintained over a certain number of hours daily; this method of administration is used commonly in long-term care or home settings. Sometimes EN is administered overnight. Continuous feedings are often started at a low rate and titrated up every few hours as the patient tolerates. In the ICU, trophic feeding (very low rates of 10–20 mL/hour) is frequently utilized early in an ICU illness.

Intermittent feedings are used commonly in long-term care or home settings. Patients frequently start with continuous feedings; transition to intermittent feedings given several times a day over about 30 to 45 minutes for each feeding and eventually are changed to bolus feedings administered over less than 10 minutes per feeding. Intermittent feedings may be administered by gravity flow adjusted with a roller clamp, although some institutions may use an infusion pump. Bolus feedings can be administered using a 60-mL syringe, although sometimes an infusion set and pump may be used. Intermittent and bolus feedings often are given in amounts of 240 to 480 mL per feeding, corresponding to one to two cans of formula.

Some institutions have volume-based feeding protocols instead of rate-based. In these protocols, nurses have the latitude to increase the rate after the feeding has been held such that the prescribed volume is administered over a 24-hour period.

EN FORMULAS

One advantage of EN over PN is the availability in the United States of certain nutrients in some EN formulations (eg, glutamine) that are not available parenterally. Many EN formulas are marketed. Hospitals and long-term care facilities limit formularies of EN formulas, stocking only a limited number of products. Manufacturers' web sites should be consulted for the most current information on content of enteral formulas as changes do occur.

Polymeric Versus Oligomeric Formulas

A major criterion for categorizing EN products is whether macronutrients (particularly protein) are more intact (polymeric) or present in simpler forms (oligomeric). **KEY CONCEPT** Standard EN formulas are polymeric; these are appropriate for most patients. Oligomeric formulas should be reserved for patients with GI dysfunction.

Polymeric formulas typically contain intact proteins. They have low osmolality (300–500 mOsm/kg [mmol/kg]). These usually supply essential vitamins and minerals in amounts similar to the adequate intakes (AIs) or recommended dietary allowances (RDAs) when the formula is delivered in amounts adequate to meet macronutrient requirements. Most modern formulas are lactose and gluten free. Products designed for use as oral supplements generally are polymeric and often have sucrose or other simple sugars added to improve taste.

Oligomeric formulas are also known as *chemically defined formulas.* These can be subcategorized based on whether the formula contains all free amino acids (elemental formulas) or peptides (peptide based) as the protein source. Some formulas contain a combination of free amino acids and small peptides. Dipeptides and tripeptides are absorbed more efficiently than free amino acids. Oligomeric formulas may be better tolerated than polymeric formulas for patients with defects in GI function and may be particularly useful with severe pancreatic dysfunction. However, adaptation of the bowel is better when intact nutrients are supplied to patients with short bowel syndrome, so those patients should be transitioned to intact nutrients as soon as possible.

Oligomeric formulas typically are more expensive than polymeric formulas and have higher osmolality. However, osmolality of these products usually does not exceed 700 mOsm/kg (mmol/kg), a value less than that of many oral medications or a regular diet. If more fluid is required, extra water can be administered as boluses through the tube. If medications are administered through the tube, generous amounts of water should be used to flush the tube before and after each medication; this practice helps prevent tube occlusion.

Oligomeric formulas are less palatable than polymeric formulas and are not designed for use as oral supplements. Many oligomeric formulas provide some fat calories as medium-chain triglycerides (MCT), a fat source that is more readily absorbed and metabolized than long-chain triglycerides (LCTs) typically found in polymeric formulas. The MCTs do not require bile salts or pancreatic enzymes for absorption. Some elemental formulas contain a low proportion of fat (< 10% of total calories), which makes them useful in certain situations where fat needs to be restricted. The carbohydrate source in oligomeric formulas is less complex than in polymeric formulas.

Fiber Content

Another distinguishing factor of enteral formulas is whether they contain fiber. Both soluble and insoluble fibers may be included. Insoluble fiber exerts an effect on gut motility by drawing water into the intestine and speeding transit, preventing constipation. Soluble fiber can help to lower blood cholesterol levels, regulate blood sugar, and prolong gastric emptying. It may also help control diarrhea. Soy fiber provides primarily insoluble fiber, but also some soluble fiber, and is the most common fiber source in tube feeding products. Fiber has been useful for regulating gut motility in some clinical studies; it certainly can be useful in selected patients.[23] Some patients may experience GI discomfort secondary to gas production with introduction of fiber.

Fructooligosaccharides (FOS) are a form of soluble fiber that pass through the stomach and small bowel undigested and are fermented by colonic bacteria to the SCFAs butyrate, propionate, and acetate. The SCFAs serve as a fuel source for colonocytes and serve other important functions.[24] The FOS are thus prebiotics that serve as fermentable substrates for normal flora of the colon. The SCFAs are not added directly to EN products because they would be absorbed completely before reaching the colon; rather, FOS are added, allowing bacterial degradation to form SCFAs. Products containing FOS are often avoided postoperatively due to increased gas, bloating, and abdominal distention.

Caloric Density

Enteral feeding formulas can be categorized based on caloric density. Standard caloric density is 1 to 1.3 kcal/mL (4.2–5.4 kJ/mL). More calorically dense formulas containing 1.5 to 2 kcal/mL (6.3–8.4 kJ/mL) are available and have higher osmolality. Fluid-overloaded patients may benefit from more calorically dense formulas. As caloric content of a formula increases, the amount of free water decreases.

Protein Content

Protein content is an important factor in choosing an EN formula. Standard protein content in EN formulas is up to about 20% of total calories as protein. High-protein formulas containing 25% or more of total calories as protein are available for highly stressed patients with elevated protein needs. Low-nitrogen formulas containing less than 10% of total calories as protein for use in patients requiring protein restriction are also available. Protein in tube feeding ranges from about 35 to 95 g/L.

Carbohydrate Content

Common carbohydrate sources in tube feeding products include maltodextrin, corn syrup solids, and hydrolyzed cornstarch. Products containing simple sugars (often those intended for oral use) tend to be higher in osmolality.

Fat Content

Both MCTs and LCTs are used in tube feeding products. Corn, soy, sunflower, and safflower oils are standard sources of fat, providing mainly ω-6 polyunsaturated fatty acids (PUFAs). Some newer EN products contain higher quantities of ω-3 PUFAs from sources such as fish oil (ie, docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]). Other formulas contain higher quantities of monounsaturated fatty acids (MUFAs) from canola oil and the high-oleic variety of certain oils (eg, safflower or sunflower). The essential fatty acid (EFA) content (mainly linoleic acid) of EN formulas is important because EFA deficiency can be induced if at least 1% to 4% of total calories are not supplied as EFAs. MCT oil does not contain EFAs.

Vitamin, Mineral, and Electrolyte Content

Most EN products contain vitamins and minerals, including major electrolytes, in amounts adequate to deliver the RDA or AI when a standard volume of formula is delivered daily. Some specialty formulas (eg, renal formulas) may have altered amounts of certain micronutrients.

Specialty Formulas

Specialty formulas designed for use in specific clinical situations generally are more expensive than standard polymeric formulas.

KEY CONCEPT Robust clinical trial data supporting use of specialty formulas in niche populations typically remain lacking in terms of improved patient outcomes.

Stress and Trauma Formulas

Historically, formulas aimed specifically for highly stressed, critically ill patients, were enriched with branched-chain amino acids (BCAAs). The rationale was that skeletal muscle BCAAs are preferentially used for energy in critical illness. Provision of BCAAs might limit breakdown of muscle in these patients. Clinical data failed to support or refute benefit of these formulas unequivocally in terms of clinical outcomes.

The newer generation of enteral feeding formulas marketed for use in these populations covers a broad spectrum of characteristics (Table 101–4). Whereas some are polymeric, others are oligomeric to address malabsorption that may accompany high stress. Some formulas marketed for use in critical illness are calorically dense (1.5–2 kcal/mL [6.3–8.4 kJ/mL]) to address fluid restrictions seen in this population, and others are less calorically dense. Most contain generous amounts of protein to address requirements of highly stressed patients. Many products contain ingredients purported to increase immune function; the term *immunonutrition* is sometimes attached to these products.

Immune-enhancing ingredients present in some enteral feeding products include arginine, glutamine, ω-3 fatty acids, nucleic acids, and antioxidants. Few products contain all of these (see Table 101–4). Arginine is an important substrate for nitric oxide (NO) synthesis, and small amounts of NO have beneficial effects on immune function under certain conditions. Arginine has been purported to have a positive influence on lymphocyte and macrophage function. Glutamine is considered conditionally essential

Table 101–4

Selected Adult Enteral Feeding Formulas Marketed for Use in Critical Illness, High Stress, Pulmonary Disease and Ventilator-Dependent, or Trauma Patients[a]

Product Name/Manufacturer	kcal/mL	Protein (g/L)	Protein (g/1000 kcal)	Enriched Ingredients[b]
Peptamen 1.5/Nestle	1.5	68	46	MCT
Nutren 2.0/Nestle	2	84	42	MCT
Promote/Abbott	1	62	62	MCT
Impact/Nestle	1	56	56	Arginine, nucleotides, omega-3 FA
Nutren 1.5/Nestle	1.5	68	46	
Pulmocare/Abbott	1.5	63	42	
Oxepa/Abbott	1.5	62	42	Omega-3 FA, GLA
Isosource 1.5 Cal/Nestle	1.5	68	46	
TwoCal HN/Abbott	2	84	42	
Nutren Pulmonary/Nestle	1.5	68	46	MCT
Impact Peptide 1.5/Nestle	1.5	94	63	Arginine, nucleotides, omega-3 FA, MCT
Pivot 1.5 Cal/Abbott	1.5	94	63	Arginine, omega-3 FA
Vivonex Plus/Nestle	1	45	45	Glutamine, arginine
Vivonex RTF/Nestle	1	50	50	MCT[c]
Peptamen Intense VHP/Nestle	1	92	92	MCT, omega-3 FA
Perative/Abbott	1.3	67	51	MCT, arginine

[a] One kcal is equivalent to 4.184 kJ.

[b] Formula considered enriched if following criteria met: arginine—greater than 8.5 g/1500 kcal (6279 kJ); glutamine—greater than 9 g/1500 kcal (6279 kJ); MCT—greater than 30% of total fat; and ω-3 fatty acid—ratio of ω-6 to ω-3 less than or equal to 2:1 or greater than 1.5 g/L ω-3 fatty acids.

[c] Low-fat product.

CI, critical illness; EPA, eicosapentaenoic acid; FA, fatty acid; GLA, γ-linoleic acid; HS, high stress; MCT, medium-chain triglycerides; PD, pulmonary disease/ventilator dependent; TR, trauma

Table 101–5

Selected Adult Enteral Feeding Formulas Marketed for Use in Adult Diabetes and Stress-Induced Hyperglycemia[a]

Product Name/Manufacturer	kcal/mL	% kcal as Fat	% kcal as Carbohydrate	Fiber (g/L)
Glytrol/Nestle	1	43	40	15
Glucerna 1.0 Cal/Abbott	1	49	34	14
Glucerna 1.2 Cal/Abbott	1.2	45	38	16
Glucerna 1.5 Cal/Abbott	1.5	45	35	16
Diabetisourse AC/Nestle	1.2	53	33	15

[a] One kcal is equivalent to 4.184 kJ.

in critical illness and is a preferred fuel source for enterocytes. Supplementation with glutamine, either parenterally or enterally, may help maintain integrity of gut mucosa, preventing translocation of bacteria and endotoxin from the gut lumen into the lymphatic system and systemic circulation. However, glutamine supplementation remains controversial.[3,6,25,26] The ω-3 fatty acids, primarily from fish oils, are included in many immunonutrition products. Metabolites of ω-6 fatty acids include mediators such as prostaglandins, leukotrienes, and thromboxanes that are primarily proinflammatory and increase coagulation. Conversely, mediators produced from ω-3 fatty acids are less proinflammatory and decrease coagulation. Limited data support nucleic acids as immunomodulators. Quantities of antioxidants (particularly vitamin C, vitamin E, and β-carotene) higher than traditionally found in standard enteral formulas are added to some immunonutrition formulas to protect body systems, including the immune system, from damage by oxygen-free radicals. **KEY CONCEPT** Use of enteral immunonutrition in certain clinical settings is widely accepted. Commercial immunonutrition products and/or specific ingredients found in these products have generally been found to have no benefit in terms of mortality rates.[3,27,28] However, infection rates, length of stay, and length of time on a ventilator may be decreased with these products. The 2016 ASPEN/SCCM ICU guidelines support use of these formulas in traumatic brain injury and surgical ICU patients but not in medical ICU patients.[6] The best timing (initiation and duration) of delivery remains to be determined.

Pulmonary Formulas

Enteral feeding formulas designed for use in patients with chronic obstructive pulmonary disease or receiving mechanical ventilation contain higher amounts of fat (40%–55% of total kilocalories) than most formulas. The rationale is that burning fat for energy is associated with less carbon dioxide production compared with burning of carbohydrate, which would be advantageous in patients with retention of this substance and might facilitate weaning from mechanical ventilation. Because part of the market targeted by the manufacturers of these products comprises mechanically ventilated patients, these products are included in Table 101–4. At conservative calorie levels, standard enteral formulas usually can be given without fear of excess carbon dioxide production.

Oxepa (Nestle) has been studied specifically in critically ill patients with acute respiratory distress syndrome (ARDS), acute lung injury (ALI), and sepsis. This formula contains high quantities of the ω-3 fatty acids EPA and γ-linolenic acid (GLA). GLA is metabolized to a prostaglandin with vasodilatory properties, whereas EPA is converted to prostaglandins and leukotrienes that are less proinflammatory than those derived from ω-6 fatty acids. This formula contains large quantities of antioxidants. Whereas the Canadian guidelines state that use of this formula should be considered in ALI and ARDS, the 2016 ASPEN/SCCM critical care guidelines do not endorse it.[3,6]

Diabetic Formulas

Like pulmonary formulas, formulas for patients with diabetes or stress-induced hyperglycemia are relatively high in fat and low in carbohydrates (Table 101–5). They typically contain fiber (primarily soluble) because it plays some role in glycemic control, and they may contain fructose and MUFAs. Data support improved blood sugar control with use of these formulas in patients with diabetes.[29] Whether or not a diabetic EN formula is chosen, avoidance of overfeeding and maintenance of good glycemic control with insulin or other hypoglycemic medications are important.

Renal Formulas

Products designed for use in renal failure have high caloric density (1.8–2 kcal/mL [7.5–8.4 kJ/mL]) to decrease administered fluid (Table 101–6). They vary in amounts of nutrients, such as protein, potassium, phosphorus, and magnesium. Products low in protein (20–35 g/L) may be appropriate in chronic renal failure patients not yet receiving dialysis. On the other hand, removal of nitrogen by dialysis, coupled with the hypercatabolic, hypermetabolic condition seen in many acute renal failure patients, makes use of higher-protein formulas (80–90 g/L) appropriate in these situations. Potassium, phosphorus, and magnesium contents of EN formulas designed for use in renal failure tend to be lower than standard formulas because these renally excreted electrolytes accumulate during renal failure.

Historically, enteral formulas designed for renal failure were enriched with essential amino acids (EAAs) and contained lesser amounts of nonessential amino acids (NEAAs) than standard formulas. Theoretically, EAAs could combine with urea nitrogen in the synthesis of NEAAs, leading to a decrease in blood urea nitrogen (BUN). The only situation in which such formulas may be appropriate is in patients with chronic renal failure who are not candidates for dialysis. Even in this setting, use of these products should be limited to no more than 2 or 3 weeks. These formulas have been supplanted largely by polymeric formulas with protein content similar to standard EN formulas. Many dialysis patients tolerate standard, high-protein EN formulas, although electrolytes must be monitored closely.

Hepatic Formulas

Specialized formulas for patients with hepatic insufficiency are limited in number. These are enriched with BCAAs while containing a reduced quantity of aromatic amino acids (AAAs) and methionine compared with standard formulas. These changes

Table 101–6

Selected Adult Enteral Feeding Products Designed for Use in Renal Failure

Product Name/Manufacturer	Protein/L	Protein (g/1000 kcal[a])	Characteristics
Nepro with Carb Steady/Abbott	80	45	Complete formula[b] for patients on dialysis
Novasource Renal/Nestle	91	46	Complete formula for patients with CKD or AKI on dialysis
Suplena with Carb Steady/Abbott	45	25	Complete formula with low amounts of protein for patients not on dialysis
Renacal/Nestle	34	17	For patients with AKI and severe electrolyte restriction not on dialysis

CKD, chronic kidney disease; AKI, acute kidney injury.

[a] One kcal is equivalent to 4.184 kJ.

[b] Complete formula—contains all nutrients in amounts sufficient to meet needs of most patients in a volume equal to or less than that usually administered.

address high levels of AAAs and low levels of BCAAs found in the blood of patients with hepatic insufficiency. Theoretically, they might help patients with hepatic encephalopathy (HE). Improvement in outcomes with short-term therapy with these products has not been consistent.[6] An example of a specialized hepatic formula is Hepatic-Aid II (Hormel Health Labs), a product supplied as a powder for reconstitution that requires vitamin, mineral, and electrolyte supplementation. A second product is NutriHep (Nestle), supplied as a liquid formula containing the recommended amounts of key vitamins, minerals, and electrolytes.

The ASPEN/SCCM guidelines for the ICU recommend against the use of protein restriction to reduce risk of development of HE.[6] These guidelines recommend use of standard EN formulas for ICU patients with acute or chronic liver disease.

Wound Healing Formulas

Tube feeding and oral supplement formulas designed for use in patients with wounds or decubitus ulcers typically supply high amounts of protein and calories. The antioxidant vitamins A, C, and E are frequently also found in high quantities as is zinc.

Patient Encounter, Part 1

TR is a moderately thin 70-year-old woman with a history of smoking and type 2 diabetes mellitus. She is admitted to the hospital with severe shortness of breath requiring mechanical ventilation. Her husband reports that she has not been feeling well for the past week, and he estimates that she has lost at least 5 lb (2.3 kg). Her COVID-19 test is positive. She requires vasopressor therapy for blood pressure maintenance and develops acute kidney injury. She is started on propofol for sedation while on the ventilator and is placed in the prone position for multiple hours each day due to an acute respiratory distress syndrome picture. Her dry weight is 60 kg (133 lb); height is 68 in (173 cm); body mass index is 20 kg/m^2.

When should EN be attempted in this patient?

What initial regimen of EN should be attempted?

What would appropriate caloric and protein goal ranges be for this patient?

Modular Components

Single nutrient components are frequently administered through feeding tubes to augment the composition of the EN formula. Protein modules are probably most used. These may be supplied as a liquid product or as a powder that must be reconstituted with water. Another modular component is fiber. These are typically given as a bolus through the feeding tube rather than being added to the feeding formula.

MONITORING AND COMPLICATIONS

Although EN complications are generally less serious than those of PN, some can be dangerous or can lead to impaired delivery of desired nutrient load. Complications can be divided into four categories: GI, technical, infectious, and metabolic. The first three categories, along with common causes, are listed in Table 101–7. Patients on EN must be monitored for prevention of complications (Table 101–8). Monitoring of many parameters can become less frequent as the patient's condition stabilizes. Monitoring for efficacy of EN is also important.

GI Complications

KEY CONCEPT GI complications are the most common complications of EN limiting the amount of feeding that patients receive. Although diarrhea frequently is blamed on feeding formula or method of EN administration, other possible causes usually exist (see Table 101–7). In the inpatient setting, patients receiving EN frequently are very sick. *Clostridioides difficile* colitis must be considered as a possible cause of diarrhea, especially in patients receiving antimicrobial therapy or proton pump inhibitors.[30] A medication-related cause of diarrhea is the sorbitol content of medications. Large quantities of sorbitol present in oral liquid medications can cause diarrhea.[31] Unfortunately, sorbitol content of many medications is not listed on their labeling, and manufacturers frequently reformulate preparations to contain varying amounts of excipients, such as sorbitol.

Determining cause of diarrhea is important to determine how to address the problem. Whereas *C. difficile* colitis should be treated with an appropriate antibiotic, medication-related diarrhea can be addressed by removal of the offending agent. Likewise, diarrhea secondary to malabsorption sometimes can be addressed by changing to an oligomeric EN formula. Antiperistaltic agents (eg, loperamide) may be useful in some noninfectious diarrhea.

Table 101–7

Complications of Tube Feeding

Complication	Causes
GI	
Diarrhea	Drug related Antibiotic-induced bacterial overgrowth Hyperosmolar medications administered via feeding tubes Antacids containing magnesium Excipients (eg, sorbitol) Malabsorption Hypoalbuminemia or gut mucosal atrophy Pancreatic insufficiency Inadequate GI tract surface area Rapid GI tract transit Radiation enteritis Tube feeding related Rapid formula administration Formula hyperosmolality Low-residue (fiber) content Lactose intolerance Bacterial contamination
Nausea and vomiting	Gastric dysmotility (surgery, anticholinergic drugs, diabetic gastroparesis) Rapid infusion of hyperosmolar formula
Constipation	Dehydration Drug induced (anticholinergics) Inactivity Low-residue (fiber) content Obstruction or fecal impaction
Abdominal distention or cramping	Too rapid formula administration
Technical	
Occluded feeding tube lumen	Insoluble complexation of enteral formula and medication(s) Inadequate flushing of feeding tube Undissolved feeding formula
Tube displacement	Self-extubation Vomiting or coughing Inadequate fixation (jejunostomy)
Aspiration	Improper patient position Gastroparesis or atony causing regurgitation Feeding tube malpositioned Compromised lower esophageal sphincter Diminished gag reflex
Peristomal excoriation	Improper skin and tube care GI tract secretions leaking peristomally
Infectious	
Aspiration pneumonia	Same as technical—aspiration comments Prolonged use of large-bore polyvinylchloride tube

GI, gastrointestinal.

From Janson DD, Chessman KH. Enteral nutrition. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 5th ed. New York, NY: McGraw-Hill; 2005.

On the other hand, constipation may occur in patients receiving EN, especially the elderly. Increased provision of fluid or fiber may be useful. Constipation may be drug related, in which case discontinuation or replacement of the offending drug may be beneficial.

Table 101–8

Suggested Monitoring for Patients on Enteral Nutrition

Parameter	During Initiation of EN Therapy	During Stable EN Therapy
Vital signs	Every 4–6 hours	As needed with suspected change (ie, fever)
Clinical assessment		
Weight	Daily	Weekly
Total intake/output	Daily	As needed with suspected changed in intake/output
Tube feeding intake	Daily	Daily
Enterostomy tube site assessment	Daily	Daily
GI tolerance		
Stool frequency/volume	Daily	Daily
Abdomen assessment	Daily	Daily
Nausea or vomiting	Daily	Daily
Gastric residual volumes	Every 4–8 hours (varies)	As needed when delayed gastric emptying suspected
Tube placement	Prior to starting; then ongoing	Ongoing
Laboratory		
Electrolytes, blood urea nitrogen/serum creatinine, glucose	Daily until stable, then 2–3 times per week	Every 1–3 months
Calcium, magnesium, phosphorus	Daily until stable, then 2–3 times a week	Every 1–3 months
Liver function tests	Weekly	Every 1–3 months
[a]Trace elements, vitamins	If deficiency/toxicity is suspected	If deficiency/toxicity is suspected

[a]Most tests for monitoring trace elements and vitamins are unreliable when an inflammatory response is present, and signs, symptoms, and risk factors should determine the need for supplementation unless accurate monitoring parameters are available.

EN, enteral nutrition.

From Kumpf VS, Mulherin DW. Enteral nutrition. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020.

Impaired gastric emptying is seen commonly in EN patients receiving gastric feedings and may be associated with nausea and vomiting. Impaired emptying may be related to disease process (eg, diabetic gastroparesis or sequelae to head injury) or to drug therapy, most notably narcotics. Gastric residual checks frequently are measured in patients receiving gastric feedings (see Table 101–8). The 2016 ASPEN/SCCM critical care guidelines recommend against routine gastric residual check and suggest that, if such checks are performed, feedings should not be held for residual volumes less than 500 mL in absence of other signs of intolerance.[6] Approaches to the patient with delayed gastric emptying might include changing to a formula containing less fat because dietary fat is associated with slower gastric emptying. Metoclopramide often is given to patients receiving gastric feedings to facilitate gastric emptying. Erythromycin is an alternative that may be useful, although it is associated with drug–drug interactions. Patients with poor gastric emptying may be at higher risk of aspirating feedings into their lungs and should be considered for transition to postpyloric feedings. Postpyloric feedings may help relieve EN-related nausea and vomiting and are preferred for patients without an intact gag reflex. An important practice to help prevent aspiration is elevation of the head of the bed to at least 30 degrees during continuous feedings as well as during and for 30 to 60 minutes after intermittent and bolus feedings. Prone positioning (ie, placing the patient on the stomach) in conditions such as ARDS seen in severe COVID-19 is not a contraindication for EN.

Technical Complications

Technical or mechanical complications are encountered frequently in EN patients. Tube occlusion most commonly is related to formula occlusion or medication administration through the tube.[32] **KEY CONCEPT** An important practice to help prevent medication-related occlusion is adequate water flushing of the tube before, between, and after each medication administration. If intermittent feedings are used, water flushing after each feeding is recommended. Clearing of occlusions using water or pancreatic enzymes plus sodium bicarbonate can be attempted, and special devices and kits are available.[4,32]

Tube displacement is a potentially significant complication. This may be seen in an agitated patient pulling at the tube, or the tube tip may migrate spontaneously. If the tip of the tube is positioned in the tracheobronchial tree and feeding is delivered to this area, pneumonia, pneumothorax, and other problems could potentially occur. Location of the tip of the feeding tube (eg, nasogastric) may be confirmed by chest radiograph or, perhaps, ultrasound. For ongoing assessment of tube placement, auscultation and measurement of aspirate pH can be utilized.

Endoscopic and surgical feeding tubes can cause erosion of the exit site due to leakage of gastric or intestinal contents onto the skin. This complication must be addressed by good wound care and repair or replacement of the access device. Similarly, NG, ND, and NJ tubes can be complicated by nasopharyngeal irritation or necrosis. This is one reason why such tubes should be considered for short-term use only.

Infectious Complications

Infectious complications of EN include aspiration pneumonia and infections related to delivery of contaminated EN formula. Although GI infections owing to industrial contamination of enteral formulas have been reported uncommonly, formulas are more commonly seeded with organisms during the processes of transferring from can to delivery bag or during the process of reconstitution of powdered formulas. So-called closed systems of delivery, wherein the formulas come from the manufacturer premixed in a delivery bag, should help decrease possibility of formula contamination.

Metabolic Complications

Metabolic complications of EN most commonly include disorders of fluid and electrolyte homeostasis and hyperglycemia. More severely ill patients require more frequent monitoring (see Table 101–8). Both dehydration and fluid overload can occur. Careful monitoring of fluid inputs and outputs as well as body weight is important. Dehydration may be caused by either excessive fluid losses or inadequate fluid intake. The trend in the ratio of BUN to serum creatinine can be useful in helping monitor fluid status; a ratio greater than 15:1 (60:1 for SI mmol/L:mmol/L) may be an indicator of dehydration. High ratios may also be a result of high-protein provision by the feeding. Attention should be paid to free-water content of EN formulas. Free-water content varies from about 70% to 85%; percentage free water typically drops as caloric density of the formula rises. If dehydration develops, switching to a less calorically dense formula or using larger water flushes is appropriate. Fluid overload is reflected by increases in weight, lower extremity edema, and pulmonary rales and particularly may be a problem in patients with renal or cardiac insufficiency. Use of a more calorically dense EN formula may be helpful, and diuretic therapy may be necessary. Fluid imbalances often are associated with abnormalities of sodium homeostasis that should be addressed in concert with fluid imbalance.

Hypokalemia, hypomagnesemia, and hypophosphatemia are some of the most common electrolyte abnormalities in sick, hospitalized patients. These can occur in context of the refeeding syndrome, which may be seen in chronically malnourished patients aggressively started on feeding. Careful monitoring of electrolytes, coupled with a feeding regimen increased gradually to goal rate over a period of several days, should help protect at-risk patients from this complication. Hypokalemia and hypomagnesemia also are associated with excessive losses through the GI tract or urine and are associated with various medications, including diuretics. Repletion may be accomplished enterally in asymptomatic patients or parenterally if the patient is symptomatic or the abnormality is severe. Enteral repletion with magnesium and phosphate can cause diarrhea. Hyperkalemia, hypermagnesemia, and hyperphosphatemia are less common and usually are associated with renal insufficiency. Hyperkalemia also is associated with medications, including potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.

Although hyperglycemia is less common with EN than PN, it can occur. Many severely ill patients (eg, septic, highly stressed) receiving EN have a metabolic milieu promoting hyperglycemia. For ICU patients with hyperglycemia receiving continuous EN, an IV insulin drip may be the most effective way to achieve good glycemic control. Scheduled intermediate- or long-acting insulin plus nutritional and correctional regular- or rapid-acting insulin can be utilized after stabilization on the feeding regimen or for patients in whom insulin drips are not feasible.[33] Administration of a higher fat, lower carbohydrate EN formula may be useful in selected patients.

Monitoring for Efficacy and Outcome Evaluation

A useful physical measurement of EN efficacy in the long-term patient is body weight. Depending on the clinical situation, the goal may be weight gain, weight maintenance, or weight loss. Whereas day-to-day fluctuations in weight generally reflect fluid changes, week-to-week variations are more useful in determining if caloric provision is appropriate.

The amount of EN administered is often less than the amount ordered owing to interruptions in therapy. It is imperative to monitor volume of feedings actually received and to make adjustments in rates or amounts of EN as necessary.

Biochemical markers have been used historically to help interpret EN adequacy. Use of visceral proteins such as albumin or prealbumin is limited by the effects of inflammation on serum levels of these biomarkers.[34] In the acute phase of illness characterized by a proinflammatory state, proteins known as *acute-phase reactants* are preferentially synthesized. One of these measured clinically is C-reactive protein (CRP). In some patients with significant illness, prealbumin may not rise, even though the patient is receiving appropriate EN, until CRP begins to fall.

Patient Encounter, Part 2

On day 5, vasopressor requirements are minimal, but feeding via nasogastric tube has only been able to be advanced to one-quarter of goal rate. Propofol is changed to dexmedetomidine on day 5.

Why is it important to monitor triglycerides in this patient?

Should a postpyloric tube be placed in this patient, or would supplemental PN be more appropriate?

What is refeeding syndrome, and is this patient at risk for it? If so, how could it be prevented?

Collection of urine to calculate nitrogen balance can help analyze adequacy of caloric and protein provision.

In patients with wounds (eg, decubitus ulcers, surgical wounds), a goal of therapy is to facilitate wound healing. Monitoring status of the wound becomes part of ongoing nutritional assessment. In debilitated patients, particularly on long-term EN, measures of functional status such as grip strength and ability to perform activities of daily living become important components of nutritional assessment.

MEDICATION ADMINISTRATION IN PATIENTS RECEIVING EN

Medication Administration Through Feeding Tubes

If a patient receiving EN is alert and can swallow oral medications, then medications should be given by mouth. Many patients are not able to receive medications by this route, and the feeding tube may be considered as a delivery route. Effects of medication administration through feeding tubes on the delivery of both the drug and the EN formula nutrients have been inadequately studied.[35,36]

KEY CONCEPT Compatibility of medication with EN formula is of concern when administering medications through feeding tubes. An important technical complication of EN is tube occlusion, related most commonly to medication administration. Not only must compatibility of medication and EN formula be considered, but interactions between medications and the feeding tube itself must be considered. Strict protocols for flushing the tube before, between, and after administration of medications are important.[4] The best fluid for flushing is warm water. At least 15 mL of water should be used as a flush before and after medication administration through a feeding tube. Medications should be administered one at a time sequentially rather than being mixed together for simultaneous administration down the tube; ideally 15 mL of water should be used as a flush between medications. This should help prevent interactions between drugs within the tube itself that could lead to occlusion.

Different dosage forms present unique challenges for administration through feeding tubes. Certain solid dosage forms should not be crushed because crushing would alter release characteristics.[37] For example, controlled-release, extended-release, and sustained-release preparations should not be crushed, nor should sublingual dosage forms. Enteric-coated dosage forms generally are designed to protect acid-labile medications from stomach acid; when these dosage forms reach the small bowel with its higher pH, the drug is released into an environment in which it is more stable. Alternatively, enteric-coated dosage forms protect the stomach from medications that could cause irritation. Thus, crushing the enteric coating defeats the purpose of the dosage form and could lead to decreased efficacy or increased adverse events when administered down a gastric tube.

Medications available commercially as compressed tablets can generally be crushed for administration through tubes. After crushing, the fine powder should be mixed with 10 to 30 mL of fluid (usually warm water) for administration. A powdered dosage form inside a hard-gelatin capsule can be poured out and mixed with water for administration through tubes. Soft-gelatin capsules can be dissolved in warm water. Some enteric-coated and delayed-release microencapsulated products can be opened and individually coated particles administered through the tube without crushing if the tube has a large enough diameter.

If a liquid dosage form of a medication exists, it would seem rational to use this for administration through a feeding tube. This may decrease potential for tube clogging but may decrease tolerability of medication administration. Sorbitol is an excipient found in many liquid medications in amounts sufficient to cause diarrhea.

Another potential problem with administration of liquid medications through feeding tubes is high osmolality of some products. Dilution of hypertonic medications with 30 to 60 mL of water or administration of smaller dosages more frequently may help prevent diarrhea. Although administration of IV medications through feeding tubes may be entertained, these dosage forms frequently are hypertonic and contain problematic excipients when given via the GI tract.

It is generally not recommended to mix medications directly into EN formula because physical incompatibilities might lead to tube occlusion. It would seem logical that medications considered better absorbed in the fasted state either should be given between feedings on an intermittent feeding schedule, or feedings should be held before and after medication administration. However, not all studies have supported this idea, therefore this issue deserves further study.

Location of feeding tube tip is important when considering medication administration. This is particularly true if the medication acts locally in the GI tract. For example, sucralfate and antacids act locally in the stomach; administration through a duodenal or jejunal tube is illogical. For medications requiring acid for best absorption, administration directly into the duodenum or jejunum may result in suboptimal absorption. Absorption of drugs when administered directly into the small bowel, especially the jejunum, is a topic where more research would be useful.

Problem Medications

▶ *Phenytoin*

Certain medications present challenges when administered through feeding tubes. The medication studied most thoroughly is phenytoin. Most studies have shown significant decreases in phenytoin absorption when administered enterally to patients receiving EN. Several mechanisms have been proposed. Liberal dilution of phenytoin suspension before its administration down the tube may improve delivery. Many institutions hold tube feedings for 1 or 2 hours before and after administration of phenytoin, although some EN patients subjected to this routine still require high dosages to achieve therapeutic serum concentrations. Holding feeding around medication administration can make meeting nutritional requirements difficult with continuous feedings, especially if phenytoin is administered several times daily. Diligent monitoring of serum concentrations is necessary for the patient on EN receiving this medication. In some cases, use of IV phenytoin or another anticonvulsant may be prudent.

▶ *Warfarin*

EN formulas contain vitamin K, which can antagonize the pharmacologic activity of warfarin. Vitamin K content of EN formulas has been adjusted down over several decades, resulting in products that contain amounts of vitamin K unlikely to affect anticoagulation by warfarin significantly. However, inadequate warfarin anticoagulation in EN patients receiving formulas containing minimal vitamin K has been reported. A component of certain tube feedings, perhaps protein, may bind warfarin and result in suboptimal activity, as might the feeding tube itself. One small study indicated a better response in terms of the international normalized ratio (INR) when feedings were held for 1 hour before and after warfarin compared with administration of the drug without holding feedings.[38] When tube feedings are started, changed, or discontinued, INR should be monitored closely. Alternatively, a different oral anticoagulant may be considered.

▶ *Fluoroquinolones*

Absorption of antimicrobial agents, such as fluoroquinolones and tetracyclines, that can be bound by divalent and trivalent cations potentially could be compromised by administration with EN formulas containing these cations. Fluoroquinolones (eg, levofloxacin and ciprofloxacin) have been best studied in this regard, and results of studies are not consistent.[39] Some institutions hold tube feedings for 1 to 2 hours or more before and after enteral dosages of fluoroquinolones. Not all fluoroquinolones are affected by the interaction, suggesting that a mechanism other than chelation by divalent cations may also be significant.

Patient Encounter, Part 3

Supplemental PN is initiated on day 6, and trophic gastric feedings are continued. By day 10, advancement of the gastric feeding to goal rate is achieved, and PN is discontinued. TR is extubated on day 13. Concern regarding her swallowing strength leads to a speech pathology consult. On day 14 an order to advance oral diet as tolerated is written following the speech pathology assessment.

How should the transition from EN to oral feedings be accomplished?

A FEW NOTES ABOUT PEDIATRIC PATIENTS

Although many of the principles outlined in this chapter primarily geared toward adults receiving enteral nutrition would be similar in pediatrics, younger patients present challenges that sometimes necessitate a slightly different approach.[40-42] Younger pediatric patients and prematurely born infants have fewer nutritional reserves and are therefore at more risk for malnutrition. Like adults, if nutrition support is deemed necessary, the enteral route is preferred over parenteral.

Common pediatric scenarios leading to the use of EN due to unsafe or impractical oral intake include neurologic impairment,

Patient Care Process

Collect the Information:

- Based on patient's disease states and severity, estimate the amount of time until adequate oral intake resumes (Table 101–1).
- Are there any contraindications or precautions regarding use of EN (Table 101–2)? When the GI tract is nonfunctional, either PN or no SNS is indicated.
- If inadequate intake has occurred or is anticipated for 7 or more days, start SNS. The threshold for starting SNS is lower for previously malnourished patients. Critically ill patients at high nutritional risk should generally be started on EN within 24 to 48 hours of ICU admission.
- Choose the appropriate type of enteral access device based on expected duration of use and whether any condition exists which precludes gastric feeding (Table 101–3).
- Choose the method of feeding administration (eg, intermittent or continuous) based on feeding location (ie, gastric vs postpyloric) and other patient factors.

Assess the Information:

- Estimate calorie, protein, and fluid goals based on patient parameters.
- Are medications being administered down the feeding tube? If so, assess the appropriateness of this route.

Develop a Care Plan:

- Choose an appropriate tube feeding formula that best matches patient characteristics and estimated nutritional needs.
- Start tube feeding at full strength and increase rate as tolerated to goal that will meet patient's nutritional requirements.
- Develop plan to include monitoring at appropriate intervals for metabolic, GI, technical, or infectious complications (Table 101–8).
- Develop monitoring plan for adequacy of nutritional regimen. This may include serial weights, intakes and outputs, and measures of functional status.

Implement the Care Plan:

- If patient is to be discharged home on EN, educate patient or caregiver on enteral access device care, feeding delivery, troubleshooting, and complications to observe for and who should be contacted when complications occur (Table 101–7).

Follow-up: Monitor and Evaluate:

- Adjust formula, rate of administration, and/or route of administration if intolerance develops or nutritional goals (eg, weight loss, weight maintenance, weight gain, maintenance of muscle mass, slowing of functional decline) are not met.

neuromuscular disorders, genetic and metabolic disorders, prematurity, congenital abnormalities involving the GI tract, and other obstructive or injurious conditions or accidents to the oral cavity and GI tract. As in adults, EN is also used in critical illness due to accidents, infections, or other causes. Long-term EN becomes necessary for some children with neurologic impairment. Sometimes supplemental EN is utilized in children who can eat but are nevertheless malnourished, such as in patients with cystic fibrosis.

The routes of EN administration in children are similar to those used in adults and include NG, OG, and NJ for short-term use and PEG, PEJ, and surgically placed tubes for long-term EN. As in adults, usually either a bolus or continuous method of feeding is chosen. In children, these two modalities are sometimes combined, with small bolus feedings given during the day and continuous feedings at night to improve feeding tolerance.

Monitoring parameters in children on longer-term EN must measure growth. In addition to monitoring of weight as in adults, weight as well as length and head circumference are compared to growth charts to delineate trajectories of growth.

Feeding tubes used in infants and young children are typically very small in diameter, making medication administration down these tubes particularly challenging. Concentrations of standard pediatric formulas are lower than those of adults at 0.8 kcal/mL (20 kcal/oz or 3.3 kJ/mL). The reader is referred to specialized references for a more detailed discussion of pediatric tube feeding.[40-42]

SUMMARY AND CONCLUSION

EN is an important method of feeding patients who cannot or should not eat enough to meet nutrient requirements for a prolonged time. When the GI tract can be used safely, EN is preferred over PN. Various types of enteral access devices are available. Whereas tubes inserted through the nose often are adequate for patients expected to receive EN for a short time, devices that are more permanent are preferred for longer-term patients. The choice of whether to feed into the stomach or postpylorically is patient specific. Although numerous EN formulas are available, many products are very similar, making a limited formulary feasible. Data supporting many specialized types of EN formulas are limited. Although complications of EN tend to be less serious than those of PN, adverse effects encountered can be significant, and ongoing monitoring is necessary. Although medications can be administered through feeding tubes, various factors must be considered in each individual patient.

Abbreviations Introduced in This Chapter

ALI	Acute lung injury
AI	Adequate intake
AAA	Aromatic amino acid(s)
ARDS	Acute respiratory distress syndrome
ASPEN	American Society for Parenteral and Enteral Nutrition
BCAA	Branched-chain amino acid(s)
BUN	Blood urea nitrogen
CRP	C-reactive protein
DHA	Docosahexaenoic acid
EAA	Essential amino acid(s)
EFA	Essential fatty acid(s)
EN	Enteral nutrition
EPA	Eicosapentaenoic acid
ESPEN	European Society for Clinical Nutrition and Metabolism
FOS	Fructooligosaccharide
GALT	Gut-associated lymphoid tissue
GI	Gastrointestinal
GLA	γ-Linolenic acid
HE	Hepatic encephalopathy
IBD	Inflammatory bowel disease
ICU	Intensive care unit
INR	International normalized ratio
LCT	Long-chain triglyceride
MCT	Medium-chain triglyceride
MUFA	Monounsaturated fatty acid
ND	Nasoduodenal
NEAA	Nonessential amino acid
NG	Nasogastric
NJ	Nasojejunal
NO	Nitric oxide
OG	Orogastric
PEG	Percutaneous endoscopic gastrostomy
PEJ	Percutaneous endoscopic jejunostomy
PN	Parenteral nutrition
PUFA	Polyunsaturated fatty acid
RDA	Recommended dietary allowance
SCFA	Short-chain fatty acid
SCCM	Society for Critical Care Medicine
SNS	Specialized nutrition support

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Overweight and Obesity

April Smith

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain the underlying causes of overweight and obesity.
2. Identify parameters used to diagnose obesity and indicate the severity of disease.
3. Identify desired therapeutic goals for patients with obesity.
4. Recommend appropriate nonpharmacologic and pharmacologic therapeutic interventions for overweight or obese patients.
5. Implement a monitoring plan that will assess both the efficacy and safety of therapy initiated.
6. Educate patients about the disease state and associated risks, comprehensive lifestyle interventions, drug therapy, and surgical options necessary for effective treatment.

INTRODUCTION

Overweight and obesity are terms used to describe weight measurements greater than what is considered healthy for a given height.[1] KEY CONCEPT Body mass index (BMI), waist circumference (WC), comorbidities, and readiness to lose weight are used in the assessment of overweight or obese patients. BMI should be used to identify adults at increased risk for cardiovascular disease (CVD) and other obesity-related disorders. Evaluation of the patient's risk status involves not only calculation of the BMI but also the measurement of waist circumference. KEY CONCEPT The presence of comorbidities (CVD, type 2 diabetes mellitus, and sleep apnea) and cardiovascular risk factors (cigarette smoking, hypertension, elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, impaired fasting glucose) requires identification and aggressive management for overall effective treatment of the overweight or obese patient to reduce their risk of mortality. Obesity contributes to some of the leading causes of preventable death including hypertension, dyslipidemia, diabetes mellitus, CVD, stroke, sleep apnea, gallbladder disease, osteoarthritis, and certain cancers.[2] Obesity is officially recognized as a disease by the American Medical Association with a pathophysiological basis for metabolic and biochemical dysfunctions.

ETIOLOGY AND EPIDEMIOLOGY

Obesity is a multifactorial, complex disease that occurs because of an interaction between genotype and the environment. Although the etiology is not completely known, it involves overlapping silos of social, behavioral, hormonal, and genetic influence.[3] The majority of overweight or obese individuals are adults, but obesity is also prevalent in children between 2 and 19 years of age. Just over one-third of US adults 20 years of age and older are currently considered obese. The prevalence of obesity in men and women of various racial and ethnic origins differ. Thirty-six percent of non-Hispanic White adults are obese, where approximately 40% of Hispanics and 50% of non-Hispanic Black adults are obese.[4]

Thirty-two percent of children and adolescents aged 2 to 19 years are overweight or obese. Overweight children typically become overweight adults, but most obese adults were not overweight as children.[5] Psychosocial functioning also may be hindered because obese patients may be at risk for discrimination as well as higher risk of low self-esteem and depression.[2]

PATHOPHYSIOLOGY

The key factor in the development of overweight and obesity is the imbalance that occurs between energy intake and energy expenditure where intake exceeds expenditure. The extent of obesity is determined by the length of time this imbalance has been present. The hormone leptin, released from adipose tissue, is generally thought to play a major role in long-term weight homeostasis.[6] Leptin increases signaling to the hypothalamus as fat stores rise in attempt to reduce energy intake[7] (Figure 102–1). In the setting of obesity, leptin levels remain high, but eating behavior does not seem to be impaired, which is thought to be due in part to leptin resistance. Energy intake is affected by environmental influences and various gut hormones, whereas genetic composition and metabolism affect energy expenditure.[6] Many of the hormones produced in the gut that interact with the dorsal vagal complex and the hypothalamus represent target receptors or pathways for drugs that could possibly influence eating behavior. The mechanism behind most antiobesity medications is interacting with one of these signaling pathways to enhance anorexigenic signaling and thus decrease energy intake.

Energy Intake

Food intake is regulated by various receptor systems that comprise the gut-brain axis. Gut peptides travel via the vagus nerve or pass directly through the blood–brain barrier to affect the appetite control centers in the hypothalamus (see Figure 102–1).[7]. There are two groups of neurons in the arcuate nucleus (ARC) of the hypothalamus that send signals to higher brain centers and ultimately drive eating behavior. When neuropeptide Y or

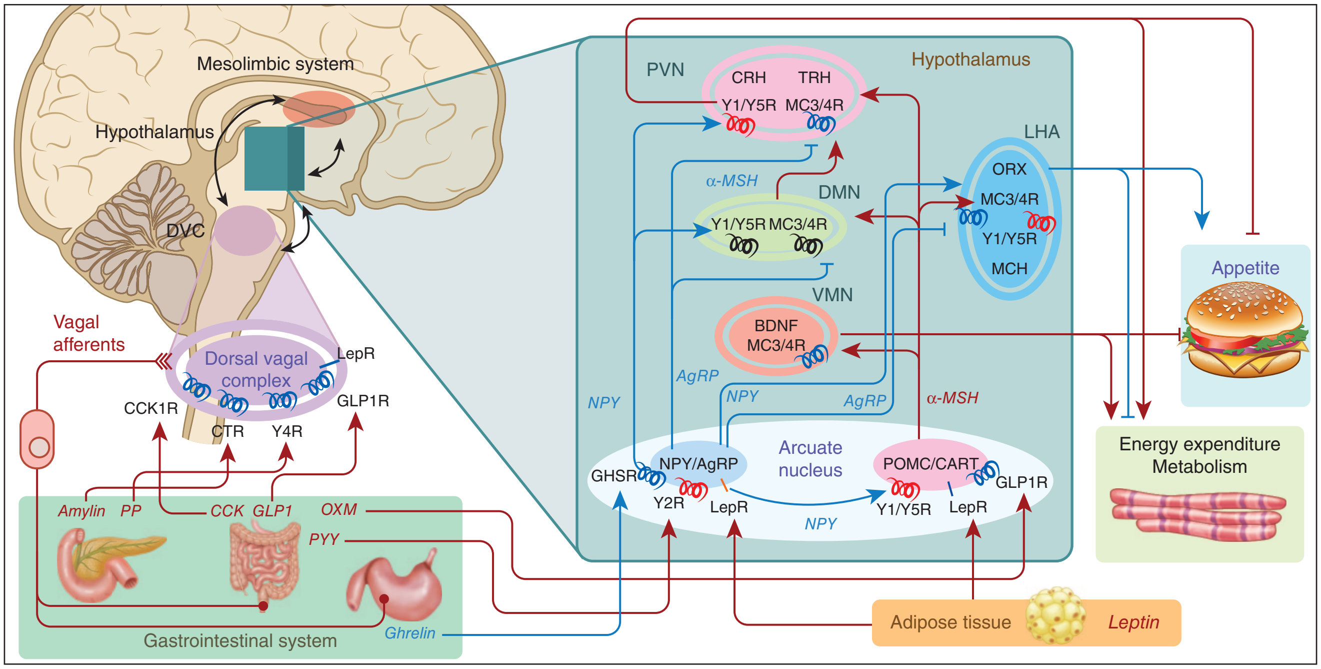


FIGURE 102–1. Central Energy of Appetite and Energy Homeostasis. (From Kim GW, Lin JE, Blomain ES, et al. Antiobesity pharmacotherapy: new drugs and emerging targets. Clin Pharmacol Ther. 2014;95(1):53–66.)

agouti-related peptide (NPY/AgRP) neurons in the ARC are stimulated by gut peptides such as ghrelin, eating ensues. When proopiomelanocortin or cocaine-amphetamine–regulated transcript (POMC/CART) neurons in the ARC are stimulated by various gut peptides or leptin, eating is halted. Stimulation of the following receptors increases and decreases food intake, respectively.

▶ *Increase Food Intake*

- Serotonin 1A subtype (5-HT$_{1A}$)
- Noradrenergic α$_2$
- Cannabinoid 1 (CB1)
- NPY/AgRP
- Melanin-concentrating hormone (MCH)
- Orexin

▶ *Decrease Food Intake*

- Serotonin 2C subtype (5-HT$_{2C}$)
- Noradrenergic α$_1$ or β$_2$
- Histamine subtypes 1 and 3
- Dopamine 1 and 2
- CART/POMC
- α-Melanocyte-stimulating hormone (α-MSH)

Targeting of this endogenous circuitry is a primary trait shared by many of the newer antiobesity medications on the market as well as those currently in development.

Energy Expenditure

A person's metabolic rate is the primary determinant of energy expenditure. The metabolic rate is enhanced immediately after food consumption and is directly related to the amount and type of food consumed.[8] After a period of weight loss, total energy expenditure is reduced as the body attempts to defend its previous "set point." Hence keeping weight off is just as challenging, if not more, than losing weight. Physical inactivity and/or endocrine-related disorders (eg, hypothyroidism and Cushing syndrome) may lower the metabolic rate, further contributing to the development of overweight and obesity.

CLINICAL PRESENTATION AND DIAGNOSIS

KEY CONCEPT Body mass index (BMI), waist circumference (WC), body fat percentage, comorbidities, and readiness to lose weight are used in the assessment of overweight or obese patients. Any interaction between a patient and a healthcare provider presents an opportunity to evaluate the patient's height and weight and calculate their BMI. These parameters should be measured no less than annually. The BMI is calculated using the measured weight in kilograms divided by the height in meters squared (kg/m^2) for all adult patients, regardless of gender and is used to classify overweight or obesity. The greater the BMI in overweight and obese individuals, the greater the risk of CVD, type 2 diabetes mellitus, and all-cause mortality.[9] The BMI distribution changes with age for children just as height and weight. Percentiles specific for age and gender are used to classify pediatric patients as overweight and obese as well as healthy and underweight.[10] BMI is classified according to Table 102–1.[2] Waist circumference should also be determined no less than annually for adult patients by placing a measuring tape at the top of the right iliac crest and proceeding around the abdomen, ensuring that the tape is tight but not constricting the skin. The value is measured after normal expiration. High-risk waist circumference is defined as greater than 40 in (102 cm) in men and greater than 35 in (89 cm) in women.[11] Measurement of waist circumference is not recommended for children and adolescents because reference values identifying risk are unavailable. After obtaining patient-appropriate parameters, further assess the adult patient for the presence of obesity-related comorbidities and cardiovascular risk factors. KEY CONCEPT The presence of obesity-related comorbidities (CVD, type 2 diabetes mellitus, and sleep apnea) and cardiovascular risk factors requires identification and aggressive management for overall effective treatment of the overweight or obese patient. A patient

Table 102–1

BMI Classification[2,10]

Adult	
Underweight	< 18.5 kg/m^2
Normal weight	18.5–24.9 kg/m^2
Overweight	25–29.9 kg/m^2
Obesity (Class 1)	30–34.9 kg/m^2
Obesity (Class 2)	35–39.9 kg/m^2
Extreme obesity (Class 3)	≥ 40 kg/m^2
Children (Only for Those > 2 Years of Age[a])	
Underweight	< 5th percentile
Healthy weight	5th–84th percentile
Overweight	85th–94th percentile
Obesity	≥ 95th percentile

[a] Weight for height values should be plotted and monitored over time for children less than 2 years of age.

is at very high absolute risk of a cardiovascular event if diagnosed with CVD, type 2 diabetes mellitus, or sleep apnea or if three or more of the following risk factors exist: cigarette smoking, hypertension, elevated low-density lipoprotein cholesterol, decreased high-density lipoprotein cholesterol, or impaired fasting glucose.[2] Aggressive disease management should be initiated and not limited to weight loss.

TREATMENT

Desired Outcome

KEY CONCEPT The treatment goals for overweight and obesity are to prevent additional weight gain, reduce and maintain a lower body weight, and control related risks. A 5% to 10% weight loss has been shown to improve obesity-related comorbidities such as hypertension, hyperlipidemia, and type 2 diabetes mellitus and thus serves as the initial goal for obesity treatment strategies.[9] A sustained 5% weight loss will likely reduce triglyceride and blood glucose values as well as risk for the development of type 2 diabetes mellitus.[9] Greater reductions in weight will reduce blood pressure and improve both low-density and high-density lipoprotein cholesterol. **KEY CONCEPT** Weight loss is indicated for patients with a BMI of 25 to 29.9 kg/m^2 with one or more indicators of increased CVD risk (eg, elevated WC, prediabetes or type 2 diabetes, hypertension, dyslipidemia, current cigarette smoker) or for any patient with a BMI of 30 kg/m^2 or greater. Weight loss should occur at a rate of 0.45 to 0.9 kg (1–2 lb) per week, meeting the initial weight loss goal within the first 6 months of therapy. If the patient achieves a 5% to 10% loss in weight, weight loss maintenance strategies should be considered. **KEY CONCEPT** Weight maintenance occurs after successful achievement of weight loss.

For children or adolescents, a BMI below the 85th percentile is warranted but is difficult to assess in frequent or short time periods. Serial weight measurements may better quantify energy balance. Goals are most likely accomplished through adaptation of lifelong healthy lifestyle habits. In doing so, weight loss or maintenance can be attained for some children. Others may need to incorporate changes that result in a negative energy balance or energy input less than energy output.[10]

General Approach to Treatment

Table 102–2

Drugs Contributing to Weight Gain[7,13]

- Anticonvulsants/mood stabilizers
  - Carbamazepine
  - Gabapentin
  - Pregabalin
  - Valproic acid
  - Lithium
- Antidepressants
  - Monoamine oxidase inhibitors (phenelzine)
  - Presynaptic α_2 antagonist (mirtazapine)
  - Selective serotonin reuptake inhibitors (citalopram, escitalopram, fluvoxamine)
  - Serotonin and norepinephrine reuptake inhibitors (duloxetine)
  - Tricyclics (amitriptyline, imipramine)
- Antidiabetics
  - Insulin
  - Meglitinides
  - Sulfonylureas (glipizide, glyburide)
  - Thiazolidinediones
- Antipsychotics
  - Atypical (clozapine, olanzapine, paliperidone, risperidone)
  - Conventional (haloperidol)
- Others
  - Antihistamines
  - Some nonselective β-blockers
  - Corticosteroids
  - Hormonal contraceptives (depot injections)

KEY CONCEPT Treatment of obesity includes comprehensive lifestyle intervention (caloric restricted diet, increased physical activity, and behavioral therapy to facilitate compliance with diet and exercise), pharmacologic treatment, surgical intervention, or a combination of modalities. Before initiating therapy, secondary causes of obesity (eg, hypothyroidism and Cushing syndrome) must be considered. Current treatment with medications that increase weight should be determined and, if present, alternative therapies should be suggested.[12,13] Table 102–2 provides a list of drugs commonly associated with weight gain. The American Association of Clinical Endocrinologists and The American College of Endocrinology have created a treatment algorithm for the treatment of obesity from patient presentation through follow-up (Figure 102–2).[14] Therapy implemented to minimize associated risk(s) may not enhance weight loss, but weight loss will positively address risk factors. Weight loss therapy should not be initiated in pregnant or lactating patients, decompensated psychiatric patients, or patients in whom reduced caloric intake can exacerbate an acute, serious illness.[2]

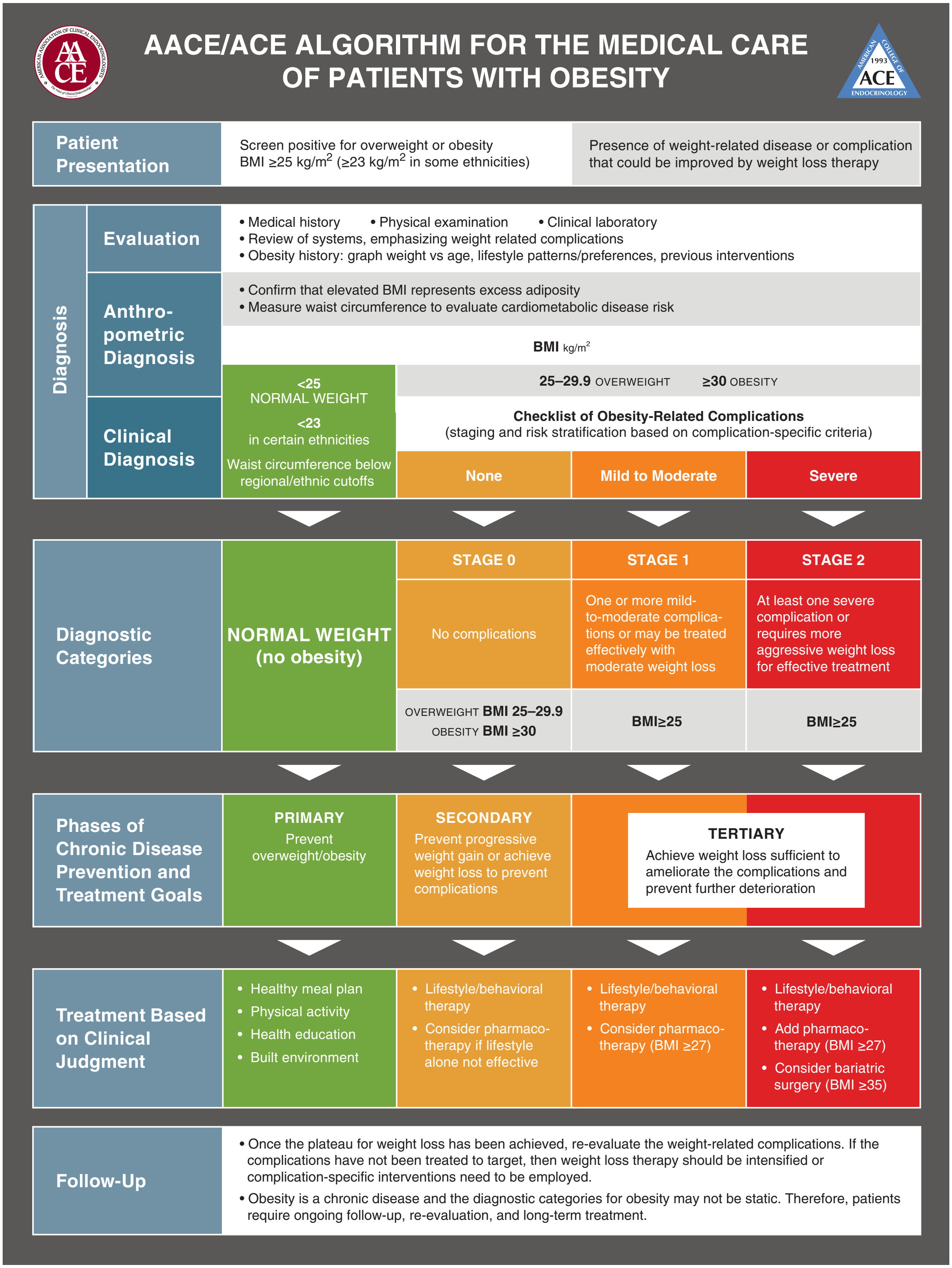
The treatment of pediatric obesity is a comprehensive strategy consisting of four main pillars: regulating quality and quantity of food intake, encouraging at least 60 minutes of physical activity daily while also limiting screen time to less than 1 to 2 hours per day, sleep regulation, and pharmacotherapy for those who qualify.[10]

Nonpharmacologic Therapy

Weight loss therapy requires the creation of an energy deficit. This may be achieved through daily caloric restriction and increased physical activity. Comprehensive lifestyle intervention and behavior modification is foundational to weight loss and should be recommended for all overweight or obese patients, even when adjunctive therapy with medications, devices, or bariatric surgery have been implemented. Table 102–3 indicates which treatment options may be appropriate according to BMI category.[11,15]

Reduced-Calorie Diet

Techniques to reduce dietary energy intake include adoption of a target energy intake less than that required for energy balance.



AACE/ACE ALGORITHM FOR THE MEDICAL CARE OF PATIENTS WITH OBESITY

Patient Presentation

Screen positive for overweight or obesity
BMI ≥25 kg/m² (≥23 kg/m² in some ethnicities)

Presence of weight-related disease or complication that could be improved by weight loss therapy

Diagnosis

Evaluation

- Medical history • Physical examination • Clinical laboratory
- Review of systems, emphasizing weight related complications
- Obesity history: graph weight vs age, lifestyle patterns/preferences, previous interventions

Anthropometric Diagnosis

- Confirm that elevated BMI represents excess adiposity
- Measure waist circumference to evaluate cardiometabolic disease risk

BMI kg/m²

<25 NORMAL WEIGHT
<23 in certain ethnicities
Waist circumference below regional/ethnic cutoffs

25–29.9 OVERWEIGHT **≥30** OBESITY

Clinical Diagnosis

Checklist of Obesity-Related Complications
(staging and risk stratification based on complication-specific criteria)

None	Mild to Moderate	Severe

Diagnostic Categories	**NORMAL WEIGHT (no obesity)**	**STAGE 0**	**STAGE 1**	**STAGE 2**
		No complications	One or more mild-to-moderate complications or may be treated effectively with moderate weight loss	At least one severe complication or requires more aggressive weight loss for effective treatment
		OVERWEIGHT **BMI 25–29.9** OBESITY **BMI ≥30**	**BMI≥25**	**BMI≥25**

Phases of Chronic Disease Prevention and Treatment Goals	**PRIMARY** Prevent overweight/obesity	**SECONDARY** Prevent progressive weight gain or achieve weight loss to prevent complications	**TERTIARY** Achieve weight loss sufficient to ameliorate the complications and prevent further deterioration	

Treatment Based on Clinical Judgment	Healthy meal plan Physical activity Health education Built environment	Lifestyle/behavioral therapy Consider pharmacotherapy if lifestyle alone not effective	Lifestyle/behavioral therapy Consider pharmacotherapy (BMI ≥27)	Lifestyle/behavioral therapy Add pharmacotherapy (BMI ≥27) Consider bariatric surgery (BMI ≥35)

Follow-Up

- Once the plateau for weight loss has been achieved, re-evaluate the weight-related complications. If the complications have not been treated to target, then weight loss therapy should be intensified or complication-specific interventions need to be employed.
- Obesity is a chronic disease and the diagnostic categories for obesity may not be static. Therefore, patients require ongoing follow-up, re-evaluation, and long-term treatment.

Abbreviation: BMI = body mass index

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FIGURE 102–2. AACE/ACE Algorithm for the Medical Care of Patients with Obesity (From Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity. Endocr Pract. 2016;22(suppl 3):1–203.

Table 102–3

Indications for Obesity Treatment by BMI Category[11,15]

	BMI Category				
Treatment	25–26.9	27–29.9	30–34.9	35–39.9	> 40
Bariatric surgery	No	No	Gastric banding with comorbidity	With comorbidity	Yes
Devices	No	No	Balloon	Aspire Assist Balloon vBloc[a] with comorbidity	Aspire Assist vBloc
Pharmacotherapy	No	With comorbidity	Yes	Yes	Yes
Lifestyle modification (diet, activity, behavior)	Yes	Yes	Yes	Yes	Yes

[a] vBloc, vagal nerve block therapy.

This can usually be accomplished by reducing the energy intake by 500 kcal/day (2100 kJ/day) or greater from current intake. Recommend total intake of 1200 to 1500 or 1500 to 1800 kcals/day (5000–6300 or 6300–7500 kJ/day) for women and men, respectively. The choice of calorie-restricted diet is based on patient preference and current health status. A variety of diets, including but not limited to, high-protein, low-carbohydrate, low-fat, Mediterranean and American Heart Association (AHA) Step-1 diet, can result in weight loss if reduction in dietary intake is achieved.[9] The AHA Step-1 diet restricts daily calories to a range of 1000 to 1200 kcal (4200–5000 kJ/day) for women weighing less than 75 kg (165 lb) and 1400 to 1600 kcal (5900–6700 kJ/day) for all others. This daily limit should be considered after assessing a patient's normal daily caloric intake and ensuring that the initial caloric restriction does not exceed 500 to 1000 kcal (2100–4200 kJ/day). For example, a male patient who consumes 3000 kcal (12,600 kJ/day) should not reduce his daily caloric intake to less than 2000 kcal (8400 kJ/day) when initially implementing a dietary program. Further reduction to the target of 1600 kcal (6700 kJ/day) can be attempted when the patient has reduced calories successfully, as initially recommended, for a period agreeable to the practitioner and the patient.[2] Diets too restrictive in calorie reduction are successful initially, but fail in the long term because compliance is difficult to sustain. Therefore, this less aggressive approach promotes gradual weight loss and weight maintenance. Consultation with a dietician is recommended when implementing a healthy meal plan tailored to the individual's nutritional needs.

Pediatric patients should be encouraged to consume three servings of protein daily, three servings of dairy daily, four to six servings of fruits and vegetables daily (majority from vegetables), avoid fast food, restrict dessert to special occasions only, and allowing the child to leave food on their plate if they feel full.[9]

▶ *Increased Physical Activity*

Although diet and exercise contribute to weight loss, combining a reduced-calorie diet with increased physical activity results in greater weight loss compared with either therapy alone.[11] In addition, physical activity can help prevent weight regain and reduce related cardiovascular risks.[9] Slow titration of both the amount and intensity of aerobic physical activity is recommended for most patients.[2] A program that incorporates walking daily is a viable option for most patients. Suggest starting with 10 minutes of physical activity 3 days/week and titrate up to 30 minutes most days as tolerated for optimal weight maintenance.[2,9] Pediatric patients should engage in at least 60 minutes of moderate-to-vigorous activity daily and limit nonacademic sedentary time.[10]

▶ *Behavioral*

Eliminating barriers through behavior modification is necessary to gain maximal benefit from both dietary modification and exercise. Successful behavioral therapy includes regular self-monitoring of food intake, physical activity, and weight.[9]

Targeted behaviors should be recommended to pediatric patients and their families because healthy habits help prevent excessive weight gain. These include, but are not limited to[10]:

- Limit the consumption of sugar-sweetened beverages.
- Limit the amount of screen time (television, computer, etc) to 2 hours or less per day.
- Limit the number meals eaten at restaurants, especially those serving fast food.
- Limit portion size when preparing and serving meals.

Pharmacologic Therapy

KEY CONCEPT Pharmacotherapy in addition to comprehensive lifestyle intervention can be considered for patients with a BMI of 30 kg/m^2 or greater, or a BMI of 27 kg/m^2 or greater with other obesity-related comorbidities. Obesity is a chronic disease that needs chronic treatment. There is no other chronic disease where therapy is withdrawn after a definitive time point. **KEY CONCEPT** Weight will likely be regained if lifestyle changes and/or therapeutic interventions are not continued indefinitely. Four drugs are approved for long-term use (at least 2 years) in promoting weight loss and preventing weight regain. If 4% to 5% weight loss is not achieved after 12 weeks of target dose therapy, the drug should be discontinued. Pharmacotherapy is not appropriate for women who are pregnant or lactating. Orlistat is the only agent approved for adolescent patients and is FDA approved for patients greater than 12 years of age.[16] All other pharmacotherapeutic agents are only approved for patients greater than 18 years of age. Table 102–4 summarizes currently available pharmacotherapeutic agents for weight management.[16-22] Much like current antiobesity medications, novel compounds in the pipeline focus on altering anorexigenic and orexigenic signaling and integration of various messages that drive eating behavior in the hypothalamus.[23]

▶ *Agents for Long-Term Use*

Orlistat Orlistat promotes and maintains weight loss by acting locally in the GI tract. It inhibits pancreatic and gastric lipases, as well as triglyceride hydrolysis. As a result, undigested triglycerides are not absorbed, causing a caloric deficit

Table 102–4

Pharmacotherapy for the Treatment of Obesity[16,22]

			Warnings	
Drug	Dose	Side Effects	Contraindications	Average Wholesale Price
Phentermine (Adipex P, Lomaira)	8–37.5mg daily (given in 1–3 divided doses)	Restlessness, tremor, palpitations or tachycardia, hypertension, cardiac valvulopathy, pulmonary hypertension	Tolerance develops after a few weeks Do not discontinue abruptly from max dose (seizure possible), avoid alcohol, hypokalemia if used with diuretics, avoid in hepatic dysfunction, take in morning to avoid insomnia History of drug abuse, cardiovascular disease, hyperthyroidism, glaucoma, administration of a monoamine oxidase inhibitor within 14 days	~$15–50
Phentermine/topiramate (Qsymia) Risk Evaluation and Mitigation Strategy (REMS) Program—pregnancy warning; cleft palate	3.75/23 mg daily × 14 days, 7.5/46 mg × 12 weeks Titrate up to 11.25/69 mg × 14 days then 15/92 mg daily if first 12 weeks successful Max dose 7.5/46 mg for CrCL < 50 mL/min (0.83 mL/s)	Constipation, paresthesias, xerostomia, blurred vision, impaired cognition, headache, kidney stones, increased upper respiratory tract infection, tachycardia, metabolic acidosis	Do not discontinue abruptly from max dose, avoid alcohol, hypokalemia if used with diuretics, avoid in hepatic dysfunction, take in morning to avoid insomnia Glaucoma, hyperthyroidism, administration of a monoamine oxidase inhibitor within 14 days	~$200–250
Bupropion/naltrexone (Contrave)	8/90 mg ER tab titrate up by 1 tab each week over 4 weeks to 32/360 mg given twice daily Limit to 1 tab twice a day for moderate-severe renal, and 1 tab daily for hepatic dysfunction	Nausea, vomiting, constipation, headache, dizziness, tachycardia, hypertension, insomnia, mood disturbances—report suicidal ideation immediately	Do not take with high-fat meals, **potential drug interactions:** other serotonergic drugs, antipsychotics, clopidogrel, antiretrovirals Seizure disorder, uncontrolled hypertension, history of eating disorder, **chronic opioid use**, administration of a monoamine oxidase inhibitor within 14 days	~$300
Liraglutide 3 mg (Saxenda) REMS: Thyroid C-cell tumors, acute pancreatitis	0.6 mg subcutaneously daily, increase by 0.6 mg each week up to 3 mg	Nausea, vomiting, diarrhea, constipation, headache, dizziness, dyspepsia (delayed gastric emptying), increased heart rate, acute pancreatitis, cholelithiasis	↓ Sulfonylurea or insulin dose by 50% Personal or family history of medullary thyroid cancer or endocrine neoplasia type 2	~$1500
Orlistat (Xenical—prescription) (Alli—OTC)	Xenical 120 mg three times daily with meals Alli 60 mg three times daily with meals	Abdominal pain, fecal urgency, leakage, incontinence, flatulence, steatorrhea	Take a multivitamin containing vitamins A, D, E, and K Cholestasis, malabsorption syndromes	~$500–550 ~$50–75

and weight loss. Two different orlistat products are available; prescription strength (Xenical 120 mg) and over-the-counter strength (Alli 60mg), and both are taken with each meal. Initiate orlistat with a well-balanced but reduced-caloric meal containing no more than 30% of calories from fat. Orlistat may be taken during or up to 1 hour after the meal. If a meal is missed or contains little fat, the dose of orlistat may be omitted. Doses above 360 mg/day provide no greater benefit and thus are not recommended.[16]

Prescription strength orlistat in combination with diet, exercise, and behavior modification resulted in a significant reduction in BMI and waist circumference in adolescents. In addition, orlistat-treated subjects exhibited minimal weight increase after 1 year.[16]

The safety and efficacy of orlistat have not been determined beyond 4 years of use. Orlistat's product label contains liver injury warning. Signs and symptoms of liver injury include itching, yellowing of the eyes or skin, dark urine, decreased appetite, and light-colored stools. Orlistat should be stopped if the patient complains of these signs and symptoms. In addition, liver function tests, should be assessed.[24]

Orlistat reduces the absorption of some fat-soluble vitamins. Daily intake of a multivitamin containing fat-soluble vitamins is recommended. Because the absorption of vitamin K may be reduced in patients receiving orlistat therapy, closer monitoring of coagulation status should occur in patients also taking warfarin.[16] Simultaneous administration of orlistat and some other medications may cause reduced absorption of the other medication and put the patient at increased risk of clinical adverse effects. Patients should take levothyroxine 4 hours before or after the orlistat dose and be monitored for changes in thyroid function. Administration of orlistat in conjunction with cyclosporine can result in decreased cyclosporine plasma levels. Cyclosporine should be taken 2 hours before or after the dose of orlistat, and cyclosporine levels should be monitored more frequently.[16]

Phentermine-Topiramate Phentermine-topiramate is an extended-release combination product. Phentermine decreases food intake by increasing norepinephrine and dopamine release in the central nervous system (CNS) which suppresses appetite. Topiramate is an antiepileptic drug whose exact mechanism of action is unknown. It is thought to increase satiety and suppress appetite through multiple pathways.[18]

Phentermine-topiramate use is associated with increased heart rate. Monitor resting heart rate frequently and have patients report the presence of palpitations. Topiramate can increase a patient's risk for suicidal thoughts and behaviors and alter mood. Patients should be monitored for worsening depression, thoughts of suicide, and unusual mood or behavior. Topiramate is contraindicated in patients with glaucoma or hyperthyroidism. Cognitive impairment is also associated with use of phentermine-topiramate; patients should proceed with caution when operating hazardous machinery including driving a car until the extent of impairment is known. An increase in serum creatinine and decrease in both potassium and bicarbonate have been reported.[18]

Because topiramate is a known teratogen, use of phentermine-topiramate during pregnancy is contraindicated. All women of childbearing potential should have a documented negative pregnancy result before this drug is initiated and monthly while on therapy.

Coadministration of phentermine-topiramate and monoamine oxidase inhibitor (MAOI) could result in a hypertensive crisis. Do not initiate phentermine-topiramate within 14 days of MAOI discontinuation. Phentermine-topiramate used in patients taking an oral contraceptive may cause irregular bleeding but not an increased risk of pregnancy. Advise patients to continue the oral contraceptives even if spotting occurs.

Initiate phentermine-topiramate at a dose of 3.75/23 mg daily and titrate to maximum dose as per Table 102–4. Discontinue drug or increase the dose of phentermine-topiramate if a 3% weight loss is not achieved in 12 weeks. If the decision is made to increase the dose, recommend 11.25/69 mg daily for 14 days then increase to 15/92 mg daily. Discontinue drug if a 5% weight loss is not achieved after 12 weeks at the highest drug dose. Due to the potential for drug abuse, phentermine-topiramate is a federally controlled substance (CIV). Gradually discontinue the 15/92 mg dose to prevent possible seizures from abrupt withdrawal.

Naltrexone-Bupropion Naltrexone-bupropion is an extended-release combination product. The exact mechanisms by which this opioid antagonist/antidepressant combination product decreases food intake and weight are not fully known but involve two separate areas of the brain (hypothalamus and mesolimbic dopamine circuit).[19]

Patients taking this product should be monitored for emergence or worsening of suicidal thoughts and behaviors and neuropsychiatric reactions. Bupropion inhibits CYP2D6 and can therefore increase the concentration of antidepressants, antipsychotics, and β-blockers. When taken with a CYP2B6 inhibitor (eg, clopidogrel), the concentration of bupropion increases. Reduce maximum daily dose by half in these patients. CYP2B6 inducers may reduce bupropion efficacy.[19]

Each extended-release tablet contains 8 mg of naltrexone and 90 mg of bupropion. Patients should be advised to not cut, crush, or chew tablets. Patients should also avoid taking naltrexone-bupropion with high-fat meals to minimize the risk of enhanced bupropion absorption and subsequent seizure occurrence. To further reduce the risk of seizures, the dose must be titrated slowly as suggested in Table 102–4.

Liraglutide 3 mg Liraglutide is an injectable analog of GLP-1 with a sequence that is 97% homologous with endogenously produced GLP-1.[17] When liraglutide stimulates GLP-1 receptors in the brain, signals of satiety are received and gastric emptying is delayed. A 50% dose reduction of sulfonylureas or any insulin is recommended with concomitant administration of liraglutide 3 mg in patients with type 2 diabetes. Acute pancreatitis occurs in 0.3% of patients taking liraglutide.[17]

Liraglutide is administered subcutaneously at a starting dose of 0.6 mg daily and increased to a target dose of 3 mg as suggested in Table 102–4. The dose increase may be delayed by 1 week if the patient is experiencing intolerable gastrointestinal adverse effects.

▶ *Agents for Short-Term Use*

Agents for short-term use are indicated as an adjunct to lifestyle modifications for no more than 12 weeks of use.[20,25,26] They are structurally related to amphetamine and work to suppress appetite. They can cause CNS stimulation and carry a potential for abuse. They should also not be used concurrently or within 14 days of an MAOI. These agents are cheaper than chronic obesity medications but often have more risky side effect profiles. These centrally acting sympathomimetic amines are generally not recommended for the treatment of chronic obesity.[14] Tolerance to the anorectic effect has been demonstrated, and these agents generally fail to produce long-term health benefits since weight regain tends to occur upon discontinuation of the drug.

Phentermine An average weight loss of 3.6 kg (7.9 lb) was demonstrated for patients treated with phentermine compared with placebo.[20]

Common adverse reactions seen with phentermine use include heart palpitations, tachycardia, elevated blood pressure, stimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, dry mouth, constipation, and diarrhea. Avoid phentermine in patients with CVD, hypertension, hyperthyroidism, and agitated states. Because phentermine is related to the amphetamines, the potential for abuse is high.[20] Alcohol is not recommended for patients prescribed phentermine.[20]

Phentermine is available as an immediate- and sustained-release product. In conjunction with a healthy lifestyle, 30 to 37.5 mg of phentermine is administered once daily, typically before breakfast or 1 to 2 hours after the morning meal. The dosage should be individualized; some patients may be managed adequately at 15 to 18.75 mg/day, but a dose of 18.75 mg twice daily may be used to minimize side effects, excluding insomnia. To lessen the risk of insomnia, dosing phentermine in the evening should be avoided.[20] A lower dose, 8-mg tablet, is given three times daily prior to meals.

Diethylpropion and Phendimetrazine These older sympathomimetic amines exhibit pharmacologic activity similar to amphetamines, resulting in CNS stimulation and appetite suppression.

Use of diethylpropion for a period longer than 12 weeks is associated with an increased risk for development of pulmonary hypertension.[25] When used as directed, reported common CNS adverse effects of these amphetamine derivatives included restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, anxiety, tachycardia, palpitations, dry mouth and constipation, mydriasis, and blurred vision.[25,26] In addition, diethylpropion can decrease the seizure threshold.[25] These agents are contraindicated in patients with pulmonary hypertension, advanced arteriosclerosis, severe hypertension, hyperthyroidism, agitated states, or glaucoma. Because these medications are related to the amphetamines, the potential for abuse is high.

Use of diethylpropion and phendimetrazine should be avoided in patients receiving or having an MAOI within the preceding 14 days to prevent hypertensive crisis. Combination with other anorectic agents should be avoided.[25,26]

Diethylpropion is available as both an immediate- and a controlled-release product. In conjunction with a reduced-calorie diet and/or exercise, dose diethylpropion (immediate release) 25 mg three times a day before meals or 75 mg (controlled release) once a day, usually midmorning.[25] Dose phendimetrazine extended release (105 mg) in the morning, 30 to 60 minutes before the morning meal or 35mg immediate release two to three times per day prior to meals. Phendimetrazine is a federally controlled substance (CIII).[25]

▸ Surgical Intervention

KEY CONCEPT Weight loss (bariatric) surgery is warranted when other treatment attempts have failed in severely obese patients (BMI $\geq 40\ \text{kg/m}^2$, or $\geq 35\ \text{kg/m}^2$ with obesity-related comorbidities).[2,11] Several surgical techniques exist; however, three are currently recognized as contemporary procedures: gastric bypass, which induces weight loss through both malabsorptive and restriction, sleeve gastrectomy, and laparoscopic adjustable gastric banding (LAGB), which achieve weight loss through restriction of food intake only.[27] Currently, the sleeve gastrectomy is the most commonly performed bariatric surgery procedure.[28]

Patient Encounter 1, Part 1

A 34-year-old woman presents to your weight loss clinic for an initial evaluation. She reports that her blood pressure was elevated upon screening while attending a community health fair. She followed up with her primary care provider who recommended adding another antihypertensive to her regimen, but she is wondering if weight loss may help her avoid being on more medications. Patient has gained 25 lb (11.3 kg) since her last check up 2 years ago. She is not currently following any specific diet. She admits to eating fast food 2 to 3 days per week. Patient is recently divorced (1 year ago) and does not enjoy cooking for one. This patient is currently part of a walking group where she walks 20 minutes per day roughly 2 days per week. The patient does not smoke and consumes one beer at least three nights per week. Her BMI is 39.3 kg/m^2, and her waist circumference is 39 in (99 cm).

What classification of overweight and obesity is appropriate for this patient?

Does this patient have a high-risk waist circumference?

Does she have other risk factors that may contribute to morbidity or mortality?

What are the treatment goals for the patient?

What additional information do you need to know before creating a treatment plan for this patient?

Patient Encounter 1, Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Type 2 diabetes mellitus, persistent lower back pain, heartburn, depression, insomnia, kidney stones × 2

FH: Father alive and 68 years of age. Mother also alive (age 65) with history of obesity.

SH: (–) Tobacco, (+) alcohol

Meds: Hydrocodone/acetaminophen 5/325 one tablet orally at bedtime, pantoprazole 40 mg orally once per day, citalopram 20 mg orally once per day, metformin 1000 mg orally twice per day, sitagliptin 50 mg orally once per day, Bydureon 2 mg subcutaneously once weekly, lisinopril 20 mg orally daily, and zolpidem 5 mg orally at bedtime for sleep

ROS: (+) Heartburn; (–) chest pain, nausea, vomiting, diarrhea, change in appetite, shortness of breath, or cough

PE:

VS: BP 147/88 mm Hg, P 92 beats/min, RR 16 breaths/min, T 98.6°F (37°C)

Weight: 193 lb (87.5 kg); ht: 64 in (163 cm)

Cardiovascular: Normal S_1S_2; no murmurs, rubs, gallops

Abdominal: Obese, soft, nontender, nondistended; (+) bowel sounds

Extremities: (–) Edema

Labs: Glucose (118 mg/dL [6.5 mmol/L]) and HbA_{1C} (6% [0.06 or 42 mmol/mol Hgb]).

ECG: Normal. No evidence of past ischemia

Given this additional information, do you recommend weight loss? If so, how much weight should the patient lose and how fast?

What nonpharmacologic and pharmacologic treatments are available for the patient?

Would you recommend any changes to her current medication regimen to assist with her weight loss?

If you elected to start her on a pharmacotherapeutic agent for weight loss, what would you need to monitor and when would you recommend the patient come back for follow-up?

Surgical options for obesity provide the most effective and sustainable weight loss results and may produce a loss of two-thirds of excess body weight after 2 years.[2] Additionally, very favorable outcomes for obesity-related comorbid conditions are observed.[29] Risk versus benefit must be considered as complications are inherent to any surgical procedure, but the overall likelihood of major complications is less than 4%. Possible short-term complications include pulmonary embolism, wound infection, and anastomotic leak. The overall risk of mortality from bariatric surgery is about 0.1%. Several studies have compared mortality in obese patients who have underwent bariatric surgery to those who have not and consistently found reduced mortality rates in the surgical population.[29]

Bariatric surgery is an alternative offered to adolescents because it results in substantial weight loss and medical health improvement.[30] Adolescent patients should be managed by a multidisciplinary team that can provide psychosocial, nutritional, and exercise support.[31] Both adult and pediatric surgical patients must understand and commit to a substantial change in eating and activity patterns to maintain long-term weight reduction.

Postoperatively, healthcare providers should also make considerations for medication management as these procedures may alter drug and nutrient absorption.[32]

- If safe to do so for individual medications, crush tablets, open capsules, or use liquid formulations to replace sizeable pills until appropriate to restart solid foods (likely variable per program.
- Avoid nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, oral bisphosphonates, and potentially extended- or delayed-release products for malabsorptive procedures.
- Certain micronutrient supplements may be indicated depending on procedure type (eg, fat-soluble vitamins, iron, vitamin B_{12}).
- Nonoral routes of administration may be considered if available.

Devices

Weight loss devices require a minimally invasive outpatient procedure since most of them are endoscopically placed. There are currently three types of devices approved for use in adult patients by the FDA: vagal nerve blocking stimulators (vBloc), gastric balloons, and gastric emptying systems. Indications for use are dependent on BMI category and/or presence of obesity-related comorbidities (see Table 102–3), and some are only approved for short-term therapy (6 months).[11,15] Devices are associated with an overall equal to or greater weight loss profile compared to pharmacotherapy but are not quite as effective as bariatric surgery.[15] Devices are associated with some similar adverse effects but an overall lesser serious complication rate compared to bariatric surgery.[15]

Patient Encounter 2, Part 1

A 51-year-old White man presents to your CVD Risk Reduction Clinic. The patient currently denies chest pain, shortness of breath, dizziness, or light-headedness. He just mentions being fatigued a lot. He is supposed to wear a CPAP machine at night but admits he frequently takes it off in the middle of the night. You review his labs today and find his LDL to be elevated. As a computer programmer who works from home, he finds himself sitting more than engaging in physical activity. He frequently eats fast food for lunch. Evenings are spent in watching TV. He claims his knee arthritis limits his exercise ability. He is a half pack per day smoker. The patient's BMI is 34 kg/m^2, and waist circumference is 40 in (102 cm). He presents to the clinic today seeking recommendation for weight loss and says he is willing to make changes to better his health.

What classification of overweight and obesity is appropriate for this patient?

Does this patient have a high-risk waist circumference?

Does he have other risk factors that may contribute to morbidity or mortality?

What are the treatment goals for the patient?

What additional information do you need to know before creating a treatment plan for this patient?

Patient Encounter 2, Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Occasional headache, hypertension, osteoarthritis of the left knee, irritable bowel syndrome (diarrhea predominant)

FH: Father alive and 78 years of age. Mother also alive and 77 years of age.

SH: Drinks alcohol occasionally (socially) but denies any alcohol-related problems

Meds: Lisinopril/hydrochlorothiazide 10/25 mg orally daily, aspirin 81 mg orally daily, metformin 1000 mg orally twice a day, atorvastatin 10 mg orally daily, amitriptyline 25 mg orally at bedtime, Excedrin migraine two tabs orally as needed headache, acetaminophen 650 mg orally four times a day as needed for knee pain

ROS: (–) Heartburn, regurgitation; (–) chest pain, nausea, vomiting, diarrhea, no change in appetite, no shortness of breath, or cough

VS: BP 129/79 mm Hg, P 72 beats/min, RR 15 breaths/min, T 98.7°F (37.1°C)

Weight: 262 lb (119 kg)

Height: 73 in (185 cm)

Waist circumference: 40 in (102 cm)

PE:

General: Well developed, in no acute distress

HEENT: Conjunctiva clear

CV: Regular rhythm, no S_3 or S_4 noted

Lungs: Clear to auscultation (CTA) bilaterally

Abd: Obese, soft, nontender, nondistended; (+) bowel sounds

Neuro: Normal gait, normal speech

Ext: (–) Edema

Labs:

Na: 142 mEq/L (mmol/L); **K:** 4.6 mEq/L (mmol/L); **Cl:** 107 mEq/L (mmol/L); **CO2:** 23 mEq/L (mmol/L); **BUN:** 18 mg/dL (6.4 mmol/L); **Creatinine:** 0.9 mg/dL (80 μmol/L); **glucose:** 110 mg/dL (6.1 mmol/L); **HbA1C:** 6.9% (0.069; 52 mmol/mol Hgb)

TC: 213 mg/dL (5.51 mmol/L); **LDL:** 110 mg/dL (2.84 mmol/L); **HDL:** 30 mg/dL (0.78 mmol/L); **TG:** 152 mg/dL (1.72 mmol/L)

AST: 24 U/L (0.40 μkat/L); **ALT:** 30 U/L (0.50 μkat/L)

What would be the optimal treatment strategy for this patient?

Vagal Nerve Block Stimulator The vBloc system contains a pacemaker-like device that is implanted under the skin and connects to electrodes that are attached to the vagus nerve. It blocks hunger signals sent from the stomach to the brain along the vagus nerve. The vBloc system is not appropriate for patients with hepatic cirrhosis or those who have another electronic medical device already implanted.[33]

Gastric Balloons Three medical-grade silicone gastric balloons are currently available for endoscopic placement and inflation in the stomach: Reshape, Orbera, and Obalon. The balloon reduces the amount of food that a patient can consume by taking up significant space in the stomach. After 6 months, balloons must be removed. Most common adverse events are nausea/vomiting, abdominal pain, and gastric ulcers.

Reduced calorie absorption system The Aspire Assist device works by removing roughly one-third of the food consumed from the stomach before it reaches the intestinal tract, effectively reducing the calories absorbed from food.[15] A tube is placed into the stomach and connects to a small button on the outside of the abdomen. Roughly 20 to 30 minutes after a meal, the patient connects the tube to a handheld device that then pumps food out of the stomach and into the toilet. The most common adverse effects are abdominal discomfort and button site irritation.

OUTCOME EVALUATION

Successful management of overweight and obesity is determined by the ability the treatment plan has to (a) prevent weight gain, (b) reduce and maintain a lower body weight, and (c) decrease the risk of obesity-related comorbidities. Obesity management may encompass more than weight loss or maintenance in the presence of other conditions such as hypertension, type 2 diabetes mellitus, hyperlipidemia, CVD, sleep apnea, hypothyroidism, osteoarthritis, gallbladder disease, gout, or cancer. Measure blood pressure and heart rate before implementation of any therapy and assess basic metabolic panel, liver function tests, complete blood count, fasting lipid profile, thyroid function tests, and other laboratory studies at baseline and as clinically indicated. Additionally, obtain an electrocardiogram if recent results are unknown.

When considering various approaches to behavioral therapy for weight loss, in-person, high-intensity (defined as a minimum of 14 sessions within 6 months) behavioral therapy is the most effective. During each session, assess compliance with comprehensive lifestyle intervention, as well as measure weight, blood pressure, and heart rate. Measure waist circumference intermittently. Identify presence of adverse drug reactions or drug interactions if weight loss medications have been initiated.

When the patient has achieved the recommended weight loss, he or she then enters the weight maintenance phase, which includes continued contact for education (no less than monthly), guidance, and risk factor assessment. Self-weighing, at least weekly, is associated with better weight maintenance over time. Counsel patient to address small weight gains before they become larger.[9]

If weight loss is not attained, further assess why the goals of therapy are unmet. Direct the interaction toward determining the motivation to lose weight, balance between caloric intake and physical activity, adherence to behavioral therapy, and determination of psychological stressors present. Refer patient to a nutrition professional or for evaluation for bariatric surgery if eligibility criteria are met. If adjunctive pharmacotherapy has not been initiated, consider antiobesity drugs approved for long-term use.

Patient Care Process

Collect Information:

- Measure weight and height.
- Calculate and classify BMI.
- Medical history, current medications, and laboratory data for secondary causes of weight gain.
- Current lifestyle and history of weight gain/loss.

Assess the Information:

- CVD risks and obesity-related comorbidities.
- Need to lose weight (candidates include obese patients or overweight patients with at least one indicator of increased CVD risk).
- Readiness to make lifestyle changes.
- Weight loss goals.

Develop a Care Plan:

- Comprehensive lifestyle intervention strategies (restricted caloric-diet, increased physical activity, and behavioral therapy).
- Determine eligibility for obesity pharmacotherapy and, if so, verify if insurance coverage exists for the patient or if they qualify for any manufacturer offered discount cards.
- If patient is already receiving an antiobesity medication, assess efficacy, safety, adherence, and potential drug interactions.

Implement the Care Plan:

- Manage CVD risk factors such as hypertension, dyslipidemia, etc.
- Encourage self-weighing, at least weekly, for better weight loss and maintenance over time.
- Keep weight monitoring log to take to future follow-up visits.

Follow-up: Monitor and Evaluate:

- In 2 weeks, patient may self-assess weight, blood pressure, heart rate, and adherence with comprehensive lifestyle intervention. Assess weight monitoring log.
- Every 4 weeks, reassess patient in person.
- Once weight loss is achieved, continue contact with patient monthly, if possible. Address small weight gains and continued adherence with comprehensive lifestyle intervention.

Abbreviations Introduced in This Chapter

AST	Aspartate transaminase
ALT	Alanine aminotransferase
BMI	Body mass index
CB1	Cannabinoid receptor
CNS	Central nervous system
CVD	Cardiovascular disease
FDA	Food and Drug Administration
5-HT$_{1A}$	Serotonin 1A subtype
5-HT$_{2C}$	Serotonin 2C subtype
GI	Gastrointestinal
MAOI	Monoamine oxidase inhibitor

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Appendix A: Prescription Writing Principles

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Approximately 4 billion prescriptions are written and dispensed in the United States annually, with 80% of those prescribed digitally.[1] This reflects a need for prescribers and dispensers to fully understand prescriptive privileges and rational prescribing.[2] The following outlines principles of pharmacotherapy, including general considerations of prescribing, rational prescribing of medications, types of prescription orders, safe prescribing practices including the importance of handwriting and electronic prescribing, adverse event reporting, and medication education.

It is essential that the prescriber and dispenser familiarize themselves with professional guidelines, state laws, and federal laws. In addition, they must understand the components of rational prescribing. Table A–1 provides key elements a prescriber should understand as well as useful resources.

TYPES OF PRESCRIPTION ORDERS

Prescription orders can be provided in a variety of ways by authorized prescribers. Outpatient prescriptions may be generated in a format that is handed to the patient directly. For example, prescriptions can be handwritten, typed, or computer generated and printed. A verbal format could also be used, making the prescription available for retrieval at the pharmacy without a physical prescription in hand. This can be accomplished by verbally authorizing the prescription with a phone call to the pharmacy staff or leaving a message on the pharmacy voicemail, which must be immediately reduced to written format when received. A fax could also be used to generate the prescription. Most commonly, the prescription can be provided electronically through e-prescribing. This allows the prescription to be communicated directly from the provider's electronic medical record to the pharmacy's database for dispensing. All outpatient prescriptions are subject to federal regulations and contain the same basic components. Laws and regulations for outpatient prescription requirements can vary from state to state, so prescribers should be knowledgeable of all applicable laws. The basic components of a prescription are listed below as well as numbered in Figure A–1.[3]

- Prescriber information: name, address, and phone number
- Prescriber's signature and prescriptive authority number or Drug Enforcement Administration (DEA) number (if applicable)
- Patient information: full name and address, and weight and age if appropriate
- Date the prescription was written
- Superscription (Rx symbol), meaning "you take" or "recipe"; not required but traditionally seen
- Inscription: medication being prescribed (name of medication, strength, and dose)
- Signa, sig, or signature: directions to the patient (eg, take one tablet daily)
- Subscription: dispensing instructions to the pharmacist (number, quantity, or volume to dispense)
- Number of refills allowed
- Generic substitution requirement: "DAW (dispense as written)" or "no substitution" if brand name medication only is desired. The specific wording requirement may vary by state.

Further regulations are in place for prescriptions written for controlled substances.[4] In addition to the above elements, prescriptions for controlled substances must also include the patient's full name and address as well as the full name, address, and DEA number of the prescriber. Stricter regulations exist for schedule II–controlled substances compared with schedules III and IV. Schedule II prescriptions must be written and can only be provided orally in an emergency situation. When provided orally, this must be documented and matched with a written authorization within 7 days. However, with advancements in security capabilities of electronic medical records (EMR), the DEA amended this to provide an option to issue schedule II prescriptions electronically. Federal and state rules must be followed. In cases where federal and state laws conflict, the stricter law must be adhered to.[5] Refills are prohibited with schedule II prescriptions, with partial refills allowed under specific circumstances; however, this practice must adhere to both federal and state laws.[6] Schedule III and IV prescriptions may be refilled up to five times within 6 months of when the prescription was issued. Due to the opioid epidemic, many states have enacted stricter prescribing laws to reduce prescription fraud and abuse. Prescribers need to be aware of individual state requirements.

Orders listed in the medical record for hospitalized patients are not considered prescriptions and are not subject to the same requirements. However, in most hospitals, almost all orders are done electronically, with written orders being the exception. Typically, medical record orders include:

- Patient identifiers including name, account number.
- Prescriber name.
- Medication name, dose, route, and frequency of administration.
- Date and time of order.
- Prescriber signature (electronic).
- If the order was given verbally, the person reducing the order to writing must sign the order and the ordering provider countersign.

Table A–1

Pharmacotherapy Principles

Pharmacotherapy Principle	Description	Online Resources
Prescriptive privileges	Dictated by federal and state law	
	Scope of practice and formularies vary by profession. Physicians, nurse practitioners, physician assistants, and dentists all have varying scopes of practice, which may include formularies or supervising prescribers. Each provider must become familiar with his or her profession's scope of practice.	
	Pharmacology courses in program of study and Continuing Education required	
	Prescribing legend drugs requires board examination and National Provider Identifier (NPI)	https://nppes.cms.hhs.gov/NPPES/Welcome.do
	Prescribing controlled substances requires DEA registration number	http://www.justice.gov/dea/
Rational prescribing	Ensure necessity of medication	
	Obtain pertinent history	
	• Health history: comorbidities or contraindications (ie, pregnancy, hepatic failure, or renal failure)	
	• Medication history: prior and current prescription, OTC, or herbal use; drug allergies or sensitivities; compliance issues	
	• Family and social history	
	Select correct medication	http://www.jointcommission.org/
	• It is important to know the following components of each medication when prescribing or dispensing:	
	• Pharmacokinetics	
	• Pharmacodynamics	
	• Drug interactions	
	• Drug–disease interactions	
	• Interdisciplinary collaboration when necessary	

DEA, Drug Enforcement Administration; OTC, over the counter.

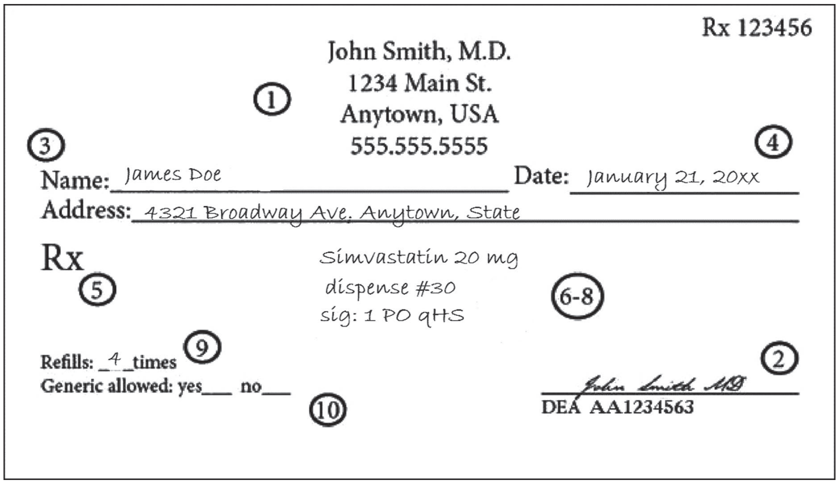
Electronic prescribing has become common practice because of government incentives aimed at moving health records to electronic databases with the goal of improving healthcare processes.[7] Principles discussed previously in regard to requirements of a prescription hold true for electronic orders; however, additional considerations must be taken to ensure safe prescribing habits. A brief list of potential barriers and benefits is summarized in Table A–2.

Electronic prescribing is no longer a projection of the future but instead has become the norm. With appropriate use of this technology, patients are provided with safer and more efficient care.

Omission of any of the above-discussed elements on a prescription order can be considered erroneous and poses a danger to patient care. Responsibility lies with the prescriber as well as the pharmacist dispensing the medication to ensure prescriptions are accurate and appropriate for each patient. State laws for electronic prescribing must also be considered.

SAFE PRESCRIBING PRACTICES

Safe prescribing should be a priority for all healthcare providers. To avoid inappropriate use of medications, prescribers should take careful consideration in writing clear and descriptive prescriptions. This ensures appropriate communication among the interdisciplinary healthcare team.



Rx 123456

John Smith, M.D.
1234 Main St.
Anytown, USA
555.555.5555

Name: James Doe
Date: January 21, 20xx
Address: 4321 Broadway Ave. Anytown, State

Rx

Simvastatin 20 mg
dispense #30
sig: 1 PO qHS

Refills: 4 times
Generic allowed: yes___ no___

John Smith MD
DEA AA1234563

FIGURE A–1. Example of a prescription.

Table A–2

Electronic Prescribing[8-9]

Benefits	Barriers
Reduce medication errors	Cost of software programs
Reduce adverse drug events	Lack of financial benefit seen immediately
Improves efficiency	Lack of software standardization
Improved recognition of drug–drug and drug–disease interactions	Indirect costs: training personnel, reduced patient visits during training period
Improved recognition of medication allergy cross-sensitivity	Clinician resistance: worry of worsening relationship with patient, negative impact on workflow, and fears of restrictions on prescribing habits
Enhanced prescriber knowledge of patient adherence	
Enhanced prescriber knowledge of insurance coverage for medications	

Table A–3

Sound-Alike/Look-alike Medications[10]

Medication Name	Misinterpreted Medication Name
aceto**HEXAMIDE**	aceta**ZOLAMIDE**
chlordiaze**POXIDE**	chlorpro**MAZINE**
CISplatin	**CARBO**platin
e**PHED**rine	**EPINEPH**rine
hydr**ALAZINE**	hydr**OXY**zine
LORazepam	**ALPRAZ**olam
NIFEdipine	ni**CAR**dipine
RABEprazole	**ARIP**iprazole
risperi**DONE**	r**OPINIR**ole
sulf**ADIAZINE**	sulfa**SALA**zine
val**ACY**clovir	val**GAN**ciclovir
Zantac	Xanax

A thorough understanding of the medication prescribed, including its expected risks and benefits, should be realized by the prescriber ensuring appropriate drug selection. Providers must also be able to recognize and avoid common errors related to prescription writing. These errors include sound-alike/look-alike medications and inappropriate use of shorthand language and abbreviations. The Joint Commission, as well as the Institute for Safe Medication Practices (ISMP), has collected common examples of these errors seen during the ordering process. Common examples are described in Tables A–3 and A–4.

Table A–4

Error-Prone Abbreviations[11]

Abbreviation	Anticipated Meaning	Misinterpretation	Correction
µg	Microgram	Mistaken as “mg”	Use “mcg”
IJ	Injection	Mistaken as “IV” or “intrajugular”	Use “injection”
q.d. or QD	Every day	Mistaken as qid, especially if the period after the “q” or the tail of the “q” is misunderstood as an “i”	Use “daily”
U	Units	May appear as a µ or 0	Use “units”
IU	International Units	IV (intravenous)	Use “units”
bid, tid, qid	Twice daily, three times daily, four times daily	Depending on handwriting, may be misinterpreted a number of ways.	Write out the words “twice daily,” etc.
biw, tiw, qiw	Twice weekly, three times weekly, four times weekly	Two times per day, three times per day, four times per day	Write out the words “twice weekly,” etc.
Dose Designation	**Anticipated Meaning**	**Misinterpretation**	**Correction**
Trailing zero after decimal point (eg, 4.0 mg)	4 mg	Mistaken as 40 mg if the decimal point is not seen	Do not use trailing zeros for doses expressed in whole numbers
No leading zero before a decimal point (eg, .8 mg)	0.8 mg	Mistaken as 8 mg if the decimal point is NOT seen	Use zero before a decimal point when the dose is less than a whole unit
Large doses without properly placed commas (eg, 100000 units;1000000 units)	100,000 units 1,000,000 units	100000 has been mistaken as 10,000 or 1,000,000; 1000000 has been mistaken as 100,000	Use commas for dosing units at or above 1,000 or use words such as 100 “thousand” or 1 “million” to improve readability
Drug Name Abbreviation	**Anticipated Meaning**	**Misinterpretation**	**Correction**
AZT	Zidovudine (Retrovir)	Mistaken as azathioprine or aztreonam	Use complete drug name
MS, MSO4	Morphine sulfate	Mistaken as magnesium sulfate	Use complete drug name
PCA	Procainamide	Mistaken as patient-controlled analgesia	Use complete drug name
T3	Tylenol with codeine No. 3	Mistaken as liothyronine	Use complete drug name
Stemmed Drug Names	**Anticipated Meaning**	**Misinterpretation**	**Correction**
“Nitro” drip	Nitroglycerin infusion	Mistaken as sodium nitroprusside infusion	Use complete drug name
“IV Vanc”	Intravenous vancomycin	Mistaken as Invanz	Use complete drug name
Symbol	**Anticipated Meaning**	**Misinterpretation**	**Correction**
x3d	For three days	Mistaken as 3 doses	Use “for three days”
&	And	Mistaken as “2”	Use “and”
°	Hour	Mistaken as a zero (eg, q2° seen as q 20)	Use “hr,” “h,” or “hour”

Available from: http://ismp.org/tools/errorproneabbreviations.pdf

Other commonly used medical abbreviations used in prescription writing can be found in Appendix C: Common Medical Abbreviations.

Adverse Event Reporting

Adverse events may occur related to inappropriate prescribing, dispensing, or administering medications. Inappropriate prescribing may be avoided by ensuring care is taken to determine all pertinent patient-related issues are discussed during the encounter. Additionally, appropriate interdisciplinary care where multiple healthcare providers are evaluating and treating the patient's problem may help avoid adverse events from occurring. Inappropriate dispensing and administration may be avoided through use of clear order entry that undergoes multiple checks by a variety of providers before a prescription reaches the patient. Movement to electronic prescribing has helped eliminate many issues with misinterpreting handwritten orders; however, should they still be encountered, providers should take care to write prescriptions very legibly. If any questions remain upon receipt of a questionable order, verification should occur with the writing provided by the dispensing pharmacist. If adverse events related to medication use are determined, the healthcare provider who discovers the event is responsible for reporting it. The Food and Drug Administration's reporting system for such adverse events is MedWatch.[12] This online database archives medication-related adverse events, and providers are able to report errors seen in clinical practice.

Medication Education

After a prescription has been written, counseling patients on newly prescribed therapies is an essential responsibility of the prescriber and pharmacist. The patient should be made aware of the rationale for drug use, the dose, route, and frequency at which they should administer the medication and expectations of the prescribed drug. Expectations should include risks and benefits to avoid patient confusion about side effects or efficacy measures. Thorough discussion with the patient about the selected medication therapy may identify contraindications previously unknown or a patient history of failure or success with the selected agent in the past. Some high-risk medications require special programs that must be completed by prescribers and/or patients as well.

CONCLUSION

Multiple principles must be exercised for appropriate drug delivery from the bedside to the patient. As a healthcare provider, understanding these processes helps to ensure safe medication prescribing.

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Appendix B: Conversion Factors and Anthropometrics*

CONVERSION FACTORS

SI Units

SI (*le Systéme International d'Unités*) units are used in many countries to express clinical laboratory and serum drug concentration data.* Instead of using units of mass (eg, micrograms), the SI system uses moles (mol) to represent the amount of a substance. A molar solution contains 1 mole (the molecular weight of the substance in grams) of the solute in 1 L of solution. The following formula is used to convert units of mass to moles (mcg/mL to µmol/L or, by substitution of terms, mg/mL to mmol/L or ng/mL to nmol/L).

▶ *Micromoles per Liter*

$$\text{Micromoles per liter } (\mu\text{mol/L}) = \frac{\text{drug concentration (mcg/mL)} \times 1000}{\text{molecular weight of drug (g/mol)}}$$

▶ *Milliequivalents*

An equivalent weight of a substance is the weight that will combine with or replace 1 g of hydrogen; a milliequivalent is 1/1000 of an equivalent weight.

Milliequivalents per Liter

$$\text{Milliequivalents per liter (mEq/L)} = \frac{\text{weight of salt (g)} \times \text{valence of ion} \times 1000}{\text{molecular weight of salt}}$$

$$\text{Weight of salt (g)} = \frac{\text{mEq/L} \times \text{molecular weight of salt}}{\text{valence of ion} \times 1000}$$

Approximate Milliequivalents: Weight Conversions for Selected Ions

Salt	mEq/g Salt	mg Salt/ mEq
Calcium carbonate ($CaCO_3$)	20.0	50.0
Calcium chloride ($CaCl_2 \cdot 2H_2O$)	13.6	73.5
Calcium gluceptate ($Ca[C_7H_{13}O_8]_2$)	4.1	245.2
Calcium gluconate ($Ca[C_6H_{11}O_7]_2 \cdot H_2O$)	4.5	224.1
Calcium lactate ($Ca[C_3H_5O_3]_2 \cdot 5H_2O$)	6.5	154.1
Magnesium gluconate ($Mg[C_6H_{11}O_7]_2 \cdot H_2O$)	4.6	216.3
Magnesium oxide (MgO)	49.6	20.2
Magnesium sulfate ($MgSO_4$)	16.6	60.2
Magnesium sulfate ($MgSO_4 \cdot 7H_2O$)	8.1	123.2
Potassium acetate ($K[C_2H_3O_2]$)	10.2	98.1
Potassium chloride (KCl)	13.4	74.6
Potassium citrate ($K_3[C_6H_5O_7] \cdot H_2O$)	9.2	108.1
Potassium iodide (KI)	6.0	166.0
Sodium acetate ($Na[C_2H_3O_2]$)	12.2	82.0
Sodium acetate ($Na[C_2H_3O_2] \cdot 3H_2O$)	7.3	136.1
Sodium bicarbonate ($NaHCO_3$)	11.9	84.0
Sodium chloride ($NaCl$)	17.1	58.4
Sodium citrate ($Na_3[C_6H_5O_7] \cdot 2H_2O$)	10.2	98.0
Sodium iodide (NaI)	6.7	149.9
Sodium lactate ($Na[C_3H_5O_3]$)	8.9	112.1
Zinc sulfate ($ZnSO_4 \cdot 7H_2O$)	7.0	143.8

Valences and Atomic/Molecular Weights of Selected Ions

Substance	Electrolyte	Valence	Atomic/Molecular Weight
Calcium	Ca^{2+}	2	40.1
Chloride	Cl^-	1	35.5
Magnesium	Mg^{2+}	2	24.3
Phosphate	HPO_4^{2-} (80%)	1.8	96.0[a]
(pH = 7.4)	$H_2PO_4^-$ (20%)		97.0
Potassium	K^+	1	39.1
Sodium	Na^+	1	23.0
Sulfate	SO_4^-	2	96.0[a]

[a] The atomic/molecular weight of phosphorus is only 31; that of sulfur is only 32.1.

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*This appendix contains information from Appendices 1 and 2 of Smith KM, Riche DM, Henyan NN (eds.), Clinical Drug Data, 11th ed. New York: McGraw-Hill, 2010:1239–1246; With permission.

Anion Gap

The anion gap is the concentration of plasma anions not routinely measured by laboratory screening. It is useful in the evaluation of acid–base disorders. The anion gap is greater with increased plasma concentrations of endogenous species (eg, phosphate, sulfate, lactate, and ketoacids) or exogenous species (eg, salicylate, penicillin, ethylene glycol, ethanol, and methanol). The formulas for calculating the anion gap are as follows:

$$\text{Anion gap} = (\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)$$

or

$$\text{Anion gap} = \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$$

where the expected normal value for the first equation is 11 to 20 mmol/L and for the second equation is 7 to 16 mmol/L. Note that there is a variation in the upper and lower limits of the normal range.

Temperature

Fahrenheit to Celsius: (°F – 32) × 5/9 = °C

Celsius to Fahrenheit: (°C × 9/5) + 32 = °F

Celsius to Kelvin: °C + 273 = °K

Weights and Measures

▶ *Metric Weight Equivalents*

1 kilogram (kg) = 1000 grams

1 gram (g) = 1000 milligrams

1 milligram (mg) = 0.001 gram

1 microgram (mcg, µg) = 0.001 milligram

1 nanogram (ng) = 0.001 microgram

1 picogram (pg) = 0.001 nanogram

1 femtogram (fg) = 0.001 picogram

▶ *Metric Volume Equivalents*

1 liter (L) = 1000 milliliters

1 deciliter (dL) = 100 milliliters

1 milliliter (mL) = 0.001 liter

1 microliter (µL) = 0.001 milliliter

1 nanoliter (nL) = 0.001 microliter

1 picoliter (pL) = 0.001 nanoliter

1 femtoliter (fL) = 0.001 picoliter

▶ *Apothecary Weight Equivalents*

1 scruple (э) = 20 grains (gr)

60 grains (gr) = 1 dram (ʒ)

8 drams (ʒ) = 1 ounce (℥)

1 ounce (℥) = 480 grains (gr)

12 ounces (℥) = 1 pound (lb)

▶ *Apothecary Volume Equivalents*

60 minims (m) = 1 fluidram (fl ʒ)

8 fluidrams (fl ʒ) = 1 fluid ounce (fl ℥)

1 fluid ounce (fl ℥) = 480 minims (m)

16 fluid ounces (fl ℥) = 1 pint (pt)

▶ *Avoirdupois Equivalents*

1 ounce (oz) = 437.5 grains

16 ounces (oz) = 1 pound (lb)

▶ *Weight/Volume Equivalents*

1 mg/dL = 10 mcg/mL

1 mg/dL = 1 mg%

1 ppm = 1 mg/L

▶ *Conversion Equivalents*

1 gram (g) = 15.43 grains (gr)

1 grain (gr) = 64.8 milligrams (mg)

1 ounce (℥) = 31.1 grams (g)

1 ounce (oz) = 28.35 grams (g)

1 pound (lb) = 453.6 grams (g)

1 kilogram (kg) = 2.2 pounds (lb)

1 milliliter (mL) = 16.23 minims (m)

1 minim (m) = 0.06 milliliter (mL)

1 fluid ounce (fl oz) = 29.57 milliliters (mL)

1 pint (pt) = 473.2 milliliters (mL)

1 US gallon = 3.78 liters (L)

1 Canadian gallon = 4.55 liters (L)

0.1 milligram = 1/650 grain

0.12 milligram = 1/540 grain

0.15 milligram = 1/430 grain

0.2 milligram = 1/320 grain

0.3 milligram = 1/220 grain

0.4 milligram = 1/160 grain

0.5 milligram = 1/130 grain

0.6 milligram = 1/110 grain

0.8 milligram = 1/80 grain

1 milligram = 1/65 grain

▶ *Metric Length Conversion Equivalents*

2.54 cm = 1 inch

30.48 cm = 1 foot

1 m = 3.28 feet

1.6 km = 1 mile

ANTHROPOMETRICS

Creatinine Clearance Formulas

▶ *Formulas for Estimating Creatinine Clearance in Patients with Stable Renal Function*

Cockcroft-Gault Formula

Adults (age 18 years and older)[1]:

$$\text{CrCl (men)} = \frac{(140 - \text{age}) \times \text{weight}}{\text{SCr} \times 72}$$

$$\text{CrCl (women)} = 0.85 \times \text{above value}^*$$

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*Some studies suggest that the predictive accuracy of this formula for women is better *without* the correction factor of 0.85.

where CrCl is creatinine clearance (in mL/min), SCr is serum creatinine (in mg/dL [or µmol/L divided by 88.4]), age is in years, and weight is in kilograms.

Traub-Johnson Formula

Children (age 1–18 years)[2]:

$$\text{CrCl} = \frac{0.48 \times \text{height} \times \text{BSA}}{\text{SCr} \times 1.73}$$

where BSA is body surface area (in m^2), CrCl is creatinine clearance (in mL/min), SCr is serum creatinine (in mg/dL [or µmol/L divided by 88.4]), and height is in centimeters.

▸ *Formula for Estimating Creatinine Clearance from a Measured Urine Collection*

$$\text{CrCl (mL/min)} = \frac{U \times V}{P \times T}$$

where U is the concentration of creatinine in a urine specimen in mg/dL, V is the volume of urine in mL, P is the concentration of creatinine in serum at the midpoint of the urine collection period in mg/dL, and T is the time of the urine collection period in minutes (eg, 6 hours = 360 minutes; 24 hours = 1440 minutes). Procedures for obtaining urine specimens should stress the importance of complete urine collection during the collection time period.

▸ *IDMS-Traceable MDRD Equation (Used for Creatinine Methods with Calibration Traceable to IDMS)*

For creatinine in mg/dL:

$$X = 175 \times \text{creatinine}^{-1.154} \times \text{age}^{-0.203} \times \text{constant}$$

For creatinine in µmol/L:

$$X = 175 \times (\text{creatinine}/88.4)^{-1.154} \times \text{age}^{-0.203} \times \text{constant}$$

where X is the glomerular filtration rate, constant for white men is 1 and for women is 0.742, and constant for African Americans is 1.212.

Ideal Body Weight

IBW is the weight expected for a non-obese person of a given height. The IBW formulas below and various life insurance tables can be used to estimate IBW. Dosing methods described in the literature may use IBW as a method in dosing obese patients.

Adults (age 18 years and older)[3]:

$$\text{IBW (men)} = 50 + (2.3 \times \text{height in inches over 5 ft})$$
$$\text{IBW (women)} = 45.5 + (2.3 \times \text{height in inches over 5 ft})$$

where IBW is in kilograms.

Children (age 1–18 years)[2] under 5-feet tall:

$$\text{IBW} = \frac{\text{height}^2 \times 1.65}{1000}$$

where IBW is in kilograms and height is in centimeters.

Children (age 1–18 years) 5 feet or taller:

$$\text{IBW (males)} = 39 + (2.27 \times \text{height in inches over 5 ft})$$
$$\text{IBW (females)} = 42.2 + (2.27 \times \text{height in inches over 5 ft})$$

where IBW is in kilograms.

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Appendix C: Common Medical Abbreviations

These are the abbreviations used commonly in medical practice both in verbal communication and in the medical record.

A&O	alert and oriented
A&O×3	awake (or alert) and oriented to person, place, and time
A&O×4	awake (or alert) and oriented to person, place, time, and situation
A&P	active and present; anterior and posterior; assessment and plans; auscultation and percussion
A&W	alive and well
A1c	hemoglobin A1c
AA	aplastic anemia; Alcoholics Anonymous
AAA	abdominal aortic aneurysm
AAO	awake, alert, and oriented
AAO×3	awake and orientated to time, place, and person
ABC	absolute band counts; absolute basophil count; apnea, bradycardia, and cytology; aspiration, biopsy, and cytology; artificial beta cells
Abd	abdomen
ABG	arterial blood gases
ABO	blood group system (A, AB, B, and O)
ABP	arterial blood pressure
ABW	actual body weight
ABx	antibiotics
AC	before meals (*ante cibos*)
ACE	angiotensin-converting enzyme
ACE-I	angiotensin-converting enzyme inhibitor
ACLS	advanced cardiac life support
ACS	acute coronary syndromes
ACTH	adrenocorticotropic hormone
AD	Alzheimer disease; right ear (*auris dextra*)
ADA	American Diabetes Association; adenosine deaminase
ADE	adverse drug effect (or event)
ADH	antidiuretic hormone
ADHD	attention-deficit hyperactivity disorder
ADL	activities of daily living
ADR	adverse drug reaction
AF	atrial fibrillation
AFB	acid-fast bacillus; aortofemoral bypass; aspirated foreign body
AFEB	afebrile
AI	aortic insufficiency
AIDS	acquired immune deficiency syndrome
AKA	above-knee amputation; alcoholic ketoacidosis; all known allergies; also known as
AKI	acute kidney injury
ALFT	abnormal liver function test
ALL	acute lymphoblastic leukemia; acute lymphocytic leukemia
ALP	alkaline phosphatase
ALS	amyotrophic lateral sclerosis
ALT	alanine transaminase (SGPT); alanine aminotransferase
AMA	against medical advice; American Medical Association; antimitochondrial antibody
AMI	acute myocardial infarction
AML	acute myelogenous leukemia
Amp	ampule
ANA	antinuclear antibody
ANC	absolute neutrophil count
ANLL	acute nonlymphocytic leukemia
AODM	adult-onset diabetes mellitus
AOM	acute otitis media
AP	anteroposterior
APAP	acetaminophen (acetyl-*p*-aminophenol)
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
ARC	AIDS-related complex
ARD	acute respiratory disease; adult respiratory disease; antibiotic removal device; aphakic retinal detachment
ARDS	adult respiratory distress syndrome
ARF	acute renal failure; acute respiratory failure; acute rheumatic fever
AROM	active range of motion
AS	left ear (*auris sinistra*)
ASA	aspirin (acetylsalicylic acid)
ASCVD	arteriosclerotic cardiovascular disease
ASD	atrial septal defect
ASH	asymmetric septal hypertrophy
ASHD	arteriosclerotic heart disease
AST	aspartate transaminase (SGOT); aspartate aminotransferase
ATG	antithymocyte globulin
ATN	acute tubular necrosis
AU	each ear (*auris uterque*)
AV	arteriovenous; atrioventricular; auditory visual
AVR	aortic valve replacement
BBB	bundle branch block; blood–brain barrier
BC	blood culture
BCOP	Board Certified Oncology Pharmacist
BCP	birth control pill
BCPP	Board Certified Psychiatric Pharmacist
BCPS	Board Certified Pharmacotherapy Specialist
BE	barium enema
BG	blood glucose
bid	twice daily (*bis in die*)
BKA	below-knee amputation
BM	bone marrow; bowel movement; an isoenzyme of creatine phosphokinase
BMC	bone marrow cells
BMD	bone mineral density
BMI	body mass index

BMP	basic metabolic panel
BMR	basal metabolic rate
BMT	bone marrow transplantation
BP	blood pressure
BPD	bronchopulmonary dysplasia
BPH	benign prostatic hyperplasia
bpm	beats per minute
BR	bed rest
BS	bowel sounds; breath sounds; blood sugar
BSA	body surface area
BUN	blood urea nitrogen
Bx	biopsy
C&S	culture and sensitivity
CA	cancer; calcium
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CAH	chronic active hepatitis
CAM	complementary and alternative medicine
CAPD	continuous ambulatory peritoneal dialysis
CBC	complete blood count
CBD	common bile duct
CBG	capillary blood gas; corticosteroid-binding globulin
CC	chief complaint
CCA	calcium channel antagonist
CCB	calcium channel blocker
CCE	clubbing, cyanosis, edema
CCK	cholecystokinin
CCU	coronary care unit
CF	cystic fibrosis
CFS	chronic fatigue syndrome
CFU	colony-forming unit
CHD	coronary heart disease
CHF	chronic heart failure
CHO	carbohydrate
CI	cardiac index
CIWA	Clinical Institute Withdrawal Assessment
CK	creatine kinase
CKD	chronic kidney disease
CLL	chronic lymphocytic leukemia
CM	costal margin
CMG	cystometrogram
CML	chronic myelogenous leukemia
CMV	cytomegalovirus
CN	cranial nerve
CNS	central nervous system
C/O	complains of
CO	cardiac output; carbon monoxide
COLD	chronic obstructive lung disease
COPD	chronic obstructive pulmonary disease
CP	chest pain; cerebral palsy
CPAP	continuous positive airway pressure
CPK	creatine phosphokinase (BB, MB, and MM are isoenzymes)
CPP	cerebral perfusion pressure
CPR	cardiopulmonary resuscitation
CrCl	creatinine clearance
CRF	chronic renal failure; corticotropin-releasing factor
CRH	corticotropin-releasing hormone
CRI	chronic renal insufficiency; catheter-related infection
CRNA	Certified Registered Nurse Anesthetist
CRNP	Certified Registered Nurse Practitioner
CRP	C-reactive protein
CRTT	Certified Respiratory Therapy Technician
CSF	cerebrospinal fluid; colony-stimulating factor
CT	computed tomography; chest tube
cTnI	cardiac troponin I
CTZ	chemoreceptor trigger zone
CV	cardiovascular
CVA	cerebrovascular accident
CVC	central venous catheter
CVP	central venous pressure
Cx	culture; cervix
CXR	chest x-ray
CYP	cytochrome P450
D&C	dilatation and curettage
D_5W	5% dextrose in water
DBP	diastolic blood pressure
D/C	discontinue; discharge
DCC	direct-current cardioversion
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
Diff	differential
DJD	degenerative joint disease
DKA	diabetic ketoacidosis
dL	deciliter
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DNR	do not resuscitate
DO	Doctor of Osteopathy
DOA	dead on arrival; date of admission; duration of action
DOB	date of birth
DOE	dyspnea on exertion
DOT	directly observed therapy
DPGN	diffuse proliferative glomerulonephritis
DPI	dry powder inhaler
DRE	digital rectal examination
DRG	diagnosis-related group
DS	double strength
d/t	due to
DTP	diphtheria–tetanus–pertussis
DTR	deep tendon reflex
DVT	deep vein thrombosis
Dx	diagnosis
EBV	Epstein-Barr virus
EC	enteric coated
ECF	extracellular fluid
ECG	electrocardiogram
ECHO	echocardiogram
ECT	electroconvulsive therapy
ED	emergency department
EEG	electroencephalogram
EENT	eyes, ears, nose, throat
EF	ejection fraction
EGD	esophagogastroduodenoscopy
EIA	enzyme immunoassay
ECG	electrocardiogram
EMG	electromyogram
EMT	Emergency Medical Technician
Endo	endotracheal, endoscopy
EOMI	extraocular movements (or muscles) intact
EPO	erythropoietin
EPS	extrapyramidal symptoms
ER	emergency room
ERCP	endoscopic retrograde cholangiopancreatography
ERT	estrogen replacement therapy
ESKD	end-stage kidney disease
ESLD	end-stage liver disease
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
ET	endotracheal
EtOH	ethanol
FB	finger breadth; foreign body
FBS	fasting blood sugar
FDA	Food and Drug Administration

FEF	forced expiratory flow rate
FEV$_1$	forced expiratory volume in 1 second
FFP	fresh-frozen plasma
FH	family history
FiO$_2$	fraction of inspired oxygen
FOBT	fecal occult blood test
FPG	fasting plasma glucose
FPIA	fluorescence polarization immunoassay
FSH	follicle-stimulating hormone
FTA	fluorescent treponemal antibody
FT$_4$	free thyroxine
F/U	follow-up
FUO	fever of unknown origin
Fx	fracture
g	gram
G-CSF	granulocyte colony-stimulating factor
G6PD	glucose-6-phosphate dehydrogenase
GB	gallbladder
GBS	group B *Streptococcus*; Guillain-Barre syndrome
GC	gonococcus
GDM	gestational diabetes mellitus
GE	gastroesophageal; gastroenterology
GERD	gastroesophageal reflux disease
GFR	glomerular filtration rate
GGT	γ-glutamyl transferase
GGTP	γ-glutamyl transpeptidase
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
GN	glomerulonephritis; graduate nurse
gr	grain
GT	gastrostomy tube
gtt	drops (*guttae*)
GTT	glucose tolerance test
GU	genitourinary
GVHD	graft-versus-host disease
GVL	graft-versus-leukemia
Gyn	gynecology
H&H, H/H	hemoglobin and hematocrit
H&P	history and physical examination
HA	headache
HAART	highly active antiretroviral therapy
HAMD	Hamilton Rating Scale for Depression
HAV	hepatitis A virus
Hb, hgb	hemoglobin
HbAlc	glycosylated hemoglobin (hemoglobin Alc)
HBIG	hepatitis B immune globulin
HBP	high blood pressure
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HC	hydrocortisone, home care
HCG	human chorionic gonadotropin
HCO$_3$	bicarbonate
Hct	hematocrit
HCTZ	hydrochlorothiazide
HCV	hepatitis C virus
HD	Hodgkin disease; hemodialysis
HDL	high-density lipoprotein
HEENT	head, eyes, ears, nose, and throat
HF	heart failure
HFA	hydrofluoroalkane
H flu	*Hemophilus influenzae*
HGH	human growth hormone
HH	hiatal hernia
Hib	*Hemophilus influenzae* type b
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HJR	hepatojugular reflux
HLA	human leukocyte antigen; human lymphocyte antigen
HMG-CoA	hydroxy-methylglutaryl coenzyme A
H/O	history of
HOB	head of bed
HPA	hypothalamic–pituitary axis
hpf	high-power field
HPI	history of present illness
HR	heart rate
H$_2$RA	H$_2$ receptor antagonist
HRSD	Hamilton Rating Scale for Depression
HRT	hormone-replacement therapy
HS	at bedtime (*hora somni*)
HSV	herpes simplex virus
HTN	hypertension
Hx	history
I&D	incision and drainage
I&O, I/O	intake and output
IBD	inflammatory bowel disease
IBW	ideal body weight
ICD	implantable cardioverter defibrillator
ICP	intracranial pressure
ICS	intercostal space; inhaled corticosteroid
ICU	intensive care unit
ID	identification; infectious disease
IDDM	insulin-dependent diabetes mellitus
IFN	interferon
Ig	immunoglobulin
IgA	immunoglobulin A
IgD	immunoglobulin D
IHD	ischemic heart disease
IJ	internal jugular
IM	intramuscular; infectious mononucleosis
INH	isoniazid
INR	international normalized ratio
IOP	intraocular pressure
IP	intraperitoneal
IPG	impedance plethysmography
IPN	interstitial pneumonia
IRB	institutional review board
ISA	intrinsic sympathomimetic activity
ISH	isolated systolic hypertension
IT	intrathecal
ITP	idiopathic thrombocytopenic purpura
IU	international units (this can be dangerous abbreviation because it may be read as "IV" for "intravenous")
IUD	intrauterine device
IV	intravenous; Roman numeral four; symbol for class 4 controlled substances
IVC	inferior vena cava; intravenous cholangiogram
IVDA	intravenous drug abuse
IVDU	injection drug use; intravenous drug use
IVF	intravenous fluids
IVIG	intravenous immunoglobulin
IVP	intravenous pyelogram; intravenous push
JODM	juvenile-onset diabetes mellitus
JRA	juvenile rheumatoid arthritis
JVD	jugular venous distension
JVP	jugular venous pressure
K	potassium
kcal	kilocalorie
KCl	potassium chloride
KOH	potassium hydroxide
KUB	kidney, ureter, and bladder
KVO	keep vein open
L	liter
LABA	long-acting beta agonist

LAD	left anterior descending; left axis deviation
LAO	left anterior oblique
LBBB	left bundle branch block
LBP	low-back pain
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LE	lower extremity
LES	lower esophageal sphincter
LFT	liver function test
LHRH	luteinizing hormone-releasing hormone
LLE	left lower extremity
LLL	left lower lobe
LLQ	left lower quadrant (abdomen)
LMD	local medical doctor
LMP	last menstrual period
LMWH	low-molecular-weight heparin
LOS	length of stay
LP	lumbar puncture
LPN	Licensed Practical Nurse
LPT	Licensed Physical Therapist
LR	lactated Ringer's
LS	lumbosacral
LT_4	levothyroxine
LUE	left upper extremity
LUL	left upper lobe
LUQ	left upper quadrant
LUTS	lower urinary tract symptoms
LVH	left ventricular hypertrophy
MAP	mean arterial pressure
MAR	medication administration record
MB-CK	a creatine kinase isoenzyme
mcg	microgram
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MD	Medical Doctor
MDI	metered-dose inhaler
MDRD	modification of diet in renal disease
MEFR	maximum expiratory flow rate
mEq	milliequivalent
mg	milligram
MHC	major histocompatibility complex
MI	myocardial infarction; mitral insufficiency
MIC	minimum inhibitory concentration
mL	milliliter
MM	multiple myeloma; an isoenzyme of creatine phosphokinase
MMR	measles–mumps–rubella; midline malignant reticulosis
MOM	milk of magnesia
MPV	mean platelet volume
m/r/g	murmur/rub/gallop
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MRSE	methicillin-resistant *Staphylococcus epidermitis*
MS	mental status; mitral stenosis; musculoskeletal; multiple sclerosis; morphine sulfate
MSE	mental status exam
MSW	Master of Social Work
MTD	maximum tolerated dose
MTX	methotrexate
MVA	motor vehicle accident
MVI	multivitamin
MVR	mitral valve replacement; mitral valve regurgitation
MVS	mitral valve stenosis; motor, vascular, and sensory

N&V	nausea and vomiting
NAD	no acute (or apparent) distress
N/C	noncontributory; nasal cannula
NG	nasogastric
NGT	nasogastric tube; normal glucose tolerance
NIDDM	non–insulin-dependent diabetes mellitus
NIH	National Institutes of Health
NKA	no known allergies
NKDA	no known drug allergies
NHDA	nonketotic hyperosmolar acidosis
NL	normal
NOS	not otherwise specified
NPN	nonprotein nitrogen
NPO	nothing by mouth (*nil per os*)
NS	normal saline solution (0.9% sodium chloride solution); neurosurgery
NSAID	nonsteroidal anti-inflammatory drug
NSR	normal sinus rhythm
NSS	normal saline solution
NTG	nitroglycerin
NT/ND	nontender, nondistended
NVD	nausea/vomiting/diarrhea; neck vein distension; neovascularization of the disk; neurovesicle dysfunction; nonvalvular disease
N&V	nausea and vomiting
NYHA	New York Heart Association
O&P	ova and parasites
OA	osteoarthritis
OB	obstetrics
OCD	obsessive-compulsive disorder
OD	right eye (*oculus dexter*)
OGTT	oral glucose tolerance test
OPV	oral poliovirus vaccine
OR	operating room
OR×1	oriented to time
OR×2	oriented to time and place
OR×3	oriented to time, place, and person
OS	left eye (*oculus sinister*)
OSA	obstructive sleep apnea
OT	occupational therapy
OTC	over the counter
OU	each eye (*oculus uterque*)
P	pulse; plan; percussion; pressure
P&A	percussion and auscultation
P&T	peak and trough
PA	physician assistant; posteroanterior; pulmonary artery
PAC	premature atrial contraction
Paco_2	arterial carbon dioxide tension
Pao_2	arterial oxygen tension
PAOP	pulmonary artery occlusion pressure
PC	after meals (*post cibum*)
PCA	patient-controlled analgesia
PCI	percutaneous coronary intervention
PCKD	polycystic kidney disease
PCN	penicillin
PCP	*Pneumocystis carinii* pneumonia (also known as *Pneumocystis jirovecii* pneumonia); pneumocystis pneumonia; primary care physician; phencyclidine
PCWP	pulmonary capillary wedge pressure
PDE	paroxysmal dyspnea on exertion
PE	physical examination; pulmonary embolism
PEEP	positive end-expiratory pressure
PEFR	peak expiratory flow rate

PEG	percutaneous endoscopic gastrostomy; polyethylene glycol
Peg-IFN	pegylated interferon
PERL	pupils equal, reactive to light
PERRLA	pupils equal, round, and reactive to light and accommodation
PERRRLA	pupils equal, round, regular, and reactive to light and accommodation
PET	positron emission tomography
PFT	pulmonary function test
pH	hydrogen ion concentration
PH	past history; personal history; pinhole; poor health; pubic hair; public health
PHx	past history
PharmD	Doctor of Pharmacy
PID	pelvic inflammatory disease
PJD	*Pneumocystis jirovecii* pneumonia (also known as *Pneumocystis carinii* pneumonia)
PKU	phenylketonuria
PMH	past medical history
PMI	past medical illness; point of maximal impulse
PMN	polymorphonuclear leukocyte
PMS	premenstrual syndrome
PND	paroxysmal nocturnal dyspnea
Po	by mouth (*per os*)
Po$_2$	partial pressure of oxygen
POAG	primary open-angle glaucoma
POD	postoperative day
PPBG	postprandial blood glucose
ppd	packs per day
PPI	proton pump inhibitor
PPN	peripheral parenteral nutrition
PR	per rectum
PRBC	packed red blood cell
PRERLA	pupils round, equal, reactive to light and accommodation
PRN	when necessary, as needed (*pro re nata*)
PSA	prostate-specific antigen
PSH	past surgical history
PST	paroxysmal supraventricular tachycardia
PSVT	paroxysmal supraventricular tachycardia
PT	prothrombin time; physical therapy; patient
PTA	prior to admission; percutaneous transluminal angioplasty
PTCA	percutaneous transluminal coronary angioplasty
PTE	pulmonary thromboembolism
PTH	parathyroid hormone
PTSD	posttraumatic stress disorder
PTT	partial thromboplastin time
PUD	peptic ulcer disease
PVC	premature ventricular contraction
PVD	peripheral vascular disease
PVR	peripheral vascular resistance
PVT	paroxysmal ventricular tachycardia
q	every (*quaque*)
QA	quality assurance
qday	every day (*quaque die*)
QI	quality improvement
qid	four times daily (*quater in die*)
QNS	quantity not sufficient
qod	every other day
QOL	quality of life
QS	quantity sufficient
QTc	corrected QT interval
R&M	routine and microscopic
R&R	rate and rhythm
RA	rheumatoid arthritis; right atrium
RAAS	renin–angiotensin–aldosterone system
RBC	red blood cell
RCA	right coronary artery
RCM	right costal margin
RDA	recommended daily allowance
RDS	respiratory distress syndrome
RDW	red blood cell distribution width
REM	rapid eye movement; recent event memory
RES	reticuloendothelial system
RF	rheumatoid factor; renal failure; rheumatic fever
Rh	rhesus factor in blood
RHD	rheumatic heart disease
RLE	right lower extremity
RLL	right lower lobe
RLQ	right lower quadrant
RML	right middle lobe
RN	Registered Nurse
RNA	ribonucleic acid
R/O	rule out
ROM	range of motion
ROS	review of systems
RPh	Registered Pharmacist
RR	respiratory rate; recovery room
RRR	regular rate and rhythm
RRT	Registered Respiratory Therapist
RSV	respiratory syncytial virus
RT	radiation therapy
RUE	right upper extremity
RUL	right upper lobe
RUQ	right upper quadrant
RVH	right ventricular hypertrophy
S$_1$	first heart sound
S$_2$	second heart sound
S$_3$	third heart sound (ventricular gallop)
S$_4$	fourth heart sound (atrial gallop)
SA	sinoatrial
SABA	short-acting beta agonist
SAD	seasonal affective disorder
SAH	subarachnoid hemorrhage
Sao$_2$	arterial oxygen percent saturation
SBE	subacute bacterial endocarditis
SBFT	small bowel follow-through
SBGM	self-blood glucose monitoring
SBO	small bowel obstruction
SBP	systolic blood pressure
SC	subcutaneous; subclavian
SCr	serum creatinine
SEM	systolic ejection murmur
SG	specific gravity
SGOT (AST)	serum glutamic oxaloacetic transaminase (aspartate transaminase)
SGPT (ALT)	serum glutamic pyruvic transaminase (alanine transaminase)
SH	social history
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SIDS	sudden infant death syndrome
SJS	Stevens-Johnson syndrome
SL	sublingual
SLE	systemic lupus erythematosus
SMA-6	sequential multiple analyzer for sodium, potassium, CO$_2$, chloride, glucose, and BUN
SMA-7	sequential multiple analyzer for sodium, potassium, CO$_2$, chloride, glucose, BUN, and creatinine
SMA-12	sequential multiple analyzer for glucose, BUN, uric acid, calcium, phosphorous, total protein, albumin, cholesterol, total bilirubin, alkaline phosphatase, SGOT, and LDH

SMA-23	includes the entire SMA-12 plus sodium, potassium, CO_2, chloride, direct bilirubin, triglyceride, SGPT, indirect bilirubin, R fraction, and BUN/creatinine ratio
SMBG	self-monitoring of blood glucose
SNF	skilled nursing facility
SNS	sympathetic nervous system
SOB	shortness of breath; see order book; side of bed
S/P	status post
SPF	sun protection factor
SQ	subcutaneous
SSKI	saturated solution of potassium iodide
SSRI	selective serotonin reuptake inhibitor
STAT	immediately; at once
STEMI	ST-segment elevated myocardial infarction
STD	sexually transmitted disease
SV	stroke volume
SVC	superior vena cava
SVRI	systemic vascular resistance index
SVR	supraventricular rhythm; systemic vascular resistance
SVT	supraventricular tachycardia
SW	social worker
Sx	signs
T	temperature
T_3	triiodothyroxine
T_4	thyroxine
T&A	tonsillectomy and adenoidectomy
T&C	type and crossmatch
TB	tuberculosis
TBG	thyroid-binding globulin
TBI	total-body irradiation; traumatic brain injury
TBW	total body weight
T bili	total bilirubin
TCA	tricyclic antidepressant
TCN	tetracycline
Tdap	tetanus, diphtheria, acellular pertussis vaccine
TEE	transesophageal echocardiogram
TFT	thyroid function test
TG	triglyceride
TIA	transient ischemic attack
TIBC	total iron-binding capacity
tid	three times daily (*ter in die*)
TLC	therapeutic lifestyle changes
TMJ	Temporomandibular joint
TMP-SMX	trimethoprim–sulfamethoxazole
TNTC	too numerous to count
TOD	target organ damage
TPN	total parenteral nutrition
TPR	temperature, pulse, respiration
T PROT	total protein
TSH	thyroid-stimulating hormone
TURP	transurethral resection of the prostate
Tx	treat, treatment
UA	urinalysis, uric acid
UC	ulcerative colitis
UE	upper extremity
UFH	unfractionated heparin
UGI	upper gastrointestinal
UOQ	upper outer quadrant
UPT	urine pregnancy test
URI	upper respiratory infection
USP	United States Pharmacopeia
UTI	urinary tract infection
UV	ultraviolet
VF	ventricular fibrillation
VLDL	very low-density lipoprotein
VO	verbal order
VOD	veno-occlusive disease
V_A/Q	ventilation–perfusion
VRE	vancomycin-resistant Enterococcus
VS	vital signs
VSS	vital signs stable
VT	ventricular tachycardia
VTE	venous thromboembolism
WA	while awake
WBC	white blood cell (count)
W/C	wheelchair
WDWN	well-developed, well-nourished
WHO	World Health Organization
WNL	within normal limits
W/U	workup
yo	year old
y	year

Appendix D: Glossary

2,3-Diphosphoglycerate: A compound in red blood cells that affects oxygen binding to and release from hemoglobin.

Ablation: Destruction of part or all of an organ or structure.

Acanthosis nigricans: Dark patches of skin with a thick, velvety texture; increased thickness and hyperpigmentation of the outer cell layers of the skin; typically observed at areas of flexure. Most commonly found in those who are overweight, have darker skin, and/or have diabetes or prediabetic conditions.

Acaricide: A chemical that kills mites and ticks.

Acetylcholine: Neurotransmitter at synapses in the ganglia of the visceral motor system and a variety of sites within the central nervous system.

Achalasia: Disorder in which the esophageal sphincter is impaired, preventing normal swallowing and often causing reflux of contents and a feeling that something is caught in the throat.

Achlorhydria: Absence of free hydrochloric acid in the stomach.

Acinar cells: The cells in the pancreas responsible for the synthesis, secretion, and storage of certain digestive enzymes.

Action potential: A rapid change in the polarity of the voltage of a cell membrane from negative to positive and back to negative; a wave of electrical discharge that travels across a cell membrane.

Acute coronary syndromes: Ischemic chest discomfort at rest most often accompanied by ST-segment elevation, ST-segment depression, or T-wave inversion on the 12-lead electrocardiogram; caused by plaque rupture and partial or complete occlusion of the coronary artery by thrombus. Acute coronary syndromes include myocardial infarction and unstable angina.

Acute interstitial nephritis: An acute inflammation of the kidney, often due to drugs; patients commonly present with fever, rash, and peripheral eosinophilia.

Acute rheumatic fever: Post-streptococcal immune sequelae occurring 2 to 3 weeks following inadequately treated throat infection with group A *Streptococcus*.

Addiction: A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. Characterized by behaviors such as impaired control over substance use, compulsive use, continued use despite harm, and craving.

Adenoma: A nonmalignant tumor of the epithelial tissue that is characterized by glandular structures.

Adenomatous polyposis coli: A gene associated with familial adenomatous polyposis, an inherited disorder characterized by the development of myriad polyps in the colon, often occurring in adolescents and young adults ages 15 to 25.

Adjuvant chemotherapy: Treatment given after primary surgical treatment and designed to eliminate any remaining cancer cells that are undetectable, with the goal of improving survival.

Adjuvant therapy: Treatment that follows a definitive local therapy, usually surgery, to eradicate undetectable tumor cells and follows the primary modality with the intent of reducing the risk of disease relapse and prolonging survival. The ultimate goal is to cure patients who would not otherwise be cured by the primary modality alone.

Adrenalectomy: Surgical removal of an adrenal gland.

Adverse drug reaction: As defined by the American Society of Health-System Pharmacists, any unexpected, unintended, undesired, or excessive response to a medication that requires discontinuing the medication; changing the medication; modifying the dose (except for minor dosage adjustments); necessitates admission to the hospital; prolongs stay in a healthcare facility; necessitates supportive treatment; significantly complicates diagnosis; negatively affects prognosis; or results in temporary or permanent harm, disability, or death.

Aeroallergen: An airborne substance that causes an allergic response.

Afterload: The force against which a ventricle contracts that is contributed to by the vascular resistance, especially of the arteries, and by the physical characteristics (mass and viscosity) of the blood.

Ageism: Discrimination against aged persons.

Agoraphobia: Intense fear about situations (at least two different types) that escape would be difficult or help would be unavailable.

Air embolus: An obstruction in a small blood vessel caused by air that is introduced into a blood vessel and carried through the circulation until it lodges in a smaller vessel.

Akathisia: An extrapyramidal movement disorder presenting as a subjective sense of restlessness and difficulty in staying still (motor restlessness). Motor or subjective feelings of restlessness, often characterized by the urge to move limbs and inability to sit still.

Akinesia: Lack of movement.

Allodynia: Pain that results from a stimulus that does not normally cause pain.

Allogeneic: A transplant taking cells from one person and donating them to another.

Allograft: Tissue or organ transplanted from a donor of the same species but different genetic makeup; recipient's immune system must be suppressed to prevent rejection of the graft.

Allograft survival: After the transplant procedure, when the transplanted organ continues to have some degree of function, from excellent to poor.

Allorecognition: Recognition of the foreign antigens present on a transplanted organ or the donor's antigen presenting cells.

Alopecia: Hair loss.

α_2 autoreceptors: These adrenergic type receptors are located on norepinephrine neurons and respond to norepinephrine. These receptors function as a negative feedback loop such that stimulation inhibits the release of norepinephrine and thus blockade would result in release.

α_2 heteroreceptors: These adrenergic type receptors are located on serotonin neurons and respond to serotonin. These receptors function as a negative feedback loop such that stimulation inhibits the release of serotonin and thus blockade would result in release.

Ambulatory esophageal reflux monitoring: A telemetry capsule containing a tiny camera is swallowed, or a transnasal catheter is inserted to determine how often reflux is occurring as well as the incidence of abnormal esophageal acid exposure. The telemetry capsule provides about 48 hours of data, whereas the transnasal catheter provides about 24 hours of data.

Amenorrhea: Abnormal cessation or absence of menses; absence or discontinuation of regular menstrual periods.

Amotivation: Apathy, loss of effectiveness, and diminished capacity or willingness to carry out complex, long-term plans, endure frustration, concentrate for long periods, follow routines, or successfully master new material.

Ampulla of Vater: Dilation of the duodenal wall at the opening of the fused pancreatic and common bile ducts.

Amylin: A 37-amino acid polypeptide hormone secreted from the β-cells of the pancreas in response to nutrients. Mechanisms of action include slowing gastric emptying, suppressing postmeal glucagon secretion, and suppressing appetite.

Amyloid: Any of a group of chemically diverse proteins that are composed of linear nonbranching aggregated fibrils.

Analgosedation: A practice of utilizing analgesics first to treat pain and sedation.

Anaphylactic/anaphylaxis: Immediate, severe, potentially fatal hypersensitivity reaction induced by an antigen.

Anaphylactoid: An anaphylactic-like reaction, similar in signs and symptoms but not mediated by IgE. The drug causing this reaction produces direct release of inflammatory mediators by a pharmacological effect.

Anastomosis: A surgical connection between two structures that are not normally connected, often between two blood vessels; connection of two hollow organs to restore continuity after resection.

Androgen deprivation therapy: Agents such as LHRH agonists, GnRH antagonist, and antiandrogens that are used to suppress testosterone levels to that consistent with medical castration (testosterone levels < 50 ng/mL).

Anergy: A reduction or lack of an immune response to a specific antigen.

Aneurysm: A blood-filled bulge which forms in the wall of a weakened blood vessel; if ruptured, it may result in bleeding, shock, and/or other negative health outcome including mortality.

Angioedema: Swelling similar to urticaria (hives), but the swelling occurs beneath the skin instead of on the surface; characterized by deep swelling around the eyes and lips and sometimes of the hands and feet. If it proceeds rapidly, it can lead to airway obstruction and suffocation, and should therefore be treated as a medical emergency.

Angiogenesis: The formation of new blood vessels. Increased blood flow to deliver nutrients is required for tumor growth.

Angiography: Examination of blood vessels using X-rays after injection of a radiopaque substance.

Anosmia: Loss of smell.

Anovulatory cycle: A menstrual cycle where ovaries fail to produce, mature or release an egg.

Anterior circulation: Blood supply to the anterior section of the brain supplied by the internal carotid arteries, anterior cerebral artery, and middle cerebral artery.

Anterograde amnesia: Inability to remember new information; may be caused by neurodegenerative disorders or medications such as benzodiazepines.

Anticitrullinated protein antibodies: Antibodies directed against cyclic citrullinated peptide, a circular peptide (a ring of amino acids) containing the amino acid citrulline.

Anticoagulant: Any substance that inhibits, suppresses, or delays the formation of blood clots. These substances occur naturally and regulate the clotting cascade. Several anticoagulants have been identified in a variety of animal tissues and have been commercially developed for medicinal use.

Antinuclear antibodies: Autoantibodies that interact with components of cellular nuclei and DNA often presenting in connective tissues disorders.

Antiphospholipid syndrome: The association of thrombosis and/or pregnancy morbidity with antiphospholipid antibodies.

Antiprotease: A substance that inhibits the enzymatic activity of a protease.

Aortic dissection: A serious condition in which there is a tear in the wall of the aorta.

Aortic stenosis: A condition in which the aortic valve becomes thickened or calcified leading to a narrowing of the aortic valve opening and restriction of blood flow from the left ventricle.

Aphakic: The absence of a lens in the eye.

Aphasia: Impairment of language affecting the ability to speak and to understand speech; the loss of a previously held ability to speak or understand spoken or written language due to disease or injury of the brain.

Aphthous ulcer: A small superficial area of ulceration within the gastrointestinal mucosa, typically found in the oral cavity.

Aplasia cutis: A congenital defect consisting of circumscribed absence of skin involving usually the scalp and has been attributed to certain medications such as methimazole.

Apoptosis: Programmed cell death as signaled by the nuclei in normally functioning cells when age or state of cell health and condition dictates.

Arcuate scotoma: An arc-shaped area of blindness in the visual field.

Arteriovenous malformation: A tangle of blood vessels, usually in the brain, that results in abnormal connections between arteries and veins; if ruptured, it may result in hemorrhage.

Arthrocentesis: Puncture and aspiration of a joint. Certain drugs can be injected into the joint space for a local effect.

Ascites: Accumulation of fluid within the peritoneal cavity.

Asterixis: A flapping tremor of the arms and hands seen in patients with end-stage liver disease.

Astringent: A substance that causes tissues to constrict, resulting in a drying effect of the skin.

Atelectasis: Decreased or absent air in a partial or entire lung, with resulting loss of lung volume.

Atherosclerosis: Accumulation of lipids, inflammatory cells, and cellular debris in the subendothelial space of the arterial wall.

Atherosclerotic cardiovascular disease: Disease in which plaque builds up in vessels.

Atopic march: Describes the development of allergic diseases (eg, atopic dermatitis, allergic rhinitis, asthma) that often start at a young age.

Atopy: A genetic predisposition to develop allergic diseases.

Atresia: Congenital absence of a normal opening or normally patent lumen.

Atrial depolarization: Change in the membrane potential of an atrial myocyte, resulting in loss of polarization. Under normal conditions, depolarization of atrial myocytes is followed by atrial contraction.

Atrophic urethritis: Thinning and inflammation of the vaginal walls secondary to decline in estrogen, experienced by almost 50% of postmenopausal women.

Atypical femoral fracture: Stress fracture occurring in the long straight portion of the femur.

Augmentation: A complication in which symptoms worsen from dopaminergic therapy in restless legs syndrome.

Aura: Visual, but sometimes sensory, motor, or verbal disturbance usually occurring before a migraine or seizure.

Auspitz sign: Pinpoint bleeding that occurs when a psoriasis scale or lesion is peeled off of the skin.

Autologous: A transplant using one's own stem cells.

Avolition: Loss of motivation.

Azoospermic: Having no living spermatozoa in the semen, or failure of spermatogenesis.

Barium enema: A diagnostic test using an X-ray to view the lower gastrointestinal tract (colon and rectum) after rectal administration of barium sulfate, a chalky liquid contrast medium.

Barrett esophagus: A change of the normal squamous epithelium of the distal esophagus to a metaplastic, columnar-lined epithelium, usually caused by prolonged exposure of the esophageal mucosa to gastric acid. The condition is associated with an increased risk of developing esophageal cancer.

Basal Ganglia: Cluster of nerve cells deep in the brain that coordinate normal movement.

Bence-Jones proteins: Light-chained immunoglobulins found in the urine.

β-hydroxybutyric acid: A ketone body that is elevated in ketosis is synthesized in the liver from acetyl-coenzyme A and can be used as an energy source by the brain when blood glucose is low.

B_2 microglobulin: A low molecular weight protein that may be elevated in multiple myeloma.

Bilateral learning: Learning relationship where two people can simultaneously learn from each other.

Bilateral salpingo-oophorectomy: Surgical excision (removal) of both ovaries and the fallopian tubes.

Bile acids: The organic acids in bile, the yellowish-brown or green fluid secreted by the liver and discharged into the duodenum where it aids in the emulsification of fats, increases peristalsis, and retards putrefaction.

Biliary sludge: A deposit of tiny stones or crystals made up of cholesterol, calcium bilirubinate, and other calcium salts. The cholesterol and calcium bilirubinate crystals in biliary sludge can lead to gallstone formation.

Biopsy: The removal of cells or tissue for examination.

Bladder hypotonicity: Low elastic tension of the bladder.

Blast: An immature cell.

Blood urea nitrogen (BUN): A waste product in the blood produced from the breakdown of dietary proteins. The kidneys filter blood to remove urea and maintain homeostasis; a decline in kidney function results in an increase in BUN.

Body habitus: Body physique or build; describes the physical characteristics of the individual.

Body mass index: A calculation utilized to correct weight changes for height and is a direct calculation regardless of gender. It is the result of the weight in kilograms divided by the height in meters squared. If nonmetric measurements are used, it is the result of the weight in pounds multiplied by 703 and then that quantity divided by the product of height in inches squared.

Borborygmus: Rumbling or gurgling noises in the abdomen caused by movement of gas and fluid in the intestines.

Bouchard nodes: Hard, bony enlargement of the proximal interphalangeal (middle) joint of a finger or toe.

Boutonniere deformity: Joint deformity associated with rheumatoid arthritis that presents as flexion of the proximal interphalangeal (PIP) joints with hyperextension of the distal interphalangeal (DIP) joints.

Brachial plexus: Collection of nerves that arises from the spine at the base of the neck from nerves that supply parts of the shoulder, arm, forearm, and hand.

Brachytherapy: A form of radiotherapy where a sealed radiation source is placed inside or next to the area requiring treatment.

Bradycardia: Slower than normal heart rate.

Breakpoint: In antimicrobial therapy, the concentration of the antimicrobial agent that can be achieved in serum after a normal or standard dose of that agent.

Bronchiectasis: Chronic dilation of bronchi or bronchioles as a result of inflammatory disease or obstruction associated with heavy sputum.

Bronchoscopy: A specialized procedure that inserts a lighted instrument (bronscope) through the nose or mouth and into the lungs to exam the lungs.

Bullectomy: Surgical removal of one or more bullae (air spaces in the lung measuring > 1 cm in diameter in the distended state).

Burst suppression: Electroencephalography pattern characterized by electrical brain activity alternating with periods of no activity.

Calcitonin: A hormone produced by the parafollicular cells of the thyroid gland; involved in helping regulate levels of calcium and phosphate in the blood.

Calculi: The plural of calculus; stones (eg, kidney stones).

Campylobacter: Gram-negative bacillus often associated with traveler's diarrhea.

Capillary leak: Loss of intravascular volume into the interstitial space within the body.

Carcinogenesis: Production or origin of cancer.

Carcinoma: A cancerous tumor of the epithelial tissue of an organ; a malignant growth that arises from epithelium, found in skin or the lining of body organs. Carcinomas tend to infiltrate into adjacent tissue and spread to distant organs.

Carcinomatosis: Condition of having widespread dissemination of carcinoma (cancer) in the body.

Cardiac cachexia: Physical wasting with loss of weight and muscle mass caused by cardiac disease; a wasting syndrome that causes weakness and a loss of weight, fat, and muscle.

Cardiac index: Cardiac output normalized for body surface area (cardiac index = cardiac output/body surface area).

Cardiac output: The volume of blood ejected from the left side of the heart per unit of time: Cardiac output (L/min) = Stroke volume (L) × heart rate (beats/min).

Cardiac remodeling: Genome expression resulting in molecular, cellular, and interstitial changes and manifested clinically as changes in size, shape, and function of the heart resulting from cardiac load or injury.

Cardiomyopathy: Diseases of the heart muscle in which the heart muscle becomes enlarged, thick, or rigid.

Carotid bruit: Abnormal sound heard when auscultating a carotid artery caused by turbulent blood flow, usually due to the presence of atherosclerotic plaques.

Carotids: The two main arteries in the neck.

Castration-resistant prostate cancer: Prostate cancer that continues to progress despite suppression of typical hormonal growth signals (ie, despite androgen deprivation that achieves castration levels of testosterone).

Castration-sensitive prostate cancer: Prostate cancer that is controlled by typical hormonal growth signals (ie, despite androgen deprivation that achieves castration levels of testosterone). Also often referred to as castration-naive prostate cancer.

Cataplexy: Weakness or loss of skeletal muscle tone in the jaw, legs, or arms that is elicited by emotion (eg, anger, surprise, laughter, or sadness).

Causalgia: Persistent burning pain, allodynia, and hyperpathia following a traumatic nerve lesion.

Central pain: Pain that results from a lesion or dysfunction in the central nervous system.

Cervical adenopathy: Enlargement of cervical lymph nodes in the neck.

Cervicitis: Inflammation of the cervix.

Chemokines: Any of a group of cytokines produced by various cells that stimulate chemotaxis in white blood cells.

Chemokine receptor: Transmembrane or G-protein coupled receptors that upon binding of a chemokine, initiates an intracellular immune signaling cascade.

Chemoprevention: The use of drugs, vitamins, or other agents to reduce the risk of or delay the development or recurrence of cancer; clinical application of pharmacologic agents to reduce the risk of developing certain malignancies.

Chemoprophylaxis: Use of a medication (or chemical agent) to prevent disease.

Chemoreceptor trigger zone: A location in the area postrema of the fourth ventricle of the brain. It is exposed to cerebrospinal fluid and blood and is easily stimulated by circulating toxins to induce nausea and vomiting.

Chemosis: Edema of the bulbar conjunctiva.

Cheyne-Stokes respiration: Pattern of breathing with gradual increase in depth (and sometimes in rate) to a maximum, followed by a decrease resulting in apnea; the cycles ordinarily are 30 seconds to 2 minutes in duration, with 5 to 30 seconds of apnea.

Chikungunya: Mosquito-borne disease with a clinical syndrome of systemic fevers and arthritis.

Chimeric: An individual, organ, or substance composed of substances with different genetic origins.

Chloasma: Melasma characterized by irregularly shaped brown patches on the face and other areas of the skin, often seen during pregnancy or associated with the use of oral contraceptives.

Chlorpromazine equivalents: Approximate dose equivalent of a first-generation antipsychotic to 100 mg of chlorpromazine (relative potency).

Cholangitis: Inflammation of the bile duct system.

Cholecystitis: Inflammation of the gall bladder.

Cholelithiasis: Formation of stones in the gallbladder (gallstones).

Cholestasis: Reduced or lack of flow of bile, or obstruction of bile flow.

Cholesteatoma: A mass of keratinized epithelial cells and cholesterol resembling a tumor that forms in the middle ear or mastoid region.

Chorea: A type of dyskinesia with rhythmic dance-like movement. The increase in motor activity may be associated with fidgetiness, twitching, or flinging movements.

Chronotropic: Pertaining to the heart rate.

Chvostek's sign: Elicited by tapping on the proximal distribution of the facial nerve (adjacent to the ear). This will produce a brief spasm of the upper lip, eye, nose, or face in hypocalcemic patients.

Chylothorax: The presence of lymphatic fluid (chyle) in the pleural cavity.

Circadian rhythm: Natural, internal biological process that regulates the sleep–wake cycle every 24 hours.

Cirrhosis: Hepatic fibrosis and regenerative nodules that have destroyed the architecture of the liver, scarring the liver tissues. Progressive scarring of the liver results in nonfunctional hepatocytes.

Clonal expansion: An immunologic response in which lymphocytes stimulated by antigen proliferate and amplify the population of relevant T-cells.

Closed comedo: A plugged hair follicle of sebum, keratinocytes, and bacteria that remains beneath the surface of the skin. Also referred to as a "whitehead."

Clotting cascade: A series of enzymatic reactions by clotting factors leading to formation of a blood clot. The clotting cascade is initiated by several thrombogenic substances. Each reaction in the cascade is triggered by the preceding one, and the effect is amplified by positive feedback loops.

Clotting factor: Plasma proteins found in the blood that are essential to the formation of blood clots. Clotting factors circulate in inactive forms but are activated by their predecessor in the clotting cascade or a thrombogenic substance. Each clotting factor is designated by a Roman numeral (eg, factor VII) and by the letter "a" when activated (eg, factor VIIa).

Clubbing: Proliferation of soft tissues, especially in the nail bed, which results in thickening and widening of fingers and toes.

Coalescence: Fusion of smaller lipid emulsion particles forming larger particles, resulting in destabilization of the emulsion.

Cognitive deficits: An impairment in the mental process that affects the way a person interacts with their environment.

Colonocyte: Cell lining the colonic surface.

Colonoscopy: Visual examination of the colon using a lighted, lens-equipped, flexible tube (colonoscope) inserted into the rectum.

Comedolytic: An agent that can break up or destroy a comedo.

Comorbidities: Multiple disease states occurring concurrently in one patient.

Complete response: The disappearance of all signs of cancer in response to treatment.

Complex regimen: Taking medications three or more times per day, or 12 or more doses per day.

Concreteness: Inability to think in abstract terms; may be a primary developmental defect or secondary to organic mental disorder or schizophrenia.

Congenital adrenal hyperplasia: A rare inherited condition resulting from a deficiency in cortisol and aldosterone synthesis with resulting excess androgen production; clinical presentation depends on the variant of the condition but typically manifests as abnormalities in sexual development and/or adrenal insufficiency.

Conjunctivitis: Inflammation of the conjunctiva.

Conjunctival injection: Erythema of the conjunctiva.

Conjunctivitis medicamentosa: A drug-induced form of allergic conjunctivitis resulting from overuse of topical ocular vasoconstrictors.

Consolidation therapy: Treatment given after cancer has disappeared following the initial therapy; used to kill any cancer cells that may be left in the body.

Continuous positive airway pressure (CPAP): Main therapy for obstructive sleep apnea by producing a positive pressure column in the upper airway using room air.

Cor pulmonale: Right-sided heart failure caused by lung disease.

Corneal arcus: Accumulation of lipid on the cornea.

Coronary artery bypass graft surgery: Surgical intervention to improve coronary blood flow by removing a vein from the leg and attaching one end to the aorta and the other end to the coronary artery distal to the atherosclerotic plaque. Alternatively, an artery from the inside of the chest wall may be used to bypass the coronary occlusion.

Cosyntropin: A synthetic version of adrenocorticotropic hormone.

Counterirritant: A substance that elicits a superficial inflammatory response with the objective of reducing inflammation in deeper, adjacent structures.

C-peptide: Peptide made when proinsulin is split into insulin and C-peptide. They split before proinsulin is released from endocytic vesicles within the pancreas, one C-peptide for each insulin molecule. C-peptide is the abbreviation for "connecting peptide." It is used to determine if a patient has type 1 or type 2 diabetes mellitus.

Creaming: Aggregation of lipid emulsion particles that then migrate to the surface of the emulsion, can be reversed with mild agitation.

Creatinine: A waste product in the blood produced from the breakdown of protein by-products generated by muscle in the body or ingested in the diet. The kidneys filter blood to remove creatinine and maintain homeostasis; a decline in kidney function results in an increase in creatinine.

Crepitus: A grating sound or sensation typically produced by friction between bone-on-cartilage or bone-on-bone contact.

Critical care medicine: A medical practice that deals with life-threatening disease states or syndromes.

Cross-allergenicity: Sensitivity to one drug with activity to a different drug with a similar chemical structure.

Cross-cultural: Engagement involving persons from different cultures.

Crypt abscess: Neutrophilic infiltration of the intestinal glands (crypts of Lieberkühn); a characteristic finding in patients with ulcerative colitis.

Cutis laxa: Hypereflacidity of the skin with loss of elasticity.

Cyanosis: A dark blue or purple discoloration of the skin and mucous membranes due to deficient oxygenation of the blood.

Cyclooxygenase: An enzyme that catalyzes the conversion of arachidonic acid to prostaglandins and consists of two isoforms, generally abbreviated COX-1 and COX-2.

Cystocele: Herniation (abnormal protrusion) of the urinary bladder into the vagina.

Cysts: Nodules that harden into larger, pus-filled lesions.

Cytokines: Regulatory proteins, such as interleukins and lymphokines, that are released by cells of the immune system and act as intercellular mediators in the generation of an immune response.

Cytomegalovirus (CMV) disease: The term used when patients who are already infected with CMV present with the classically associated symptoms that resemble a viral infection and may include fever, malaise, arthralgias, and others.

Cytomegalovirus (CMV) infection: The term used when a patient has anti-CMV antibodies in the blood, when CMV antigens are detected in infected cells, or when the virus is isolated from a culture.

D test: Double-disk diffusion microbiological testing that indicates the presence or absence of macrolide-induced resistance to clindamycin.

Delayed peak response: The effects of a dose of medication take longer than expected to initiate.

Deliriogenic: To cause or promote increases in delirium.

Delirium: Transient brain syndrome presenting as disordered attention, cognition, psychomotor behavior, and perception.

Delirium tremens: Symptom of alcohol withdrawal characterized by hallucinations, delirium, severe agitation, fever, elevations of blood pressure and heart rate, and possible cardiac arrhythmias.

Dendritic cells: Immune regulating cells found in body tissues that serve as antigen-presenting cells.

Dengue: Mosquito-borne disease causing systemic fevers and hematologic abnormalities.

Dennie-Morgan line: A line or fold below the lower eyelids; associated with atopy.

Dermatophyte: Any microscopic fungus that grows on the skin, scalp, and nails.

Desquamation: Peeling or shedding of the epidermis (superficial layer of the skin) in scales or flakes.

Diabetes insipidus: Polyuria due to the failure of renal tubules to reabsorb water in response to antidiuretic hormone; an uncommon disorder that occurs when the kidneys pass an abnormally large volume of urine (3–20 quarts/day versus the typical 1–2 quarts/day) that is dilute and odorless ("insipid"). It is unrelated to diabetes mellitus, although both conditions cause frequent urination and constant thirst. Individuals with diabetes insipidus have normal blood glucose levels; however, their kidneys cannot balance fluid in the body.

Diabetic ketoacidosis: Reversible but life-threatening short-term complication primarily seen in patients with type 1 diabetes caused by the relative or absolute lack of insulin that results in marked ketosis and acidosis.

Dialysate: The physiologic solution used during dialysis to remove excess fluids and waste products from the blood.

Dialysis: The process of removing fluid and waste products from the blood across a semipermeable membrane to maintain fluid, electrolyte and acid–base balance in patients with kidney failure.

Diaphoresis: Sweating or profuse perspiration, generally as a symptom of a disease or an adverse drug effect.

Diarthrodial joint: A freely moveable joint (eg, knee, shoulder). Contrast with amphiarthrodial joint (a slightly movable joint; eg, vertebral joint) and synarthrodial joint (an unmovable joint; eg, fibrous joint).

Dientamoeba fragilis: Parasitic trichomonad associated with diarrheal illness in travelers.

Diffuse alveolar hemorrhage: Bleeding into the alveolar space of the lungs, resulting in hemoptysis, anemia, and diffuse alveolar infiltrates; a rare but life-threatening manifestation of systemic lupus erythematosus.

Dilated cardiomyopathy: Ability of the heart to pump blood is decreased because the left ventricle is enlarged and weakened.

Diphasic dyskinesia: Motor fluctuations occurring while plasma levodopa concentrations are rising and when they are falling. In each dosing interval, the patient may experience improvement, dyskinesia and improvement (IDI) or dyskinesia, improvement, dyskinesia (DID).

Direct current cardioversion: The process of administering a synchronized electrical shock to the chest, the purpose of which is to simultaneously depolarize all of the myocardial cells, resulting in restoration of normal sinus rhythm.

Disease progression: In cancer, at least a 20% increase in the sum of the longest diameter of target lesions from baseline, including new lesions discovered during treatment.

Disease-free survival: Period of time from the end of treatment that the patient survives without signs or symptoms of the disease.

Disseminated erythrosquamous papules: Widespread or whole body red, scaly psoriatic lesions.

DNA mismatch repair (dMMR) genes: Genes that control an intrinsic intracellular mechanism that corrects nucleotide insertion errors made during DNA replication, by excising the mismatched base pairs that escaped correction by the proofreading activities of DNA polymerases and replacing the mismatched bases with the correct ones.

Dose density: A chemotherapy treatment plan in which drugs are given with less time between treatments than in a standard chemotherapy treatment plan.

Dravet syndrome: Previously termed severe myoclonic epilepsy of infancy. Epilepsy syndrome that begins in infancy or early childhood with features of focal or generalized seizures that start before 15 months of age.

Ductus arteriosus: Shunt connecting the pulmonary artery to the aortic arch that allows blood from the right ventricle to bypass fetal lungs.

Duodenal enterocyte: Cells lining the duodenum, which is the first of three parts of the small intestine.

Dysarthria: Speech disorder due to weakness or incoordination of speech muscles; speech is slow, weak, and imprecise.

Dysesthesia: An unpleasant abnormal sensation.

Dyskinesia: Abnormal involuntary movements, which include dystonia, chorea, and akathisia.

Dyslipidemia: Elevation of the total cholesterol, low-density lipoprotein cholesterol or triglyceride concentrations, or a decrease in high-density lipoprotein cholesterol concentration in the blood.

Dysmenorrhea: Menstrual-associated crampy pelvic pain occurring with or just prior to menses. “Primary” dysmenorrhea implies pain in the setting of normal pelvic anatomy, while “secondary” dysmenorrhea is secondary to underlying pelvic pathology.

Dyspareunia: Pain during or after sexual intercourse.

Dyspepsia: Upper abdominal symptoms that may include pain or discomfort, bloating, feeling of fullness despite little food intake, unusual fullness after meals, nausea, loss of appetite, heartburn, regurgitation of food or acid, and belching.

Dysphagia: Painful or difficult swallowing, accompanied by a sensation of food being stuck in passage.

Dysphonia: Impairment of the voice or difficulty speaking.

Dyspnea: Difficult or labored breathing.

Dystonia: Disorder presenting with involuntary muscle contractions. Dystonias can also present as slow repetitive movements or abnormal postures. This is a type of dyskinesia. The movement is slow and twisting. It may be associated with painful muscle contractions or spasms.

Ebstein anomaly: Rare heart defect where the tricuspid valve is not formed properly in utero and blood leaks back into the right atrium; congenital heart defect in which the opening of the tricuspid valve is displaced toward the apex of the right ventricle. The severity can greatly vary from person to person.

Eburnation: A condition in which bone or cartilage becomes hardened and denser.

Ecchymosis: Passage of blood from ruptured blood vessels into subcutaneous tissue causing purple discoloration of the skin.

Eclampsia: Seizures associated with high blood pressure in a pregnant woman.

Ectopic pregnancy: Presence of a fertilized ovum outside of the uterine cavity.

Effector cells: Cells that become active in response to initiation of the immune response.

Electroconvulsive therapy (ECT): Administration of electric current to the brain through electrodes placed on the head in order to induce seizure activity in the brain, used in the treatment of certain mental disorders; ECT is a form of neurostimulation therapy in which patients are administered a controlled dose of electricity to induce a short, controlled seizure. Patients are unconscious and administered neuromuscular blockers to minimize movement.

Electroencephalography: The recording of brain waves via electrodes placed on the scalp or cortex.

Embolism: The sudden blockage of a vessel caused by a blood clot or foreign material which has been brought to the site by the flow of blood.

Embolization: Process by which a blood clot or foreign material dislodges from its site of origin, flows in the blood, and blocks a distant vessel.

Endometritis: Inflammation of the endometrium.

Endoscopy: A diagnostic tool used to examine the inside of hollow organs using a lighted, flexible instrument called an endoscope; refers to procedures such as gastroscopy, duodenoscopy, colonoscopy, and sigmoidoscopy.

Endothelial cell: A single layer of cells surrounding the lumen of arteries.

Endovascular: Procedures involving insertion of a catheter containing medications or instruments into a blood vessel for the treatment of vascular disease.

End-stage liver disease: Liver failure that is usually accompanied by complications such as ascites or hepatic encephalopathy.

Entamoeba histolytica: Most common cause of amoebic diarrhea in travelers.

Enteric fever/typhoid fever: Name of clinical syndrome associated with *Salmonella typhi*.

Enterotoxigenic *E. coli*: Gram-negative bacillus most commonly associated with traveler’s diarrhea.

Enthesitis: Inflammation of the sites where tendons, ligaments, or fascia attach to bone.

Enuresis: Involuntary discharge of urine.

Eosinophilic asthma: Subgroup of asthma with elevated sputum and blood eosinophils, thickening of the basement membrane zone, and corticosteroid responsiveness. Criteria that have been used for medications to treat eosinophilic asthma include blood eosinophil count ≥ 150 cells/μL (0.150 × 10^9/L), > 300 cells/μL (0.3 × 10^9/L), or 400 cells/μL (0.4 × 10^9/L) in the past year, sputum eosinophil count ≥ 3% (0.03), and exhaled nitric oxide concentration ≥ 50 ppb.

Epilepsy: A neurological disorder characterized by recurring motor, sensory, or psychic malfunction with or without loss of consciousness or convulsive seizures.

Epistaxis: Nasal hemorrhage with blood drainage through the nostrils; a nosebleed.

Erosive esophagitis: A severe form of gastroesophageal reflux disease in which the mucous membrane lining the esophagus is inflamed with areas of erosion resulting from abnormal reflux of gastric acid.

Erythrodermic psoriasis: Generalized erythema covering nearly the entire body surface area. Fever and malaise are common and while quite rare, can be severe and even fatal; it is usually associated with a worsening of other forms of psoriasis.

Erythematous: Flushing of the skin caused by dilation of capillaries. Erythema is often a sign of inflammation and infection.

Erythropoiesis stimulating agents: Agents developed by recombinant DNA technology that have the same biological activity as endogenous erythropoietin to stimulate erythropoiesis (red blood cell production) in the bone marrow.

Erythropoietin: A hormone primarily produced by the progenitor cells of the kidney that stimulates red blood cell production in the bone marrow. Lack of this hormone leads to anemia.

Esophageal manometry: Measurement of pressures and muscle contractions in the esophagus.

Esophageal stricture: Abnormal narrowing of the esophageal lumen.

Esophageal varices: Dilated blood vessels in the esophagus.

Essential fatty acid deficiency: Deficiency of linoleic acid, linolenic acid, and/or arachidonic acid, characterized by hair loss, thinning of skin, and skin desquamation. Long-chain fatty acids include trienes (containing 3 double-bonds [e.g., 5,8, 11-eicosatrienoic acid (or Mead acid), trienoic acids]) and tetraenes (containing 4 double-bonds [e.g., arachidonic acid]). Biochemical evidence of essential fatty acid deficiency includes a triene:tetraene greater than 0.2 and low linoleic or arachidonic acid plasma concentrations.

Essential medicines list: Medicines that satisfy the priority healthcare needs of the population that are selected and placed on a list by a group convened by the World Health Organization.

Euthymia: Normal or stable mood state.

Exanthem: Eruption of the skin.

Excess body weight: Calculated as the difference between actual and ideal body weight.

Excoriation: Recurrent skin picking resulting in lesions.

Exfoliative dermatitis: Severe inflammation and peeling of the entire skin surface due to a reaction to certain drugs.

Exploratory laparotomy: Surgical incision into the abdominal cavity, performed to examine the abdominal organs and cavity in search of an abnormality and diagnosis.

Extensive colitis: Inflammation that involves the majority of the colon in patients with inflammatory bowel disease.

External beam: An external source of radiation is pointed at a particular part of the body.

Extraction ratio: Fraction of the drug entering the liver in the blood that is irreversibly removed.

Extrapyramidal symptoms: Adverse effects of medications such as phenothiazine antipsychotics; types include dystonia (involuntary muscle contractions), tardive dyskinesia (repetitive, involuntary movements), parkinsonian symptoms (akinesia and tremors), and akathisia (motor restlessness or anxiety).

Extravasation: Movement of fluid from inside a blood vessel into the surrounding tissues.

Federal poverty level: A measure of income issued every year by the US Department of Health and Human Services; used to determine eligibility for certain government assistance programs and benefits.

Felty syndrome: An extra-articular manifestation of rheumatoid arthritis associated with splenomegaly and neutropenia.

Ferritin: A protein in the body that binds to iron; most of the iron stored in the body is bound to ferritin.

Festination: Walking with short, rapid, shuffling steps.

Fibrin: An insoluble protein that is one of the principal ingredients of a blood clot. Fibrin strands bind to one another to form a fibrin mesh. The fibrin mesh often traps platelets and other blood cells.

Fibrinolysis: A normal ongoing process that dissolves fibrin and results in the removal of small blood clots; hydrolysis of fibrin.

Fibroadenoma: A benign neoplasm which commonly occurs in breast tissue and is derived from glandular epithelium.

Fibrosis: Development of fibrous connective tissue in response to injury or damage.

Fluorescence in situ hybridization (FISH): A laboratory technique used to look at genes or chromosomes in cells and tissues. Pieces of DNA that contain a fluorescent dye are made in the laboratory and added to cells or tissues on a glass slide. When these pieces of DNA bind to specific genes or areas of chromosomes on the slide, they light up when viewed under a microscope with a special light.

Fistula: Abnormal connection between two internal organs (eg, arteriovenous fistula is a connection between an artery and a vein), or between an internal organ and the exterior or skin (e.g., enterocutaneous fistula is a connection between the intestine and the skin).

Fistulogram: X-ray photograph (or radiograph) taken after injection of a contrast material or radiopaque material (material that will not allow passage of x-rays and will be visible in an x-ray photograph, or radiograph).

Flexural psoriasis: Characterized by lesions found in skin folds that tend to be erythematous plaques which are often found in the axillary, genital, perineal, intergluteal, and inframammary regions. While shiny, smooth, and deep red in color, there may be skin fissures and the absence of the silvery scales.

Flight of ideas: A nearly continuous flow of rapid speech and thought that jumps from topic to topic, usually loosely connected.

Floppy iris or small pupil syndrome: A triad of pupillary constriction, iris prolapse, and billowing, which can complicate cataract surgery.

Flow cytometry: A method of measuring the number of cells in a sample, the percentage of live cells in a sample, and certain characteristics of cells, such as size, shape, and the presence of tumor markers on the cell surface. The cells are stained with a light-sensitive dye, placed in a fluid, and passed in a stream before a laser or other type of light. The measurements are based on how the light-sensitive dye reacts to the light.

Foam cell: Lipid-laden white blood cell.

Focal seizures: Seizures that start in a small area of the brain. They may stay localized or spread to involve larger areas or the entire brain.

Forced expiratory volume in the first second (FEV_1): The volume of air that a patient can forcibly exhale in the first second of forced exhalation after taking a maximal breath.

Forced vital capacity: The maximum volume of air that can be forcibly exhaled after taking a maximal breath.

Fraction of exhaled nitric oxide (FeNO): A noninvasive test that, when elevated, is an indicator of inflammation in the airways and likely responsiveness to inhaled corticosteroids.

Frailty: Excess demand imposed on reduced capacity; a common biological syndrome in the elderly.

Frank-Starling mechanism: Increase in stroke volume in response to an increase in volume of blood filling the heart (ie, end-diastolic volume) when all other factors remain constant.

Freezing: In Parkinson disease, a sudden but temporary inability to move.

French (scale): A scale used to measure the external diameter of a feeding tube.

Frequency (urinary): Eight or more micturitions in 24 hours.

Gallstone (cholelithiasis): A solid formation in the gallbladder or bile duct composed of cholesterol and bile salts.

Gamma knife: A type of radiation therapy that targets cancer cells within the head and brain with high precision. The treatment delivers intense radiation doses to the target area while sparing surrounding tissue.

γ-Aminobutyric acid (GABA): An inhibitory neurotransmitter.

Gastric bypass: A surgical procedure for weight loss that elicits its effectiveness through malabsorption and gastric volume limitation. The procedure involves full partitioning of the proximal gastric segment into a jejunal loop.

Gastritis: Inflammation of the stomach lining.

Gastroparesis: A form of autonomic neuropathy involving nerves of the stomach. It may include nausea, vomiting, feeling full, bloating and lack of appetite, and may cause wide fluctuations in blood sugars due to insulin action and nutrient delivery not occurring at the same time.

Gastrostomy: Operative placement of a new opening into the stomach, usually associated with feeding tube placement.

Generalized seizures: A seizure where the entire cerebral cortex is involved from the onset of the seizure.

Geniculate nucleus: The portion of the brain that processes visual information from the optic nerve and relays it to the cerebral cortex.

Geriatric syndrome: Age-specific presentations or differential diagnoses, including visual and hearing impairment, malnutrition and weight loss, urinary incontinence, gait impairment and falls, osteoporosis, dementia, delirium, sleep problems, and pressure ulcers; commonly seen conditions in elder patients.

Giardia: Protozoal gastrointestinal disease acquired by ingesting contaminated water.

Gleason score: System of histological grading used in prostate cancer. Individual scores range from 2 to 5. The two highest scores from each sample are combined for a total score (up to 10). Higher scores indicate higher-grade and more aggressive tumor.

Glomerular filtration rate: The volume of plasma that is filtered by the glomerulus per unit of time, usually expressed as mL/min or mL/min/1.73 m^2 (and in some areas in SI units of mL/s or mL/s/m^2), which adjusts the value for body surface area. This is the primary index used to describe overall renal function.

Glomerulonephritis: A general term for an inflammatory disease that affects the glomerulus of the kidney and is immunologically mediated. Glomerular lesions that are characterized by the inflammation of the capillary loops of the glomerulus. These lesions are generally caused by immunologic, vascular, or idiopathic diseases and lead to high blood pressure and possible loss of kidney function.

Glucagon: Hormone involved in carbohydrate metabolism produced by the pancreas and released when glucose levels in the blood are low. When blood glucose levels decrease, the liver converts stored glycogen into glucose, which is released into the bloodstream. The action of glucagon is opposite of insulin.

Gluconeogenesis: Formation of glucose from precursors other than carbohydrates especially by the liver and kidney using amino acids from proteins, glycerol from fats, or lactate produced by muscle during anaerobic glycolysis.

Glucose 6 phosphate dehydrogenase (G6PD) deficiency: A generally asymptomatic genetic condition known to cause life-threatening hemolysis when patients are prescribed certain medications or triggers; enzymatic deficiency that may result in hemolytic anemia when exposed to substrate that is metabolized by G6PD.

Glucosuria: Presence of glucose in the urine.

Glutamate: An excitatory amino acid found in the central nervous system.

Glycogenolysis: The process by which glycogen is broken down to glucose in body tissues.

Glycoprotein: A protein containing an attached carbohydrate chain.

Goiter: An enlargement of the thyroid gland, causing a swelling in the front part of the neck.

Gonioscopy: Examination of the anterior-chamber angle. A gonioprism or Goldman lens is used to perform gonioscopic evaluation.

Grandiosity: Exaggerated sense of self-importance, ideas, plans, or abilities.

Gut-associated lymphoid tissue: Lymphoid tissue, including Peyer patches, found in the gut that are important for providing localized immunity to pathogens.

Guttate psoriasis: Characterized a heavy or light sprinkling of teardrop-like, salmon-pink papules covered with a fine scale. These lesions are found primarily on the trunk and proximal extremities.

Gynecomastia: Excessive development of breasts in males.

Harm reduction: Interventions aimed at reducing the negative health or social consequences associated with substance use.

Hashimoto Disease: Condition in which the immune system attacks the thyroid gland; may result in hypothyroidism. Symptoms may include fatigue, weight gain, pale or puffy face, feeling cold, joint and muscle pain, constipation, dry and thinning hair, heavy menstrual flow or irregular periods, depression, a slowed heart rate, and problems getting pregnant and maintaining pregnancy. Occurs more commonly in women than in men.

Health literacy: Degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions.

Heavy menstrual bleeding: Prolonged menstrual bleeding lasting more than 7 days or cyclic, heavy menstrual bleeding (> 80 mL per cycle).

Heberden nodes: Hard, bony enlargement of the distal interphalangeal (terminal) joint of a finger or toe.

Hematemesis: Vomiting of blood.

Hematochezia: Passage of stool that is bright red or maroon, usually because of bleeding from the lower gastrointestinal tract.

Hematoma: A localized swelling in an organ or soft tissue that is filled with clotted or partially clotted blood resulting from a break in a blood vessel wall.

Hemiparesis: A slight paralysis or weakness on one side of the body.

Hemisensory deficit: Loss of sensation on one side of the body.

Hemithorax: A single side of the trunk between the neck and the abdomen in which the heart and lungs are situated.

Hemolytic anemia: Low hemoglobin resulting from hemolysis of red blood cells.

Hemoptysis: The expectoration of blood or blood-tinged sputum from the larynx, trachea, bronchi, or lungs.

Heparin-induced thrombocytopenia: A clinical syndrome of IgG antibody production against the heparin-platelet factor 4 complex occurring in approximately 1% to 5% of patients exposed to either heparin or low-molecular-weight heparin. Results in excess production of thrombin, platelet aggregation, and thrombocytopenia (due to platelet clumping), often leading to venous and arterial thrombosis, amputation of extremities, and death.

Hepatic encephalopathy: Confusion and disorientation experienced by patients with advanced liver disease due to the accumulation of ammonia in the bloodstream.

Hepatic steatosis: Accumulation of fat in the liver.

Hepatocellular carcinoma: Cancer of the liver.

Hepatorenal syndrome: Acute kidney injury occurring in individuals with disease of the liver or biliary tract due to decreased renal blood flow and conditions that damage both organs.

Hepatotoxicity: Toxicity to the liver causing damage to liver cells.

HER2 positive: Tumor positivity is defined by IHC (3+ when > 10% of the cells harbor complete membrane staining) and FISH (if the number of HER2 gene copies is ≥ 6, or the HER2/chromosome 17 ratio is ≥ 2).

Herniation: Abnormal protrusion of an organ through a defect or natural opening; for example, protrusion of the brain through the cranial wall.

Hesitancy (urinary): A decrease in the force of the stream of urine (usually the result of an obstruction or stricture between the bladder and the external urethral orifice).

Heterotopic: Placing a transplanted organ into an abnormal anatomic location.

Heterozygous: Having different alleles at a gene locus.

Hiatal hernia: Protrusion of a portion of the stomach through the esophageal hiatus of the diaphragm.

Hirsutism: Excessive body and facial hair, especially in a female.

Homeostenosis: Impaired capability to withstand stressors and decreased ability to maintain physiological and psychosocial homeostasis; a state commonly found in elderly.

Homozygous: Having identical alleles at a gene locus.

Hormone receptor positive: Expression of estrogen and/or progesterone receptors in breast cancer cells.

Hot flashes: A feeling of warmth that is commonly accompanied by skin flushing and mild-to-severe perspiration.

Human leukocyte antigens (HLA): Groups of genes found on the major histocompatibility complex that contain cell-surface antigen presenting proteins. The body uses HLA to distinguish between self cells and non–self cells.

Humoral: A substance that acts as a result of contact with targets for activity through blood or body fluids.

Hydronephrosis: Swelling of the renal pelvis and calyces of the kidney due to a back-up of urine due to obstruction.

Hyperalgesia: An exaggerated intensity of pain sensation.

Hypercalcemia: Excessive amount of calcium in the blood.

Hypercalciuria: Excessive amount of calcium in the urine.

Hypercapnia: Excessive carbon dioxide in the bloodstream, typically caused by inadequate respiration.

Hypercoagulable state: A disorder or state of excessive or frequent thrombus formation; also known as thrombophilia.

Hyperemesis gravidarum: A rare disorder of severe and persistent nausea and vomiting during pregnancy that can result in dehydration, malnutrition, weight loss, and hospitalization.

Hyperopia: Farsightedness.

Hyperglycemic hyperosmolar nonketotic syndrome: Severe increase in serum glucose concentration without the production of ketones, leading to an increase in serum osmolality and symptoms such as increased thirst, increased urination, weakness, fatigue, confusion, and in severe cases, convulsions and/or coma.

Hyperpigmentation: A common darkening of the skin, which occurs when an excess of melanin forms deposits in the skin.

Hypertrichosis: Excessive growth of hair.

Hypogammaglobulinemia: Low production of gamma globulins, resulting in reduced antibodies.

Hypogonadism: A medical condition resulting from or characterized by abnormally decreased functional activity of the gonads, with retardation of growth and sexual development. Associated with testosterone deficiency resulting from either testicular or pituitary/hypothalamic diseases.

Hypomania: Characterized by a persistently elevated, expansive, or irritable mood with related symptoms of increased goal-directed activity or energy including inflated self-esteem, decreased need for sleep, excessive talkativeness, racing thoughts, distractibility, and a propensity to be involved in high-risk activities with the symptoms lasting 4 to 6 days and does not require hospitalization or significant functional impairment.

Hypomimia: Lack of facial expression. Often termed masked face.

Hypophonia: Decreased voice volume.

Hypopituitarism: A clinical disorder characterized by complete or partial deficiency in pituitary hormone production.

Hyposmia: Reduced ability to smell.

Hypoxemia: Deficiency of oxygen in the blood.

Hypoxia: Deficiency of oxygen in body tissues.

Hysterectomy: Surgical removal of the uterus.

Immunoassay: A laboratory technique that uses the binding of antibodies to detect the presence or quantity of a certain substrate or antigen.

Immunoglobulin G index: The ratio of immunoglobulin G to protein in the serum or cerebrospinal fluid.

Immunophenotyping: A process used to identify cells, based on the types of antigens or markers on the surface of the cell. This process is used to diagnose specific types of leukemia and lymphoma by comparing the cancer cells to normal cells of the immune system.

Immunotherapy: A type of biological therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases.

Implantable cardioverter-defibrillator: A device implanted into the heart transvenously with a generator implanted subcutaneously in the pectoral area that provides internal electrical cardioversion of ventricular tachycardia or defibrillation of ventricular fibrillation.

Impulse control disorders: Urges and behaviors that are excessive and/or harmful to the individual or others; may include behaviors such as gambling, compulsive shopping or sexual behavior.

Incretin effect: A greater insulin stimulatory effect after an oral glucose load than that caused by an intravenous glucose infusion. The majority of the effect is thought to be due to glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1). Patients with type 2 diabetes have a significant reduction of the incretin effect, implying these patients either have decreased concentration of incretin hormones, or a resistance to their effects. GLP-1 concentrations are reduced in patients with type 2 diabetes in response to a meal, while GIP concentrations are either normal or increased, suggesting a resistance to actions of GIP, thus making GLP-1 a more logical target for therapeutic intervention.

Induction: The first treatment given for a disease; often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation.

Induction therapy: The first series of a treatment regimen typically designed to put a person into remission.

Infantile spasms (West syndrome): A seizure syndrome in infants younger than 1 year of age. It is characterized by a specific electroencephalogram pattern and spasms or jitters.

Initiation: In carcinogenesis, a cancer-causing substance encounters a normal cell to produce genetic damage, resulting in a mutated cell.

Inotropic: Relating to or influencing the force of muscular contractions.

In-stent restenosis: Complex process following stent implantation resulting in smooth muscle cell proliferation within an implanted stent, renarrowing of the arterial lumen, and recurrent ischemia.

Insulin resistance: Decreased response to insulin found before or early in the diagnosis of type 2 diabetes mellitus.

International normalized ratio (INR): Ratio of the patient's clotting time to the clinical laboratory's mean reference value, normalized by raising it to the international sensitivity index (ISI) power to account for differences in thromboplastin reagents. Therefore: INR = (patient's prothrombin time/laboratory's mean normal prothrombin time)^{ISI}.

Intra-articular: Administered to or occurring in the space within joints.

Intraperitoneal: Within the peritoneal cavity.

Intravesicular: Situated or occurring in the bladder.

Intussusception: The enfolding of one segment of the intestine within another.

Iontophoresis: Introduction of a medication into tissue through use of an electric current.

Ipsilateral: Occurring on the same side.

Irritant (venous): A drug that causes a burning sensation in the vein during intravenous administration; sometimes referred to as chemical phlebitis.

Ischemic penumbra: Ischemic, but still viable cerebral tissue. Typically, a rim of mild to moderately ischemic tissue in between normally perfused tissue and the area of evolving infarction; may remain viable for several hours.

Japanese encephalitis: A viral mosquito-borne disease endemic to Southeast Asia.

Jejunal entercocyte: Cells lining the jejunum, a section of the small intestine connecting the duodenum to the ileum.

Jejunostomy: Operative placement of a new opening into the jejunum, usually associated with feeding tube placement.

Juvenile myoclonic epilepsy: An epilepsy syndrome that typically occurs during teenage years and consists of generalized tonic-seizures and myoclonic jerks. Absence seizures may also occur with this syndrome.

Keratinization: The sloughing of epithelial cells in the hair follicle.

Keratinocytes: Predominant cell type in the outermost layer of the skin.

Keratitis: Infection of the cornea.

Keratoconjunctivitis sicca: An eye disease caused by eye dryness, which results from either decreased tear production or increased tear film evaporation. Also known as dry eye syndrome.

Kernicterus: A type of encephalopathy (brain disease or damage) as a result of high levels of bilirubin in the blood reaching the central nervous system.

Ketosis: Abnormal increase of ketone bodies present in conditions of reduced or disturbed carbohydrate metabolism.

Korotkoff sounds: The noise heard over an artery by auscultation when pressure over the artery is reduced below the systolic arterial pressure.

Kyphosis: Abnormal curvature of the spine resulting in protrusion of the upper back.

Lactose intolerance: The inability to digest lactose, a sugar found in milk products, resulting in diarrhea, bloating, and gas after ingestion.

Lagophthalmos: Poor closure of the upper eyelid.

Lamina cribrosa: Series of perforated sheets of connective tissue that the optic nerve passes through as it exits the eye.

Laminectomy: A type of surgery in which a surgeon removes part or all of the vertebral bone.

Laparoscopic: Abdominal exploration or surgery employing a type of endoscope called laparoscope.

Laparoscopic adjustable gastric banding: A surgical procedure for weight loss that elicits its effectiveness through gastric volume limitation; involves inserting a silicone band lined with an inflatable donut-shaped balloon around the neck of the stomach to be filled with isotonic liquid.

Laparotomy: Surgical opening of the abdominal cavity.

Laryngoscopy: Endoscopy of the larynx.

Left shift: An increase in the number of immature neutrophils. These immature cells may also be referred to as band neutrophils. Mature neutrophils may be referred to as segs.

Lennox–Gastaut syndrome: An epilepsy syndrome that often appears early in life that consists of a distinct electroencephalogram pattern, mild-to-severe developmental delay, and multiple seizure types.

Lesch-Nyhan syndrome: A rare inherited gene mutation that results in accumulation of abnormally high uric acid levels.

Leukocytoclastic vasculitis: Acute cutaneous vasculitis characterized by purpura (especially of the legs) and histologically by exudation of neutrophils and sometimes fibrin around dermal venules, with extravasation of red blood cells.

Leukocytosis: A condition in which the number of white blood cells circulating in the blood is increased.

Leukopenia: A condition where the number of circulating white blood cells are abnormally low due to decreased production of new cells, possibly in conjunction with medication toxicities.

Lewy bodies: Abnormal deposits of a protein called alpha-synuclein inside some nerve cells. They occur in a variety of locations, and their structure and composition vary depending on location.

Lhermitte sign: Tingling or shock-like sensation passing down the arms or trunk when the neck is flexed.

Libido: Sexual drive or desire.

Lichenification: Thickened, leathery, and hyperpigmented skin as a result of recurrent rubbing.

Ligament of Treitz: Landmark in the proximal portion of the jejunum beyond which it is preferred that postpyloric feedings be delivered for minimization of aspiration.

Linea nigra: Dark vertical line that appears on the abdomen during pregnancy.

Linear accelerator: A medical device that customizes high energy X-rays or electrons to conform to a tumor's shape and destroy cancer cells while sparing surrounding normal tissue.

Lipophilic: Having affinity for fatty substances.

Livedo reticularis: Purple mottling of the skin.

Low trauma fracture: A fracture resulting from a fall from standing height or less amount of trauma.

Lower esophageal sphincter: A manometrically defined zone of the distal esophagus with an elevated basal resting pressure that prevents the reflux of gastric material from the stomach. It relaxes on swallowing to permit the free passage of food into the stomach.

Lymphadenopathy: Enlargement greater than 1 cm of one or more lymph nodes.

Lymphatic: The network of vessels carrying tissue fluids.

Lymphoproliferative: Of or related to the growth of lymphoid tissue.

Macrocytosis: Enlargement of red blood cells with near-constant hemoglobin concentration.

Macrophage: A type of white blood cell that recognizes, surrounds, and ingests foreign particles and infectious microorganisms.

Maintenance therapy: The second phase of a treatment regimen, occurring after induction; typically designed to maintain remission.

Major malformation A defect that has either cosmetic or functional significance.

Maltodextrin: Easily digestible partially hydrolyzed starch.

Mania: Persistently elevated, expansive, or irritable mood with related symptoms of increased goal-directed activity or energy including inflated self-esteem, decreased need for sleep, excessive talkativeness, racing thoughts, distractibility, and a propensity to be involved in high-risk activities with the symptoms lasting at least a week or requiring hospitalization.

Mastalgia: Tenderness of the breast.

Mastodynia: Pain in the breast.

Maternal mortality ratio: The number of maternal deaths during a given time period per 100,000 live births during the same time period; highlights the risk of maternal deaths relative to the number of live births.

Matrix metalloproteinases: Any of a group of enzymes, normally located in the extracellular space of tissue, that function to break down proteins (eg, collagen) and require zinc or calcium atoms as cofactors for enzymatic activity. Responsible for the degradation of connective tissue.

Meatal stenosis: Narrowing in the opening of the urethra.

Meconium: First intestinal discharge ("stool") of a newborn infant, usually green in color and consisting of epithelial cells, mucus, and bile.

Mediastinal: Part of the chest that lies between the sternum and the spinal column, and between the lungs. This area contains the heart, large blood vessels, trachea, thymus gland, esophagus, and connective tissues.

Mediastinoscopy: A procedure that inserts a lighted instrument (mediastinoscope) used to examine the mediastinum.

Medication-assisted treatment: Use of medications with counseling and other behavioral therapies for the treatment of substance use disorders.

Melasma: Patchy skin pigmentation, often seen during pregnancy.

Melena: Abnormally dark black, tarry feces containing blood (usually from gastrointestinal bleeding).

Meningococcal: A term used to describe a disease caused by *Neisseria meningitidis* bacteria.

Menopause: Marked by final menstrual period due to loss of follicular activity and confirmed by 12 months of amenorrhea.

Mesial temporal lobe epilepsy: Involves medial or internal structures of the temporal lob and accounts for almost 80% of all temporal lobe seizures.

Mesocortical: A neural pathway that connects the ventral tegmentum to the cortex, particularly the frontal lobes. It is one of the major dopamine pathways in the brain.

Mesolimbic: One of the four major dopamine pathways in the brain, connecting the ventral tegmental area to the nucleus accumbens.

Mesothelioma: A benign or malignant tumor affecting the lining of the chest or abdomen. Commonly caused by exposure to asbestos fibers.

Metabolic Acidosis: A condition in the blood and tissues that is a consequence of an accumulation of lactic acid resulting from tissue hypoxia and anaerobic metabolism; may also be caused by a decrease in the concentration of alkaline compounds (typically bicarbonate).

Metabolic syndrome: Constellation of cardiovascular risk factors related to hypertension, abdominal obesity, dyslipidemia, and insulin resistance diagnosed by the presence of at least three of the following criteria: increased waist circumference, elevated triglyceride concentrations, decreased high density lipoprotein (HDL) cholesterol or active treatment to raise HDL cholesterol, elevated blood pressure or active treatment with antihypertensive therapy, or elevated fasting glucose or active treatment for diabetes.

Metastasis: Cancer that has spread from the original site of the tumor.

Methemoglobinemia: Condition caused by elevated levels of methemoglobin in red blood cells, resulting in enhanced oxygen affinity in heme sites and reduced oxygen delivery to tissues; leads to hypoxia, cyanosis, shortness of breath, mental status changes, and dizziness. In severe cases, it can lead to seizures, coma, or death.

Michaelis–Menten: Another term for zero-order pharmacokinetics. Drugs that follow zero-order pharmacokinetics reach saturation of metabolism within the usual dose ranges. This results in large changes in concentrations with small changes in doses.

Microalbuminuria: Urinary excretion of small but abnormal amounts of albumin. Confirmed spot urine albumin to creatinine ratio of 30 to 300 mg/g (3.4–34 mg/mmol creatinine) is consistent with microalbuminuria. Considered an early sign of chronic kidney disease.

Microcytosis: A condition in which the erythrocytes are smaller than normal.

Micrognathia: Abnormal smallness of the jaws.

Micrographia: Small handwriting, often seen in patients with Parkinson disease.

Microsatellite instability (MSI): The condition of genetic hypermutability that results from impaired DNA mismatch repair (MMR). The presence of MSI represents phenotypic evidence that MMR is not functioning normally.

Microvascular: Pertaining to the smaller vessels of the circulatory system such as capillaries, venules, and arterioles.

Microvascular pulmonary emboli: An obstruction in the small blood vessels in the lung caused by material (eg, blood clot, fat, air, foreign body) that is carried through the circulation until it lodges in another small vessel.

Micturition: Act of passing urine.

Minor malformation: Defect that has neither cosmetic nor functional significance.

Miosis: Pupil constriction.

Moebius syndrome: Rare congenital neurological disorder that is characterized by facial paralysis and affects eye movement.

Monoamine neurotransmitter: Serotonin, norepinephrine, and dopamine.

Monocyte: A large, phagocytic white blood cell that can further differentiate into macrophages or dendritic cells.

Monoparesis: Slight or incomplete paralysis affecting a single extremity or part of one.

Monosodium urate: A crystallized form of uric acid that can deposit in joints leading to an inflammatory reaction and signs and symptoms of gout.

Morphine equivalents: Dose of an opiate equivalency as it relates to morphine.

Mucositis: A complication of some cancer therapies in which the lining of the digestive system becomes inflamed. Often seen as sores in the mouth.

Multiparity: Condition of having given birth to multiple children.

Muscularis mucosa: The thin layer of smooth muscle found in most parts of the gastrointestinal tract.

Myalgia: Muscle aches or pains not necessarily associated with creatine kinase elevations.

Mydriasis: Pupil dilation.

Myelin: A protein and phospholipid sheath that surrounds the axons of certain neurons. Myelinated nerves conduct impulses more rapidly than nonmyelinated nerves.

Myelodysplastic syndrome: A type of cancer in which the bone marrow does not make enough healthy blood cells (white blood cells, red blood cells, and platelets) and there are abnormal cells in the blood and/or bone marrow.

Myelopathy: A neurologic deficit related to the spinal cord.

Myelosuppression: Reduction in white blood cells, red blood cells, or platelets.

Myocardial infarction: Myocardial cell death secondary to prolonged or severe local lack of oxygen supply (ischemia) to the myocardium; formation of an infarct, an area of tissue death, due to a local lack of oxygen.

Myoglobinuria: Presence of myoglobin in urine.

Myonecrosis: Necrotic damage to muscle tissue.

Myopathy: Unexplained muscle pain or weakness with creatine kinase elevations greater than 10 times the upper limit of normal.

Myringotomy: A surgical incision made in the tympanic membrane to relieve pressure and drain fluid from the middle ear.

Myxedema: Hypothyroidism characterized by a relatively hard edema of subcutaneous tissue, with increased content of proteoglycans in the fluid; characterized by somnolence, slow mentation, dryness and loss of hair, increased fluid in body cavities such as the pericardial sac, subnormal temperature, hoarseness, muscle weakness, and slow return of a muscle to the neutral position after a tendon jerk.

Nail psoriasis: Characterized by pitting, onycholysis, hyperkeratosis, and an oil-drop sign.

Nasal scotoma: Area of blindness in the nasal portion of peripheral vision.

Nasolacrimal occlusion: Closure of the tear duct to decrease systemic absorption of a drug.

Natriuresis: Excretion of sodium in the urine.

Necrotizing enterocolitis: Medical condition seen in premature infants, where portions of the bowel undergo necrosis.

Nelson syndrome: A condition characterized by the aggressive growth of a pituitary tumor and hyperpigmentation of the skin.

Neoadjuvant chemotherapy: Chemotherapy given before surgical resection to decrease tumor burden and make cancer more amenable to surgical resection.

Nephrolithiasis: A condition marked by the presence of renal calculi (stones) in the kidney or urinary system.

Nephron: The working unit of the kidney that filters blood to remove fluid, toxins and drugs. Each kidney contains approximately 1 million nephrons.

Nephrostomy: Narrow-gauge pigtail drain inserted into the renal pelvis for the purpose of draining urine.

Neuritic plaques: Extracellular deposits of amyloid beta with concentration markedly increased in the hippocampus, amygdala, and cerebral cortex. The plaque is thought to be formed through a cascade involving the formation of abnormally folded amyloid beta from amyloid precursor protein.

Neurofibrillary tangles: Aggregates of hyperphosphorylated tau protein, which can disrupt cellular function and lead to cellular degeneration and death.

Neuropathic pain: Pain resulting from a lesion or dysfunction of the nervous system.

Neuropathy: An abnormal and usually degenerative state of the nervous system or nerves. Damage to the small and large nerves due to glycation end products, lack of blood and nutrients to the nerves, or chemical imbalances.

Neurotransmitter: Chemical intermediary that carries messages between nerve cells.

Neutralizing antibodies: Antibodies that develop in response to a therapeutic agent that decreases the efficacy of the agent.

Nigrostriatal: One of the four main dopamine pathways in the brain, running from the substantia nigra to the caudate and putamen.

Nociception: Encoding and processing of noxious stimuli to the nervous system.

Nociceptors: Receptors for pain caused by injury from physical stimuli (mechanical, electrical, or thermal) or chemical stimuli (toxins); located in the skin, muscles, or in the walls of the viscera.

Nocturia: Excessive urination that occurs during sleep, causing patients to awaken overnight.

Nodule: An abnormal small swelling or aggregation of cells in the body.

Nonpolyposis: Absence of polyps.

Nonrapid eye movement sleep: The dreamless phases of sleep.

Non–ST-segment elevation myocardial infarction: A type of myocardial infarction that is limited to the subendocardial myocardium and is smaller and less extensive than an ST-segment elevation myocardial infarction.

Noradrenergic: Involving the transmission of norepinephrine.

Nulliparity: Condition of not having given birth to a child.

Nystagmus: Rapid, involuntary movements of the eyes.

Obtunded: Decreased level of consciousness.

Odynophagia: Pain on swallowing food and fluids, which is often due to esophageal disease.

Off time: In the context of Parkinson disease, the time when a Parkinson disease patient has poor control of their symptoms.

Off-label use: Use of a medication outside the scope of its approved, labeled use.

Oiling out: Continued coalescence of lipid emulsion particles, resulting in irreversible separation of the emulsion (also called "breaking" or "cracking" of the emulsion).

Oligoclonal immunoglobulin G bands: Small discrete bands in the gamma globulin region of fluid electrophoresis.

Oligohydramnios: Decreased amniotic fluid.

Oliguria: Reduced urine output; usually defined as less than 400 mL in 24 hours or less than 0.5 mL/kg/hour.

Omentumectomy: Excision of the double fold of peritoneum attached to the stomach and connecting it with abdominal viscera (omentum).

On time: In the context of Parkinson disease, the time when the Parkinson disease patient has good control of their symptoms.

Oncogene: A gene that is a mutated form of a gene involved in normal cell growth.

Open comedo: A plugged hair follicle of sebum, keratinocytes, and bacteria that protrudes from the surface of the skin and appears black or brown in color. Also referred to as a "blackhead."

Opportunity cost: The benefits foregone by selecting one alternative over another, for example, spending on healthcare reduces disposable income that may have been used on savings or investment.

Opsonization: The process by which an antigen is altered so as to become more readily and more efficiently engulfed by phagocytes.

Optic neuritis: Usually monocular central visual acuity loss and ocular/periorbital pain caused by demyelination of the optic nerve.

Oral glucose tolerance test: A test to measure the body's response to glucose; may be used to screen for type 2 diabetes and gestational diabetes.

Orchiectomy: Surgical removal of the testes.

Organification: Binding of iodine to tyrosine residues of thyroglobulin.

Orthopnea: Difficulty in breathing that occurs when lying down and is relieved upon changing to an upright position.

Orthostasis: Characterized by a drop in blood pressure when standing up from sitting or lying down, often causing light-headedness and dizziness.

Orthostatic hypotension/orthostasis: Significant blood pressure reduction upon standing due to the impairment of autonomic reflexes or depletion of intravascular volume.

Orthotopic: Placing a transplanted organ into the normal anatomic location.

Osmolality: A measure of the number of osmotically active particles per unit solution, independent of the weight or nature of the particle.

Osmolar gap: The difference between the measured serum osmolality and the calculated serum osmolality.

Osteoblasts: Cells that secrete the matrix for bone formation.

Osteoclasts: Cells involved in bone resorption.

Osteodystrophy: Defective bone growth, usually attributed to kidney disease or alterations in calcium and phosphorus metabolism.

Osteomalacia: Softening of the bones.

Osteonecrosis: Death of bone tissue.

Osteopenia: Reduced bone density or mass.

Osteophytes: Bony outgrowths (also called bone spurs) into the joint space.

Osteoporosis: Disease of the bones characterized by a loss of bone tissue, resulting in brittle, weak bones that are susceptible to fracture (porous bones).

Ostomy: Surgical operation where part of the abdominal wall is opened and part of the intestine is connected to the opening for intestinal draining (eg, colostomy, ileostomy).

Otalgia: Ear pain or earache.

Overall objective response rate: The proportion of patients with a complete response or partial response to anticancer treatment over a defined time period.

Ovulation: Periodic ripening and rupture of mature follicle and the discharge of ovum from the cortex of the ovary.

Palliative care: Pharmacological and nonpharmacological therapy intended to improve quality of life.

Palpable cord: Presence of an induration (cord) that is palpable, sometimes nodular, along the course of/or within an affected vein. Persistence of this cord when the extremity is raised suggests the presence of thrombus.

Pancreatitis: Inflammation of the pancreas.

Pancreatic pseudocyst: A cyst-like space not lined by epithelium and contained within the pancreas.

Panhypopituitarism: A clinical disorder characterized by complete deficiency in pituitary hormone production.

Pannus: Inflamed synovial tissue that invades and destroys articular structures.

Papilledema: Swelling of the optic disk/nerve due to increased intracranial pressure.

Papules: Solid, elevated lesion less than 0.5 cm in diameter.

Paracentesis: Removal of ascitic fluid from the peritoneal space.

Paracentral scotoma: Blind spots near the center of the visual field.

Parasomnias: Abnormal sleep behaviors such as sleep terrors and sleepwalking.

Parenchyma: The functional tissue of an organ as distinguished from connective and supporting tissue.

Parenteral nutrition: Delivery of nutrients via the intravenous route.

Paresthesia: An abnormal touch sensation, such as burning or prickling, that occurs without an outside stimulus.

Partial response: A decrease in the size of a tumor, or in the extent of cancer in the body, in response to treatment.

Paternalistic medicine: A philosophy of medicine that promotes the physicians' wishes above any other member of the health-care team or patients.

Peak expiratory flow: The maximum flow rate of air leaving the lungs upon forced exhalation. Individualized best measurements are established for each patient using a handheld peak flow meter.

Pelvic inflammatory disease: Inflammation of the endometrium, uterine tubes, and pelvic peritoneum; often due to a sexually transmitted infection.

Percutaneous coronary intervention: A minimally invasive procedure whereby access to the coronary arteries is obtained through either the femoral or radial artery up the aorta to the coronary ostia. Contrast media is used to visualize the coronary artery stenosis using a coronary angiogram. A guidewire is used to cross the stenosis and a small balloon is inflated to compress the atherosclerotic plaque and restore coronary artery blood flow. A stent is often deployed at the site to prevent acute closure and restenosis of the coronary artery. Newer stents are coated with antiproliferative drugs, such as paclitaxel, sirolimus, zotarolimus, or everolimus, which further reduce the risk of restenosis of the coronary artery.

Percutaneous endoscopic gastrostomy: Gastric feeding tube placed via endoscopic technique.

Percutaneous endoscopic jejunostomy: Jejunal feeding tube placed via endoscopic technique.

Pericarditis: Inflammation of the pericardium, the sac-like tissue that surrounds the heart.

Perihilar: The area surrounding the region where the bronchi, arteries, veins, and nerves enter and exit the lungs.

Perimenopause: Transitional period prior to menopause.

Perimetry: Measurement of the visual field.

Peripheral artery disease: Atherosclerosis of the peripheral arteries.

Peripheral vascular resistance: The sum of resistance to blood flow by systemic blood vessels.

Phagocytosis: The process of engulfing and ingesting an antigen by phagocytes.

Pharmacodynamics: Biochemical, physiologic, and molecular effects of drugs on the body.

Pharmacogenomics: The study of inherited genetic variations that dictate different drug responses. Pharmacogenomics explores the ways such variations can be used to predict responses to investigational products and plays an increasingly important role in drug discovery.

Pharmacokinetics: The movement of drug into, through, and out of the body.

Phenotype: The visible or observable properties of an organism that are produced by the interaction of the genotype and the environment.

Pheochromocytoma: A tumor arising from chromaffin cells, most commonly found in the adrenal medulla. The tumor causes the adrenal medulla to hypersecrete epinephrine and norepinephrine resulting in hypertension and other signs and symptoms of excessive sympathetic nervous system activity. The tumor is usually benign but may occasionally be cancerous.

Phlebitis: Inflammation of a blood vessel (e.g., vein).

Phobia: Excessive or unreasonable fear to a specific object (eg, people, animals) or situation (eg, flying), which are avoided or experienced with significant distress.

Photobiomodulation: Use of red or near-infrared light to stimulate healing, relieve pain and inflammation, and prevent tissue from dying.

Photochemotherapy: The use of psoralens in addition to ultraviolet rays for patients with a significant amount of body surface area affected (>10%).

Photodynamic therapy: Treatment with drugs that become active when exposed to light.

Photophobia: Intolerance to bright light.

Phototherapy: The use of ultraviolet rays for patients with a significant amount of body surface area affected (>10%).

Physical dependence: A state of adaptation that is manifested by a drug-class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Pilosebaceous unit: A hair follicle and the surrounding sebaceous glands.

Pica: An abnormal desire to eat substances (such as chalk or ashes) not normally eaten.

Plaque psoriasis: The most common form of psoriasis; manifests as well-defined, sharply demarcated, erythematous plaques typically covered with silvery scales. These plaques are irregular, round to oval in shape, and are almost always found on the scalp, trunk, buttocks, and limbs.

Plasma cell: Antibody-producing cells.

Plasmodium falciparum: The most common cause of clinical malaria globally and the cause of the most fatalities associated with malaria.

Plasmodium vivax: The most common cause of clinical malaria in the Americas. It is the species most commonly associated with a delayed onset of relapse after treatment.

Pleurisy: Chest pain upon inspiration occurring due to inflammation of the lining of the lungs.

Pleuritis: Inflammation of the lining (pleura) around the lungs.

Pneumatic otoscopy: A diagnostic technique involving visualization of the tympanic membrane for transparency, position, and color, and its response to positive and negative air pressure to assess mobility.

Pneumococcal: A term used to describe a disease caused by *Streptococcus pneumoniae* bacteria.

Pneumothorax: A condition that occurs when air leaks into the space between chest wall and lung. The air pocket exerts pressure against the lung causing it, or a portion of it, to “collapse”; often referred to as a collapsed lung.

Podagra: Gout of the foot, especially the first metatarsophalangeal joint.

Podocyte: Cells that make up the epithelial lining of Bowman’s capsule of the kidneys that surround the capillaries in the glomerulus. These cells are responsible for filtering blood in the glomerulus.

Polycystic ovary syndrome: Condition in which women have many small cysts on their ovaries that can lead to hormone imbalances and irregular periods.

Polycythemia: An abnormal increase in the number of erythrocytes in the blood.

Polycythemia vera: A hematologic cancer that is slow-growing in which the bone marrow produces excess red blood cells.

Polydipsia: Excessive thirst.

Polymerase chain reaction: A laboratory method used to make many copies of a specific DNA sequence.

Polymorphism: Occurrence in more than one form such as variance of genes.

Polyphagia: Eating excessively large amounts of food at a meal.

Polypharmacy: Taking multiple medications concurrently.

Polyps: Any growth or mass protruding from a mucous membrane.

Polysomnography: Specific type of sleep study that records brain waves, oxygen levels, heart rate, breathing, and eye and leg movements.

Polyuria: Excessive excretion of urine resulting in profuse micturition.

Posterior circulation: Blood supply to the posterior section of the brain through the vertebral, basilar, and posterior cerebral arteries (ie, brainstem, cerebellum, occipital lobe).

Post-intensive care syndrome: The disability noted after discharge from the intensive care unit and critical illness. Impairments which have been described include, but are not limited to, issues with cognition, mental health disabilities, and recurring physical ailments, specifically neuromuscular weakness.

Prader–Willi syndrome: A genetic disorder characterized by short stature, mental retardation, low muscle tone, abnormally small hands and feet, hypogonadism, and excessive eating leading to extreme obesity.

Prebiotic: Substance that can be used to nourish beneficial microbes in the gut.

Prediabetes: An asymptomatic but abnormal state that precedes the development of clinically evident diabetes.

Preload: The stretched condition of the heart muscle at the end of diastole just before contraction; volume in the left ventricle at the end of diastole estimated by the pulmonary artery occlusion pressure (also known as the pulmonary artery wedge pressure or pulmonary capillary wedge pressure).

Priapism: A prolonged, painful erection lasting more than 4 hours. Considered a medical emergency.

Primary amenorrhea: Absence of menses by age 15 in the presence of normal secondary sexual development or within 5 years of thelarche (if occurs before age 10).

Probiotic: Microorganisms administered to achieve a health benefit.

Proctitis: Inflammation confined to the rectum in patients with inflammatory bowel disease.

Proctosigmoiditis: Inflammation involving the sigmoid colon and rectum in patients with inflammatory bowel disease.

Progenitor: A primitive cell.

Prognostic factors: Biological or clinical markers associated with survival independent of therapy.

Progression-free survival: The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the progression-free survival is one way to see how well a new treatment works.

Progressive multifocal leukoencephalopathy: A neurological disorder characterized by the destruction of myelin-producing cells.

Prolapse: The dropping, falling, sinking, or sliding of an organ from its normal position or location in the body.

Promotion: The stage of carcinogenesis in which existing tumors are stimulated to grow and survive.

Proptosis: Forward displacement of the eyeball.

Prostaglandin: Any of a large group of biologically active, carbon-20, unsaturated fatty acids that are produced by the metabolism of arachidonic acid through the cyclooxygenase pathway.

Prostate-specific antigen (PSA): Protein produced by columnar secretory cells in the prostate that plays a role in the liquefaction of seminal fluid. Serum PSA levels greater than 10 ng/mL are associated with prostate cancer.

Prostatectomy: Surgical removal of the prostate gland and tissues surrounding it.

Prostatism: A syndrome associated with outlet obstruction at the bladder neck and most commonly caused by benign prostatic hyperplasia.

Protease: Any of numerous enzymes that catalyze the breakdown of proteins.

Proteasome: A large protein complex that helps destroy other cellular proteins when they are no longer needed.

Protectant: An agent that forms an occlusive barrier between the skin and surrounding moisture.

Proteinuria: The presence of measurable amounts of protein in the urine, which is often indicative of structural glomerular or tubular damage in the kidney.

Proteoglycan: Any one of a class of glycoproteins of high molecular weight that are found in the extracellular matrix of connective tissue. They are made up mostly of carbohydrate consisting of various polysaccharide side chains linked to a protein and resemble polysaccharides rather than proteins with regard to their properties.

Proteosome: An enzyme complex that degrades intracellular proteins.

Prothrombin time: A measure of coagulation representing the amount of time required to form a blood clot after the addition of thromboplastin to the blood sample; also known as Quick test.

Prothrombotic state: A state of high coagulation of the blood.

Proto-oncogene: A gene involved in normal cell growth. Mutations (changes) in a proto-oncogene may cause it to become an oncogene, which can cause the growth of cancer cells.

Pruritus: Localized or generalized itching due to irritation of sensory nerve endings.

Pseudophakic: The presence of a lens after cataract extraction.

Pseudopolyp: An area of hypertrophied gastrointestinal mucosa that resembles a polyp and contains nonmalignant cells.

Psoralens: Compounds that act as photosensitizing compounds.

Psoriatic arthritis: Inflammatory arthropathy associated with psoriasis. This condition is characterized by stiffness, pain, swelling, and tenderness around the joints and ligaments.

Pulmonary artery catheter: An invasive device used to measure hemodynamic parameters directly, including cardiac output and pulmonary artery occlusion pressure; calculated parameters include stroke volume and systemic vascular resistance.

Pulmonary artery occlusion pressure: A hemodynamic measurement obtained via catheter placed into the pulmonary artery used to evaluate patient volume status within the left ventricle.

Pulmonary embolus: An obstruction of the pulmonary artery or one of its branches by material that originated elsewhere in the body. The embolic material is often either a thrombus, air, tumor, or adipose tissue.

Pulmonary hypertension: An elevation in the pulmonary arterial pressure that can lead to right ventricular failure and heart failure symptoms.

Pulse oximetry: A noninvasive method of measuring arterial oxygen saturation. A pulse oximeter is a small device placed on a finger or earlobe that reads reflected light from capillary blood and estimates oxygen saturation.

Pulsus paradoxus: A large fall in systolic blood pressure and pulse volume during inspiration or an abnormal variation in pulse volume during respiration in which the pulse becomes weaker with inspiration and stronger with expiration.

Punding: Stereotyped behavior with repetitive movement or actions. An adverse reaction to dopaminergic therapy.

Purkinje fibers: Specialized myocardial fibers that conduct impulses from the atrioventricular node to the ventricles.

Purpura: A small hemorrhage of the skin, mucous membrane, or serosal surface.

Purulent: Containing, consisting of, or being pus.

Pustular psoriasis: A type of psoriasis associated with collection of neutrophils great enough to be seen clinically; may be generalized or localized. Often characterized by widespread sterile pustules and erythema.

Pustules: Vesicles filled with purulent fluid less than 0.5 cm in diameter.

Quality indicators: A list of indicators used by long-term care facility administrators and government overseers to identify potential problems in patient care.

Quality of life: An individual's sense of well-being and ability to carry out activities of daily living.

Quiescence: Dormant disease.

Radon: A chemically inert, radioactive gaseous element produced by the decay of radium, which is a risk factor for developing lung cancer.

Rapid cycling: Four or more mood episodes (major depressive, manic, or hypomanic) within 1 year.

Rapid eye movement sleep: Phase of sleep in which the eyes move rapidly, there is low muscle tone, and dreaming may occur.

Rapid sequence intubation: An airway procedure that aims to reduce the incidence of complications when placing an endotracheal tube. During the procedure, agents are utilized to induce an amnestic state while also causing muscle relaxation to allow for easier passage of the tube to the lungs.

Raynaud Disease: Decrease in blood flow to fingers or toes due to spasming of blood vessels; occurs in response to cold temperatures or stress; results in numbness, pain, and color changes of affected digits.

Rectal prolapse: Externally visible sinking of the rectum through the anal sphincter.

Recurrence: The development of a new episode after a patient has achieved remission of a condition or disease for a sustained period of time.

Reentry: Circular movement of electrical impulses, a mechanism of many arrhythmias.

Regurgitation: The effortless and nonprojectile passage of refluxed gastric contents into the pharynx or mouth.

Relapse: Return of symptoms prior to achieving remission or shortly after achieving remission. The relapse is typically considered a return of the original symptoms rather than a new episode as in recurrence.

Remission: A near absence of symptoms or return to baseline between episodes. Patient has no or minimal symptoms of disease. In the case of cancer in partial remission, some but not all signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although cancer still may be in the body.

Renin–angiotensin–aldosterone system: The hormonal system controlled mainly by the kidneys and adrenal glands, which regulates blood pressure, blood volume, and electrolyte balance.

Resistance-associated substitution: Resistance to a drug resulting in decreased antiviral activity caused by an amino acid change in the viral protein.

Resistant: A disease state or medical condition, such as cancer or infection, that does not respond to treatment.

Respiratory disturbance index: Measure reported on polysomnography that reports respiratory events during sleep.

Response inhibition: Ability to stay on task.

Reticulocytes: Immature blood cells that mature into erythrocytes.

Retinopathy: Occurs when the microvasculature nerve layer that provides blood and nutrients to the retina is damaged and can cause blindness.

Retrograde ejaculation: Semen flows to the bladder instead of the urethra.

Retrograde pyelography: Injection of a radiocontrast agent into the ureters to visualize the ureter and kidney with fluoroscopy or radiography.

Retrovirus: An RNA virus that uses an enzyme, reverse transcriptase, to turn the RNA into DNA in order to become part of the host cell's DNA (eg, Human Immunodeficiency Virus).

Rhabdomyolysis: Muscle symptoms with marked elevation in creatine kinase at 40 times the upper limit of normal which results in myoglobinuria and acute renal failure.

Rheumatic fever: A rare, acute immune-mediated disease that occurs mainly in children and young adults that is characterized by fever, arthritis, and inflammation of the pericardium and heart valves; it is associated with untreated or undertreated group A streptococcal disease.

Rheumatic heart disease: Valvular heart disease resulting from acute rheumatic fever.

Rheumatoid factors: Antibodies reactive with the Fc region of IgG.

Rhonchi: Abnormal, rumbling sounds heard on auscultation of an obstructed airway; more prominent during expiration and may clear somewhat on coughing.

Rickettsia: Intracellular bacteria often associated with tick bites and causing a nonspecific febrile syndrome.

Rotational thromboelastometry: A type of viscoelastic testing that measures clot formation to breakdown.

Rubefacient: A substance that produces redness of the skin.

Salicylism: A toxic syndrome caused by excessive doses of acetylsalicylic acid (aspirin), salicylic acid, or any other salicylate product. Signs and symptoms may include severe headache, nausea, vomiting, tinnitus (ringing in the ears), confusion, increased pulse, and increased respiratory rate.

Salmonella: Gram-negative enteric rod known to cause gastroenteritis.

Scleritis: Inflammation of the outer layer of the eyeball (sclera).

Scoliosis: Abnormal lateral (sideways) curvature of the spine.

Scotoma: A spot in the visual field in which vision is absent or deficient.

Sebaceous gland: Gland that produces sebum.

Sebum: Substance produced by the sebaceous gland that is composed of lipids.

Secondary amenorrhea: Absence of menses for three cycles or 6 months in a previously menstruating woman.

Seizure: A sudden electrical disturbance of the cerebral cortex, when a population of neurons fires rapidly and repetitively for seconds to minutes and electrical discharges are excessively rapid, rhythmic, and synchronous.

Sensitive: A disease state or medical condition that responds to treatment.

Sentinel lymph node: The first lymph node to which cancer is likely to spread from the primary tumor.

Sequential compression devices: A nonpharmacologic method of preventing venous thromboembolism.

Seropositive: Showing a positive reaction to a test on blood serum for a disease.

Severe myoclonic epilepsy of infancy: See Dravet syndrome.

Shigella: Gram-negative enteric bacteria causing a syndrome of explosive infectious diarrhea.

Sialorrhea: Drooling.

Sigmoidoscopy: Visual inspection of the sigmoid colon and rectum with a flexible tube called a sigmoidoscope.

Sleep apnea: Temporary stoppage of breathing during sleep; can be caused by narrowing of the airways resulting from swelling of soft tissue.

Sleep latency: Amount of time it takes to fall asleep.

Sleeve gastrectomy: A surgical treatment for weight loss that involves constructing a small gastric "sleeve" but cutting vertically and removing up to 90% of the stomach.

Slit-lamp biomicroscope: An instrument that allows for the microscopic examination of the cornea, anterior-chamber lens, and posterior chamber.

Spasticity: Feelings of stiffness and involuntary muscle contractions or sudden movements.

Sphincter of Oddi: Muscle where common bile duct empties into small intestine.

Spirometry: Measurement by means of a spirometer of the air entering and leaving the lungs.

Splanchnic: Relating to the viscera or internal organs.

Spondylolysis: A stress fracture in the lumbar spine through the pars interarticularis, a thin bone joining two vertebrae.

Stable disease: Cancer that has either insufficient increase to be defined as progressive disease or shrinkage to be defined as a response.

Steatohepatitis: A severe form of liver disease caused by fat deposition in the liver, characterized by hepatic inflammation that may rapidly progress to liver fibrosis and cirrhosis.

Steatorrhea: Passage of fat in large amounts in the feces, due to the failure to digest and absorb it.

Steatosis: Infiltration of liver cells with fat.

Stenting: Placement of a stent (a metal or plastic tube) to allow blood flow through an artery.

Stent retriever: Thrombectomy device used to trap a thrombus between the arterial wall and stent to allow rapid restoration of blood flow. The stent is pulled back to remove the thrombus.

Stevens-Johnson syndrome: A severe expression of erythema multiforme (also known as erythema multiforme major); typically involves the skin and the mucous membranes, with the potential for severe morbidity and even death.

Stimulant: Medication that increases functional activity in the body.

Stomatitis: Inflammation of mucous membranes in the mouth.

Stricture: An abnormal narrowing of a body passage, especially a tube or a canal.

Stridor: High-pitched, whistling sound.

Stroke volume: The amount of blood ejected from the heart during systole.

Strongyloides: Parasitic nematode generally causing gastrointestinal syndromes, although it does have the ability to cause disseminated disease.

ST-segment elevation myocardial infarction: A type of myocardial infarction that typically results in an injury that transects the thickness of the myocardial wall.

Subchondral: Situated beneath and supporting cartilage.

Substance use disorder: Recurrent use of a substance and the pathological pattern of behaviors that result from substance use, including significant impairment in health, disability, or failure to meet obligations at home, work, or school.

Substantia nigra: The area in the brainstem with highly pigmented cells that make dopamine.

Suspending agent: An additive used in the compounding of oral liquid medications to suspend drug particles throughout a liquid and enables resuspension of particles by agitation (e.g., shaking well).

Swan neck deformity: Joint deformity associated with rheumatoid arthritis that presents as flexion of the distal interphalangeal (DIP) joints with hyperextension of the proximal interphalangeal (PIP) joints.

Sympathomimetic: An agent that mimics the activity of a naturally occurring agonist, like epinephrine, to activate the sympathetic nervous system. Examples include ephedrine, pseudoephedrine, and phenylephrine.

Synechia: Adhesions or abnormal attachment of the iris to another structure. Peripheral anterior synechia refers to occurrence of synechia with the trabecular meshwork.

Synovitis: Inflammation of the synovial membrane, often in combination with pain and swelling of the affected joint.

Synovium: The membrane lining the internal surfaces of joints.

Systemic inflammatory response syndrome: A complex pathophysiologic response to an insult such as infection, trauma, burns, pancreatitis, and/or other injuries.

T-lymphocyte: A type of white blood cell that originates in the bone marrow and matures in the thymus and serves an essential role in the adaptive immune system.

T2-weighted magnetic resonance imaging: A setting of the magnetic resonance imaging machine that shows water and similar fluids such as cerebrospinal fluid as a bright signal.

Tachycardia: An abnormally rapid heart rate.

Tachyphylaxis: The continued or repeated exposure to a drug that may lead to a diminished pharmacological response over time.

Tachypnea: Faster than normal respiratory rate.

Tachypneic: Rapid breathing indicated by a rate of greater than 20 breaths/min.

Tangentiality: Abandoning one's ideational objective in pursuit of thoughts peripheral to the original goal. Used to describe a thought and speech pattern wherein the individual never gets to the point or answers the question.

Tardive dyskinesia: A chronic disorder of the nervous system characterized by involuntary jerky or writing movements of the face, tongue, jaws, trunk, and limbs, usually developing as a late side effect of prolonged treatment with antipsychotic drugs.

Targeted therapy: A type of treatment that uses drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cells.

Tendinosis: Tendon degeneration without accompanying inflammation.

Tenesmus: Difficulty with bowel evacuation despite the urgency to defecate.

Teratogenic: Causing malformation in a fetus.

Terminal secretions: The noise produced by the oscillatory movements of secretions in the upper airways in association with the inspiratory and expiratory phases of respiration. It is also known as "death rattle."

Tetany: A condition characterized by spasms of the hands and feet, cramps, spasm of the voice box (larynx), and overactive neurological reflexes usually due to low blood calcium.

Thelarche: Onset of breast development.

Thought blocking: Speech is halted, often in midsentence, and then picked up later, usually at another point in the thought process.

Thrombin: An enzyme formed from prothrombin which converts fibrinogen to fibrin and also activates platelets. It is the principal driving force in the clotting cascade.

Thrombocytopenia: A condition whereby the number of circulating platelets are abnormally low due to decreased production of new cells, possibly secondary to medication toxicities.

Thrombocytosis: Increased number of platelets in the blood.

Thromboelastography: A type of viscoelastic testing that measures clot formation to breakdown.

Thrombogenesis: Process of forming a blood clot.

Thrombolysis: Process of enzymatically dissolving or breaking apart a blood clot.

Thrombolytic: An enzyme that dissolves or breaks apart blood clots.

Thrombophlebitis: Inflammation of a blood vessel (eg, vein) associated with the stimulations of clotting and formation of a thrombus (or blood clot).

Thromboplastin: A substance that triggers the coagulation cascade. Tissue factor is a naturally occurring thromboplastin and is used in the prothrombin time test.

Thrombosis: A condition in which blood changes from a liquid to a solid state and produces a blood clot.

Thrombotic thrombocytopenic purpura: Condition characterized by formation of small clots within the circulation resulting in the consumption of platelets and a low platelet count.

Thrombus: Blood clot attached to the vessel wall and consisting of platelets, fibrin, and clotting factors; may partially or completely occlude the lumen of a blood vessel compromising blood flow and oxygen delivery to distal tissue.

Thyroglobulin: A thyroid hormone-containing protein, usually stored in the colloid within thyroid follicles.

Thyroid peroxidase: Enzyme that catalyzes the organification and coupling steps of thyroid hormone synthesis.

Thyroiditis: Inflammation of the thyroid gland.

Thyrotoxicosis: A syndrome caused by elevated levels of thyroid hormone; often caused by hyperthyroidism, a condition in which the thyroid gland produces excessive levels of thyroid hormone.

Tocolytic: Medication used to stop premature labor.

Tonometry: Method by which the cornea is indented or flattened to measure intraocular pressure.

Tophi: Collections of monosodium urate crystals that develop in tissues and generally appear as firm nodules under the skin.

Topoisomerase-I: Enzymes that cut one of the two strands of double-stranded DNA, relax the strand, and reanneal the strand.

Torsade de pointes: Very rapid ventricular tachycardia characterized by a gradually changing QRS complex in the electrocardiogram; may change into ventricular fibrillation.

Total abdominal hysterectomy and bilateral salpingo-oophorectomy: Surgical removal of the uterus, fallopian tubes, and ovaries which results in immediate menopause.

Total fertility rate: The average number of children a woman would have if she survives all her childbearing (or reproductive) years, which are typically considered to be between 15 and 49.

Toxic epidermal necrolysis: A life-threatening skin disorder characterized by blistering and peeling of the top layer of skin.

Transcranial magnetic stimulation (TMS): A form of neurostimulation therapy that involves the use of a magnet placed over the head. TMS is thought to induce the release of monoamine neurotransmitters.

Transesophageal echocardiogram: Procedure used to generate an image of the heart via sound waves, via a probe introduced into the esophagus (rather than the traditional transthoracic view) in order to obtain a better image of the left atrium.

Transferrin saturation: The ratio of serum iron and total iron-binding capacity, multiplied by 100.

Transformation/conversion: The change that a normal cell undergoes to become malignant.

Transmural: Existing or occurring across the entire wall of an organ or blood vessel.

Transsphenoidal pituitary microsurgery: Surgery through the nasal cavity to access the pituitary gland through the sphenoid bone.

Traveler's diarrhea: An acute infectious diarrhea that afflicts travelers during or immediately upon return and is due to ingestion of contaminated food or beverages resulting in diarrhea and other gastrointestinal symptoms.

Trigeminal neuralgia: Sudden, severe facial pain described as sharp shooting pain or electric shock in the jaw, teeth or gums.

Triple-negative breast cancer: Characterized by the absence of the three receptors used to guide treatment; this subtype is associated with the poorest prognosis.

Trismus: Limited jaw range of motion (also known as "lockjaw").

Trophic feeding: Very low-rate feedings designed to keep the gut stimulated.

Troponins T or I: Proteins found predominately in the myocardium. Troponin I and T are released into the blood from the myocytes at the time of myocardial cell necrosis secondary to infarction. These biochemical markers become elevated and are used in the diagnosis of myocardial infarction.

Trousseau's sign: Elicited by inflating a blood pressure cuff on the patient's upper arm, whereby hypocalcemic patients will experience tetany of the wrist and hand as evidenced by thumb adduction, wrist flexion, and metacarpophalangeal joint flexion.

Trypsin: A proteolytic enzyme formed in the small intestine from trypsinogen by the action of enteropeptidase, which once activated hydrolyzes peptides, amides, and esters.

Tuberoeruptive xanthomas: Small yellow-red raised papules usually presenting on the elbows, knees, back, and buttocks.

Tuberoinfundibular: One of the four main dopamine pathways in the brain, projecting from the arcuate and periventricular nuclei of the hypothalamus to the infundibular region of the hypothalamus.

Tubulointerstitial: Involving the tubules or interstitial tissue of the kidneys.

Tumor lysis syndrome: A syndrome resulting from cytotoxic therapy, occurring generally in aggressive, rapidly proliferating lymphoproliferative disorders; characterized by combinations of hyperuricemia, lactic acidosis, hyperkalemia, hyperphosphatemia, and hypocalcemia.

Tumor suppressor gene: A gene that suppresses growth of cancer cells.

Tympanocentesis: Puncture of the tympanic membrane with a needle to aspirate middle ear fluid.

Tympanostomy tube: Small plastic or metal tube surgically inserted in the eardrum to keep the middle ear aerated and improve hearing in patients with chronic middle ear effusion.

Uhthoff phenomenon: Acute worsening of multiple sclerosis symptoms on exposure to heat because high body temperatures may exceed the capacitance of the demyelinated nerve and conduction may fail.

Unknown-onset seizures: Seizures where the onset (ie, focal or generalized) cannot be determined.

Unstable angina: Pathogenically similar to non–ST-segment myocardial infarction but without muscle damage, therefore troponins are not elevated.

Uremia: A condition that results from accumulation of metabolic waste products and endogenous toxins in the body resulting from impaired kidney function; symptoms include nausea, vomiting, weakness, loss of appetite and mental confusion.

Urethral stricture: Narrowing of the urethra.

Urgency (urinary): A compelling need to urinate that is difficult to defer.

Uricosuric: Pertaining to, characterized by, or promoting renal excretion of uric acid.

Urticaria: Itchy, raised, swollen areas on the skin, also known as hives.

Uterine tachysystole: Uterine hyperstimulation with frequent contractions, hypertonus and non-reassuring fetal heart rate pattern.

Uveitis: Inflammation of the uvea. Uveal structures include the iris, the ciliary body, and the choroid.

Valsalva maneuver: A technique that forces respiratory expiration against a closed glottis.

Valvular heart disease: Damage or defects in one or more of the heart valves, disrupting blood flow into and out of the heart. The most common valves affected are the aortic and mitral valves. Valvular stenosis is a narrowing of the valve opening restricting the forward flow of blood. Valvular regurgitation or insufficiency occurs when there is inadequate closure of the valve leaflets leading to blood "leaking" backward.

Vasculitis: Inflammation of the walls of blood vessels.

Vasomotor symptoms: Menopausal symptoms that include both hot flashes (flushes) and night sweats for which women most commonly seek therapy.

Vasopressors: Medications that cause constriction of blood vessels, increase in vascular resistance, and increase in blood pressure.

Ventilation: Movement of air between the environment and the lungs.

Ventilation/perfusion ratio (V_A/Q): A comparison of the proportion of lung tissue being ventilated by inhaled air to the rate of oxygenation of pulmonary blood.

Ventricular depolarization: Change in the membrane potential of a ventricular myocyte, resulting in loss of polarization. Under normal conditions, depolarization of ventricular myocytes is followed by ventricular contraction.

Vertigo: Sensation of spinning or feeling out of balance.

Vesicants: Chemotherapy drugs that cause significant tissue damage if extravasation occurs.

Viral hemorrhagic fevers: Highly virulent viral diseases causing significant hematologic abnormalities and a high mortality rate. Ebola would be the most well-known.

Virilization: Production or acquisition of virilism, which is masculine characteristics.

Viscoelastic testing: Point-of-care testing devices utilizing thromboelastography principles to evaluate clot formation and dissolution.

Volvulus: Twisting of the intestine causing obstruction and possible necrosis.

Vulvovaginal atrophy: Thinning of vaginal tissue due to a lack of estrogen stimulation.

Wernicke syndrome: Neurologic condition caused by thiamine deficiency and characterized by mental confusion, ataxia, and ophthalmoplegia.

West Nile encephalitis: Mosquito-borne disease causing a clinical syndrome of viral encephalitis.

Wheeze: A high-pitched whistling sound caused by air moving through narrowed airways; usually heard at the end of expiration but may be heard during inspiration and expiration in acute severe asthma.

White coat hypertension: A persistently elevated average office blood pressure of greater than 140/90 mm Hg and an average awake ambulatory reading of less than 135/85 mm Hg.

Wilson Disease: A disorder of copper metabolism, characterized by cirrhosis of the liver and neurological manifestations.

Xanthomas: Firm raised nodules composed of lipid-containing histocytes.

Xerostomia: Unusual dryness of the mouth.

ZAP-70 expression: An intracellular tyrosine kinase found in CLL B-cells.

Zika virus: Mosquito-borne disease associated with fetal neurologic developmental anomalies when acquired by pregnant women.

Zymogen: An inactive protein precursor of an enzyme that is converted into an active form.

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